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Clinical Implementation of Nephrologist-Led Genomic Testing for Glomerular Diseases in Singapore: Rationale and Protocol

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Genomic test · Glomerulonephritis · Implementation science · Rare kidney disease

Abstract

Introduction: The early diagnosis and appropriate treatment of monogenic glomerular diseases can reduce kidney failure, avoid unnecessary investigations such as kidney biopsies and ineffective treatment with immunosuppressants, guide transplant decisions, and inform the genetic risks of their family members. Yet, genetic testing for kidney disease is underutilized in Singapore. We aimed to implement a nephrologist-led genetic service and evaluate the acceptance, adoption, utility, and cost-effectiveness of genetic testing for monogenic glomerular disease in Singapore. ***Methods:*** We will perform a prospective, multi-centre, type II hybrid effectiveness-implementation study with a post-design to evaluate both implementation and clinical outcomes of nephrologist-led genetic testing for suspected genetic glomerular kidney diseases. The multi-disciplinary implementation team will train "genetic nephrologists" to provide pre- and post-test counselling, order targeted exome panel sequencing for suspected glomerular kidney

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diseases (persistent microscopic haematuria and/or albuminuria or proteinuria in the absence of known causes, steroid-resistant primary nephrotic syndrome, apparent familial IgA nephropathy, or chronic kidney disease with no apparent cause), and interpret genetic test results; create workflows for patient referral, evaluation and management, and discuss genetic results at regular genomic board meetings. The outcomes are acceptance, appropriateness and adoption among patients and nephrologists, utility (proportion of patients who received genetic testing and have a confirmed diagnosis of genetic glomerular disease), and cost-effectiveness. ***Conclusion:*** This study will create and evaluate a nephrologist-led genetic service, develop an efficient variant curation process, and inform future recommendations on the optimal referral and genetic testing strategy for monogenic glomerular disease in Singapore. This will facilitate the future mainstreaming of genetic testing that will enable precision medicine in kidney care.

Introduction

The joint international consensus statement by the International Society of Nephrology, European Renal Association and American Society of Nephrology highlighted the increasing prevalence of chronic kidney disease (CKD) globally and called for early detection and treatment to prevent progression to end-stage kidney disease (ESKD) [1]. In 2020, Singapore ranked 4th and 7th in the world for prevalence and incidence of ESKD, respectively, and spent USD 190 million on dialysis [2]. As glomerular disease is a common cause of CKD and ESKD [3, 4], particularly among children and young adults [5], accurate and early diagnosis and treatment of glomerular diseases can reduce accrued kidney injury and progressive CKD. Yet, this has been challenging for monogenic glomerular diseases. Firstly, early diagnosis may be difficult in presymptomatic individuals. Among the primary glomerular diseases, Alport syndrome due to pathogenic variants in the *COL4A3*, *COL4A4*, *COL4A5* genes is the commonest cause of monogenic glomerular disease and FSGS among older children and adults [6–8]. However, Alport syndrome is often underdiagnosed [9], as it is asymptomatic with no urinary abnormalities early during its clinical course. Patients may subsequently develop microscopic haematuria and proteinuria that progresses to CKD and eventually ESKD [10]. Anti-proteinuric therapy is recommended at the genetic diagnosis of X-linked Alport syndrome in males and autosomal recessive Alport syndrome, even in the absence of urinary anomalies; or at the onset of microalbuminuria for those with autosomal dominant Alport syndrome or females with X-linked Alport syndrome [11]. The earlier the initiation of anti-proteinuric therapy, the greater the delay in the progression of CKD [12, 13]. Such early diagnosis and intervention are possible only with genetic testing since diagnostic evaluation with kidney biopsies is seldom indicated in the absence of kidney injury or proteinuria, and if performed during the early phase of the disease, may find no or only minor histological changes that are inconclusive. Secondly, patients who present with nephrotic syndrome or heavy proteinuria often require an invasive kidney biopsy to detect the histological changes and receive empiric treatment with aggressive immunosuppression to mitigate the presumed immune-driven inflammation. While a kidney biopsy may confirm a histological diagnosis of focal segmental glomerulosclerosis (FSGS), it may not differentiate between immune, toxic and genetic causes of FSGS. Moreover, 20–30% of children with steroid-resistant nephrotic syndrome and 10% of adults with FSGS have genetic causes that generally do not respond to immunosuppression [14–18]. Instead, a timely genetic diagnosis may obviate the need for an extensive evaluation process and invasive kidney biopsy with risks of bleeding and need for transfusion [19] and reduce the exposure to unnecessary, prolonged immunosuppression that are expensive and have significant side effects. Indeed, among adults with kidney failure of unknown causes, 10–30% were diagnosed with monogenic kidney diseases [7, 20, 21]. Genetic testing in these potential kidney transplant recipients and their donors found that genetic testing was able to guide decisions on kidney transplantation and selection of living donors [22–24].

In view of the potential impact of a genetic diagnosis on guiding the clinical care of individuals with kidney disease, international guidelines have recommended that genetic testing be performed routinely in children with steroid-resistant nephrotic syndrome, ideally prior to kidney biopsy and initiation of second-line immunosuppression [25]; in adults with familial, syndromic, or steroid-resistant nephrotic syndrome or FSGS; in patients with haematuria, proteinuria, and extrarenal manifestations or a family history of haematuria or kidney failure or immunoglobulin A nephropathy; and in patients with kidney failure with no obvious cause [6, 26]. Despite recommendations for genetic testing in clinical practice guidelines [6, 25, 26], genetic testing for

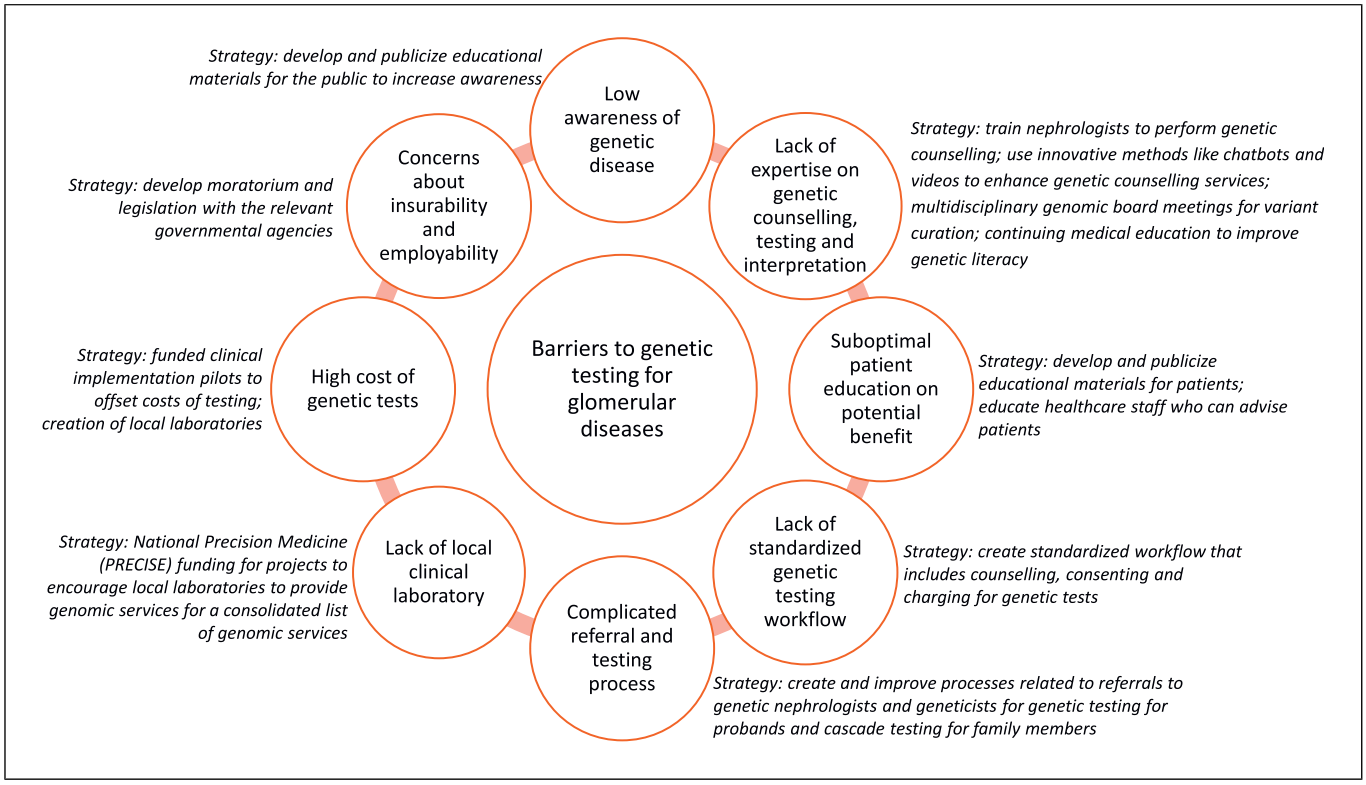

Fig. 1. Potential barriers to genetic testing for glomerular diseases and potential strategies to address the barriers.

kidney disease is not widely used in Singapore. Traditionally, paediatric and adult nephrologists in Singapore were not accredited to perform genetic counselling and order genetic testing for kidney diseases, according to the regulations imposed by the Singapore Ministry of Health [27]. Hence, children and adults with suspected monogenic glomerular diseases had to be referred by their primary physicians (paediatricians or nephrologists) to a geneticist or a genetic counsellor who were often not within the same institution, especially for adult nephrology units. Due to the lack of local clinically accredited gene sequencing laboratories, the genetic tests were performed at overseas laboratories with complicated workflows, long turnaround times, and high costs. In the absence of government subsidies or insurance coverage, these costs are paid out-of-pocket by the patients. Unsurprisingly, these costs were often prohibitive to most local patients and resulted in low uptake of genetic testing. In addition, low genetic literacy among clinicians and patients, the lack of technical expertise in genetic counselling and result interpretation among nephrologists, and unfamiliarity with genetic test requests are possible barriers to widespread clinical implementation of genetic testing in nephrology (Fig. 1; online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000542942). Our preliminary search to inform a systematic review protocol on the clinical, implementation and health economic outcomes of genetic testing in kidney diseases (PROSPERO CRD42024557003) found that published literature was dominated by narrative reviews and cross-sectional studies on the diagnostic yield of genetic tests, with few longitudinal studies and even fewer implementation studies. A study in Australia suggested genetic testing may be cost-effective in adults and children with glomerular diseases [28]. Due to different population structures, disease prevalence, cultures, and healthcare financing, an implementation study and health economic analysis in Singapore will be important to direct national policymaking [29].

Our overall goal is to implement evidence-based genetic testing in nephrology clinical practice to positively impact the clinical management of individuals with suspected and/or confirmed glomerular disease. Specifically, we aimed to evaluate the acceptance, adoption, utility, and cost-effectiveness of a nephrologist-led genetic service within the local context of laws and regulations, cultural perspectives, attitudes, and beliefs.

Methods

Study Design

We will perform a prospective, multi-centre, type II hybrid effectiveness-implementation study with a post-design to evaluate both the implementation and clinical outcomes of nephrologist-led genetic testing for suspected genetic glomerular kidney diseases. This study design allows for simultaneous testing of both the clinical intervention and implementation strategy in pragmatic, "real-world" settings that can facilitate the subsequent translation into routine practice [30].

Setting

The public healthcare system in Singapore is divided into three healthcare clusters that are geographically defined. This clinical implementation project is conducted in two paediatric nephrology units and three adult nephrology units in four tertiary care hospitals from all three healthcare clusters. Physicians from nephrology units and hospitals not involved in the implementation project can refer patients with suspected genetic glomerular kidney disease to a genetic nephrologist in the implementation team within the healthcare cluster.

Study Participants

Individuals are eligible for genetic testing if they have (1) persistent microscopic haematuria and/or albuminuria or proteinuria in the absence of known causes; (2) primary nephrotic syndrome with initial-onset steroid resistance; (3) apparent familial immunoglobulin A nephropathy; or (4) CKD stage G3–5 or rapid estimated glomerular filtration rate decline (defined as more than 5 mL/min/1.73 m^2 per year [31]) with no apparent cause. The exclusion criteria are (1) confirmed or suspected secondary causes of glomerular diseases, (2) confirmed or suspected non-glomerular kidney diseases that can account for the clinical course, (3) complex phenotypes involving multi-system disease which may suggest complex genetic alterations beyond the gene panel (these will be referred to a clinic geneticist). Probands who satisfy the inclusion criteria will be referred to the study team by their nephrologists. Family members who are eligible for variant-specific genetic testing after the genetic results are available will also be recruited for this study. We will recruit probands of ages below 70 years, while there is no age limit for family members.

After obtaining informed consent for study participation, the probands will receive pre-test genetic counselling from genetic nephrologists. After the counselling, patients who consent to genetic testing will submit 3 mL of blood or saliva or a buccal swab for gene panel testing. The same genetic nephrologist will perform post-test counselling on the genetic result. Selected family members of probands with genetic glomerular kidney diseases may be invited by the proband to participate in cascade testing. For probands with gene variants of uncertain significance that can be re-classified based on family segregation studies, selected family members may also be invited for variant-specific genetic testing. Probands must agree before the study team can approach their family members. Patient enrolment started in March 2023 as part of phase 2 by the Precision Health Research Singapore (PRECISE) [32], a government agency that coordinates the country's National Precision Medicine strategy [33]. As genetic diagnoses were confirmed in 15%–30% of individuals who received genetic testing for suspected monogenic glomerular disease [7, 34], we aimed to recruit 400 probands. Based on the estimated diagnostic yield of 20% [7], we estimated that we will diagnose genetic kidney diseases in 80 patients.

Implementation

The complex implementation was planned according to a structured road map (shown in online suppl. Fig. S1) and logic model (Fig. 2). The details are described according to the Template for Intervention Description and Replication (TIDieR) [35] in Table 1.

We established a multi-disciplinary workgroup of clinical geneticists, genetic counsellors, nephrologists, laboratory scientists, variant curation experts, and health economists. As a gene panel or targeted exome testing is recommended as first-line for glomerular diseases [25], gene panels of 84 genes ("glomerular panel") and 125 genes ("glomerular and cystic panel"; online suppl. Table S2) known to cause genetic kidney diseases were curated by the workgroup. Tailoring of the intervention was made to include kidney cystic disease gene testing for patients with kidney cysts when the cystic changes did not explain the degree of haematuria, proteinuria, or CKD (because kidney cystic diseases can be phenocopies of glomerular diseases) and whole exome sequencing for patients with CKD of unknown aetiology to better capture the breadth of possible genetic causes (online suppl. Table S3). The approaches to clinical genetic testing for actionable monogenic kidney diseases are summarized in online supplementary Table S4.

Monthly discussions were held to address implementation barriers iteratively and include feedback from patients to incorporate the "patient voice." At the start of the project, a structured training program was carried out by accredited geneticists and genetic

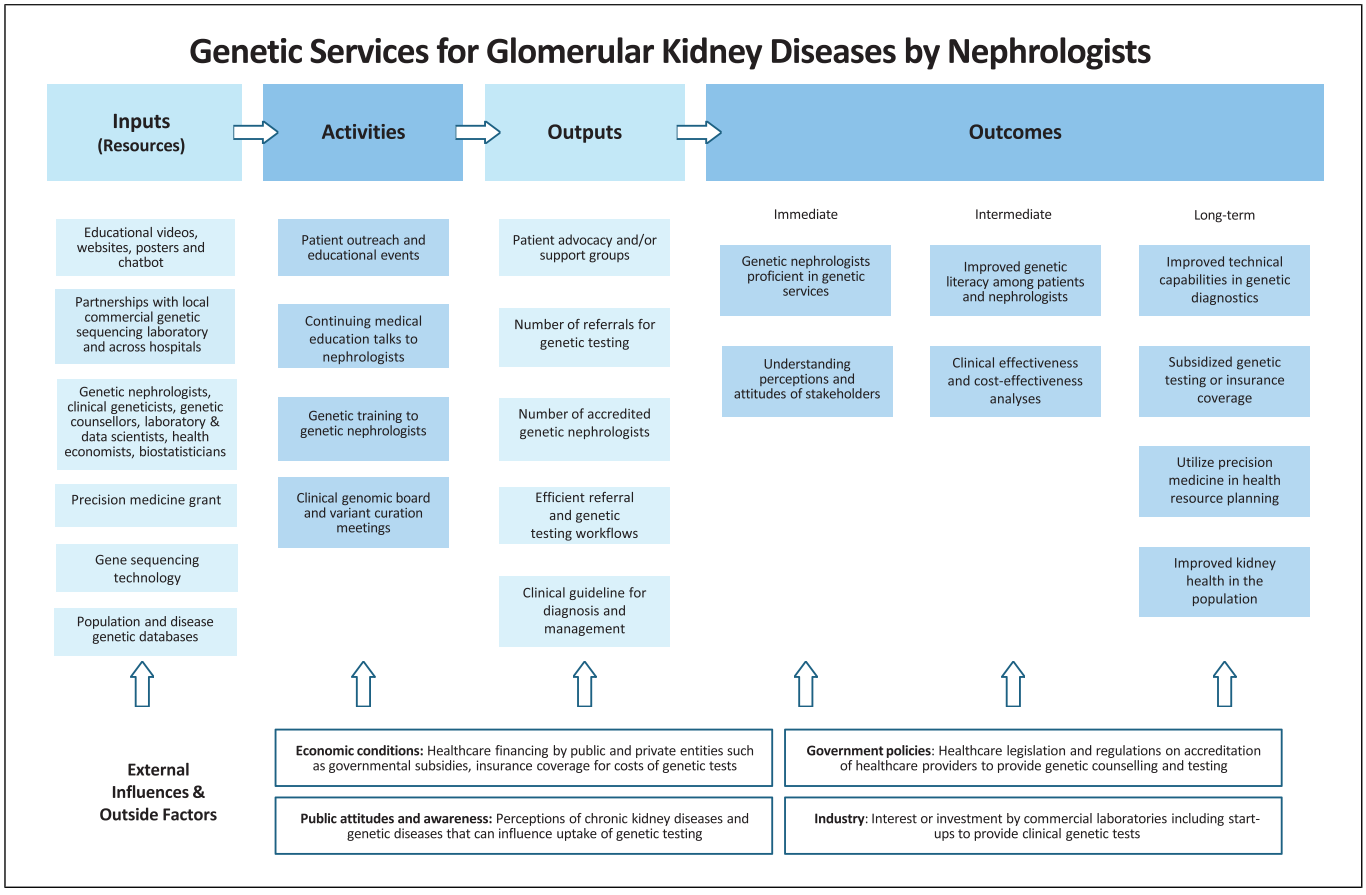

Fig. 2. Logic model for the complex implementation of genetic services by nephrologists.

counsellors to educate nephrologists on fundamental genetics knowledge. This included skills to interpret the genetic reports, pre- and post-test genetic counselling, and indications for referral to clinical geneticists, such as complex phenotypes, the need for extended genetic testing, and pre-implantation genetic testing. Additionally, geneticists and genetic counsellors were also informed on pertinent nephrology knowledge related to genetic diseases, particularly the utility and clinical impact of the genetic results. The training program included recorded lectures, case discussions, videos of simulated counselling encounters, written guides for pre-test and post-test counselling, standardized genetic testing consent templates, and direct supervision of actual patient counselling encounters with post-session feedback. Additionally, these nephrologists will attend mandatory monthly multi-disciplinary genomic board meetings. Here, the primary aim will be to discuss the pathogenic and likely pathogenic variants, the utility of genetic testing, management plans in relation to the genetic results, as well as cascade testing of the family members. Ethical issues are also routinely discussed, and these include insurability implications as well as utility and implications of genetic testing for minors. The second aim of these meetings is to evaluate the variants of uncertain significance according to the American College of Medical Genetics (ACMG) [1] and the guidelines from the Clinical Genome (ClinGen) expert panels [2]. If reclassification of the variants of uncertain significance is possible with additional evidence, a tailored plan will be made for each proband and his family (online suppl. Tables S5, S6, respectively). These steps may include functional experiments performed in the research laboratory. The workgroup also established criteria for accreditation of the nephrologists based on attendance at the training sessions and completion of supervised and independent genetic counselling encounters and case logs (online suppl. Table S7). Nephrologists who complete the genetics training will be defined as "genetic nephrologists" in this study and will be deemed capable of

Table 1. The intervention and implementation strategy according to the Template for Intervention Description and Replication (TIDieR)

Brief name	Provision of genetic services for suspected glomerular diseases by genetic nephrologists
Why	Increase implementation of evidence-based genetic services for early diagnosis and management of children and adults with genetic glomerular kidney disease By allowing accredited genetic nephrologists to provide genetic services via standardized workflows and within a pre-defined scope, we aim to overcome the barriers that contribute to under-diagnosis and suboptimal management of genetic glomerular diseases
What	Educational lectures and genetic case discussions, including monthly genomic board meetings, to increase genetic literacy among genetic nephrologists Videos to train genetic nephrologists to perform pre- and post-testing genetic counselling. Template for informed consent for genetic testing Templates for electronic medical record documentation of pre- and post-test counselling to patients Templates for reply letters to referring physicians Physician and patient education material educational shared on the official website of Singapore Society of Nephrology and as posters in the nephrology ambulatory clinics Layperson educational booklet on genetic testing will be shared with potential participants
Who will provide	Clinical geneticists and genetic counsellors will provide peer education, guidance and direct supervision to genetic nephrologists during the initial training Genetic nephrologists will provide the pre- and post-test counselling to patients Clinical geneticists, genetic counsellors, and laboratory scientists will provide input during monthly genomic board meetings Coordinators will assist in scheduling appointments and preparing redacted clinical phenotype and genetic results for genomic board meetings
How	At the start of the project, a structured training program will train and accredit selected nephrologists as genetic nephrologists, who will learn to perform pre- and post-test genetic counselling and interpret the genetic results. This will be conducted as a group via online video conferencing to facilitate multi-site participation. Training videos are also shared via online platforms for ease of access Patients with suspected monogenic glomerular diseases will be referred by their physicians (pediatricians or nephrologists) to the genetic nephrologists Patients will be assessed by genetic nephrologists for the indications for genetic testing, then undergo pre-test counselling at the genetic nephrology clinics. Those who agree to genetic testing will have their blood or saliva samples obtained for targeted exome sequencing for a curated gene panel. Genetic results will be discussed at monthly multi-disciplinary genomic board meetings via online video conferencing to assist in variant interpretation and decide on further genetic and clinical evaluation. Genetic nephrologists will perform the post-test counselling and explanation of the results to the patients in-person at the genetic nephrology clinics within 2–3 months after genetic testing
Where	Two paediatric nephrology units and three adult nephrology units in four tertiary care hospitals (Khoo Teck Puat-National University Children's Medical Institute, KK Women's and Children's Hospital [KKH], Singapore General Hospital [SGH], Tan Tock Seng Hospital, and National University Hospital) of all three public healthcare clusters in the country
When and how much	Genetic nephrology clinics will be held every 1–2 weeks, according to each institution's needs Implementation team meetings are held once a month Genomic board meetings are held once a month
Tailoring	As kidney cystic diseases can be phenocopies of glomerular diseases, stakeholders decided that in addition to the initial 84-gene panel for glomerular diseases, a 41-gene panel that included kidney cystic disease genes will be added for patients with kidney cysts but no severe enough to explain the degree of haematuria, proteinuria, or CKD. Additionally, whole exome sequencing test will be added for patients with CKD of unknown aetiology to better capture the breadth of possible genetic causes

Table 1 (continued)

Brief name	Provision of genetic services for suspected glomerular diseases by genetic nephrologists
Modifications	As the number of referrals and complexity increased, one adult nephrology centre (SGH) utilized the healthcare cluster's genomics program (the SingHealth Duke-NUS Genomic Medicine Centre that facilitated service and expertise sharing) to integrate genetic counsellors from a clinical genetic service of another hospital (KKH) into their genetic kidney clinics
How well	Twenty-two nephrologists agreed to participate and undergo training as genetic nephrologists by 30th Jun 2025. Among these nephrologists, ten had achieved initial accreditation by 30th July 2024 Patient enrolment started in March 2023. As of 30th Jun 2024, 294 had consented to participate and 246 had consented for genetic testing

providing genetics services within a pre-defined scope. Genetic services include pre- and post-test genetic counselling, ordering of appropriate genetic tests, interpreting genetic results, and providing management recommendations based on the genetic results.

To increase awareness among patients and physicians caring for individuals with kidney disease, educational content was shared on the official website of the Singapore Society of Nephrology [36, 37], and informational posters (shown in online suppl. Fig. S2) were placed in the ambulatory nephrology clinics. Potential participants will be provided with patient education booklets that describe the process and potential benefits of genetic testing. An excerpt is shown in online supplementary Figure S3. We organized patient education sessions (online suppl. Fig. S4) to inform patients and caregivers about genetic kidney diseases and encourage interactions with peer patients with lived experiences who had stepped forward to support fellow patients. A planned collaboration with health economists for a health economic analysis on the cost-effectiveness of the nephrologist-led genetic service will provide information to inform national policymaking towards healthcare financing for genetic testing for kidney diseases [38], as less costly genetic tests may encourage their uptake.

Outcomes and Explanatory Covariables

The outcomes were defined in Table 2 based on Proctor's taxonomy of implementation research outcomes [39]. Acceptance (satisfaction with various aspects of implementation) and appropriateness (perceived relevance or usefulness) will be assessed in patients and nephrologists using focused discussions and surveys (online suppl. Table S8). Adoption among nephrologists caring for patients with suspected genetic glomerular disease is defined as the proportion who refer patients with suspected genetic glomerular disease for genetic counselling and testing. Adoption among patients with suspected genetic glomerular disease is defined as the proportion of referrals who undergo genetic counselling and testing. Utility is defined as the proportion of patients who received genetic testing and have a confirmed diagnosis of genetic glomerular disease. A health economic evaluation will be performed using a Markov cost-utility analysis model conducted from a societal perspective, the preferred perspective in policy analysis [40]. The total costs and quality-adjusted life years accumulated over a patient's lifetime will be used to calculate the incremental cost-effectiveness ratio for the cost-utility study outlined in online supplementary Table S9.

Data from the patients include the demographic information (age, sex, race, and birth country); parental consanguinity; detailed family pedigree and family history of kidney disease (haematuria, proteinuria, kidney cysts, kidney failure, gout, young-onset hypertension); clinical phenotype (frothy urine, gross haematuria, lethargy, hypertension, preeclampsia, oedema, extrarenal manifestations including eye and ear abnormalities, lactic acidosis, dysmorphism, epilepsy or cognitive impairment); and laboratory findings (albuminuria, microscopic haematuria, nephrotic syndrome, estimated glomerular filtration rate) at first presentation, during follow-up and at genetic testing; kidney imaging and kidney biopsy findings; pharmacotherapy (renin-angiotensin system [RAS] blocker, antihypertensives, immunosuppressants) before and after genetic testing; healthcare utilization (type and frequency of healthcare follow-up, additional investigations such as kidney biopsy and cystoscopy, additional treatment such as kidney replacement therapy or transplant) before genetic testing; suspected clinical diagnosis and indication for genetic testing; type of genetic test performed and findings and post-test plans for evaluation and clinical management at 3 months after the return of the genetic test results. Additionally, the EuroQol, a standardized indirect measure of health utility [41], will be used to assess patient-reported

Table 2. Implementation study outcomes according to Proctor's taxonomy

Outcome	Description	Level of analysis	Measurement
Acceptance	Satisfaction with various aspects of implementation	Patients and caregivers	Focused group discussion
		Nephrologists performing genetic counselling and testing	Focused group discussion and survey
		Nephrologists caring for patients with suspected and/or confirmed genetic glomerular diseases	Survey
Appropriateness	Relevance or usefulness	Patients	Change in management such as avoidance of kidney biopsy or change in immunosuppression strategy or treatment
		Patients and caregivers	Focused group discussion
		Nephrologists caring for patients with suspected genetic glomerular diseases	Survey
Adoption	Uptake or utilization	Nephrologists caring for patients with suspected genetic glomerular diseases	Number and proportion who refer patients with suspected genetic glomerular disease for genetic counselling and testing
		Patients with suspected genetic glomerular disease	Number and proportion of referrals who undergo genetic counselling and testing
		Family members of proband offered cascade testing	Number and proportion of family members who undergo cascade testing
Utility	Feasibility	Patients who had genetic testing for suspected genetic glomerular disease	Number and proportion with confirmed genetic glomerular disease
		Family members of proband who received cascade testing	Number and proportion of family members with confirmed genetic glomerular disease
Cost-effectiveness	Cost	Societal perspective including healthcare system, patients and caregivers	Cost-utility analysis

quality of life and inform the quality-adjusted life years [42–44]. Costs data related to healthcare utilization will be obtained from the patients and from government agencies via TRUST, a national platform that facilitates the sharing of anonymized health-related research and real-world data [45].

All subjects will be given a unique study code upon study enrolment. Subject identifiers will be available only to each site's investigators who have direct patient contact. De-identified data will be collected in the Research Electronic Data Capture (REDCap) web-based software platform that allows secure access and sharing between the multiple institutions involved in the study [46]. This study was approved by the Institutional Ethics Review Committee, Domain Specific Review Boards, National Healthcare Group (2022/00108). Informed consent will be obtained from the subjects and/or parents or legal guardians. This study will be reported according to the Standards for Reporting Implementation Studies (StaRI) checklist [47] (online suppl. Table S10).

Discussion

The KDIGO 2024 clinical practice guideline for the evaluation of CKD emphasized the need for thorough evaluation "using all available information and accessible testing," including genetics [48]. A timely genetic diagnosis can provide diagnostic certainty and an end to a diagnostic journey, avoid unnecessary immunosuppression, indicate assessment or surveillance of extrarenal involvement such as hearing or vision, identify genetic susceptibility in family members, inform family planning according to the mode of Mendelian inheritance, and guide selection of living related kidney donors [6]. While the burden of genetic kidney disease in Singapore is not known, we believe that a significant number of individuals can benefit from genetic testing. The crude incidence rate of ESKD in Singapore was 503 per million population in 2018, as reported Singapore Renal Registry Report 2019 [49]. According to North American and European kidney failure registries [21], 14% were due to

"unknown aetiologies" and 15% of these "unknown aetiologies" were likely due to genetic causes [7, 20, 21]. Hence, the incidence of adult kidney failure due to genetic causes is estimated to be 42 individuals each year. This may be an under-estimation of the burden of genetic kidney disease since CKD stages G2 to G4 occur about 100 times more frequently than ESKD [2]. Although local data on the prevalence of Alport disease are lacking, universal urine screening among school children in South Korea found autosomal Alport disease in 0.6% and X-linked Alport syndrome in 0.02% [50]. Additionally, thin basement membrane nephropathy is the most common cause of persistent glomerular haematuria in children and adults and occurs in at least 1% of the population [51]. Since approximately 40% of thin basement membrane nephropathy is due to autosomal Alport disease affecting *COL4A3* and *COL4A4* [52], we hypothesized that the prevalence of autosomal Alport disease in Singapore to be 0.4% of the residential population in 2020 [53], i.e., 16,000 people. A meta-analysis of nine Asian countries found the incidence of childhood idiopathic nephrotic syndrome to be 7.14 per 100,000 per year (95% CI 4.73–9.54) [54]. Among these, an estimated 10% will be steroid-resistant [55]. Since 19.6% of children with steroid-resistant nephrotic syndrome have a genetic aetiology [31], we estimated that there will be 5 to 9 incident cases of childhood nephrotic syndrome due to monogenic kidney diseases each year. Despite this burden of monogenic kidney disease that may benefit from genetic testing [6, 25, 26], the low awareness among both physicians and patients of possible genetic causes, lack of knowledge and experience with genetic counselling and result interpretation, complicated and non-standardized workflow, and high out-of-pocket expenses may contribute to the low use of genetic testing to diagnose genetic glomerular diseases locally (shown in Fig. 1). As a result, genetic testing for glomerular disease in Singapore is performed late, inconsistently and uncommonly, usually after extensive uninformative evaluation such as autoimmune and virology testing, radiologic imaging, and kidney biopsy, or after prolonged exposure to potent immunosuppressants that do not achieve complete remission [56]. The failure to diagnose or a late diagnosis result in missed opportunities for early intervention which can impact patients' outcome. Landmark randomized controlled trials have established that early initiation of RAS blockade can delay the progression of CKD [11, 57, 58]. Specifically, in male patients with X-linked Alport syndrome, early initiation of RAS blockade can delay ESKD by 12–20 years [11, 57]. More recently, the EARLY PRO-TECT trial suggested that initiation of ramipril at an even earlier stage in the disease course of selected children with Alport disease and isolated microscopic haematuria can delay the occurrence of albuminuria by more than 40% [12]. Additionally, the failure to diagnose genetic kidney conditions can have an impact beyond the affected patient, as there are missed opportunities to diagnose presymptomatic or asymptomatic family members who may be otherwise receive earlier medical attention and interventions that prevent CKD or retard progression to ESKD. Instead, we propose that testing for genetic kidney disease should occur early during the evaluation process. Among children and adults with nephrotic syndrome resistant to steroid treatment, genetic testing should be considered before further augmentation or escalation in immunosuppressive therapy (online suppl. Fig. S5). If a genetic condition is identified, then an invasive kidney biopsy can be avoided. Additionally, unnecessary immunosuppression can be reduced or stopped, although a trial of low dose calcineurin inhibitors may reduce proteinuria in some cases [25]. The patients can have surveillance and early detection and appropriate management of extrarenal manifestations associated with the genetic condition. The appropriate family members can also be screened and diagnosed early and receive appropriate treatment. Children and adults with asymptomatic haematuria and/or albuminuria or CKD without an apparent secondary cause should also receive genetic testing early (online suppl. Fig. S6).

Additionally, the implementation project also aimed to equip nephrologists with the requisite skills to perform both pre- and post-test genetic counselling for genetic testing. This will enable a more seamless patient experience during their kidney disease evaluation and management journey. In healthcare systems where access to clinical geneticists and genetic counsellors is limited, expanding the pool of healthcare providers who can provide counselling facilitates mainstream testing (when genetic testing is arranged by non-genetics specialists) to increase patients' access to genetic testing. The World Health Organization (WHO) recommended enhancing the training of healthcare staff for the effective application of genomic technologies [59]. In our study, an accreditation process was instituted to ensure that the genetic nephrologists will attain the proposed regulatory requirements to provide Clinical Genetic and Genomic Services under the Healthcare Services Act [60], including criteria for (a) qualifications or training and (b) working experience. The multi-disciplinary collaboration between clinicians, geneticists, genetic counsellors, laboratory scientists, and even patient advocates in this project can

also be the springboard to the development of an efficient variant curation process and clinical practice guidelines. Our findings on the utility of genetic testing, factors associated with a genetic kidney disease diagnosis, and cost-effectiveness will inform recommendations for the optimal referral and genetic testing strategy in Singapore. Such guidelines should cover the indications, timing and type of genetic testing (panel testing versus whole exome sequencing) and management of established genetic glomerular kidney diseases. The 2021 Genetics in Chronic Kidney Disease Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference had identified these as priority areas for implementation [29]. More recently, the US National Kidney Foundation (NKF) Working Group developed consensus recommendations for genetic testing for monogenic kidney disorders that were based on inputs from patients and experts from nephrology, clinical and laboratory genetics, kidney pathology, genetic counselling, and ethics [61].

To successfully implement evidence-based genetic testing in routine nephrology practice, senior healthcare management and governmental support will be needed to scale and sustain genetic testing for suspected monogenic glomerular disease. At the healthcare system level, concerted efforts are needed to grow the genetics expertise among clinicians. We suggest the inclusion of a robust genetics curriculum in medical school education, medicine residency, and nephrology fellowship training; reinforcement and updates of the ethical, legal, and social issues related to genomics testing to healthcare staff [59]; and resource allocation to train genetic counsellors and genetic nephrologists [62]. At the national level, this project was aligned with PRECISE's mission for the country and thus received funding for genetic testing. However, government interventions will be required to ensure the long-term sustainability of the business model. Some countries such as Australia and the UK have plans to improve access to genetic testing by creating local clinically accredited laboratories, allowing the use of public funds for genetic tests and mandating insurance coverage for genetic diagnoses [63, 64]. In recent years, Singapore's Ministry of Health and Life Insurance Association signed a moratorium so that from October 2021, life insurers in Singapore were not allowed to use predictive genetic test results to assess or decide the outcome of insurance applications unless there were exceptions, such as life and disability insurance [65]. However, comprehensive national policies that address the ethical, legal, and social implications of genomic testing are currently lacking. These concerns can deter individuals from pursuing genomic testing to confirm a genetic kidney disease diagnosis. Thus, more can be done to reduce potential discrimination based on genetic testing and increase genetic testing uptake. Ground-up initiatives and patient advocacy groups such as the Alport Syndrome Foundation advocate for the dissemination of accurate information and reduce misinformation that can otherwise be a barrier to genetic testing to diagnose genetic glomerular disease and for legislation to improve access to diagnostic tools, insurance, and drug development that affect patients [66].

This study has some limitations. The panel test will not detect deep intronic variants, low level mosaicism in nuclear genes, stretches of mononucleotide repeats, large deletions or duplications, variants within pseudogene regions/duplicated segments. Hence, there will be some genetic kidney conditions who will be tested "negative." The likelihood of such scenarios is unknown but is expected to be low with only a few case reports in the literature [67–69]. Missed genetic diagnoses due to complex inversions, gene conversions, balanced translocations, repeat expansion disorders are less likely since these gene changes tend to result in complex phenotypes that are excluded from this study. While WES can detect variants in novel or undiscovered genes and will be performed for our study participants with CKD of unknown aetiology, its use did not increase the diagnostic yield in patients with steroid-resistant nephrotic syndrome [17], possibly because novel candidate gene changes may require further functional validation to fulfil the pathogenicity criteria [70]. The likelihood of false-negative and positive genetic results will be reduced by re-analysing the raw sequencing data generated by the clinical laboratory at a research laboratory. We will also discuss the results of the clinical panel tests at the genomic board meetings to decide regarding further genetic analysis using nanopore long-read sequencing, such as when WES does not identify pathogenic gene changes despite strong clinical concerns of a genetic aetiology, such as a significant family history with clear patterns of inheritance. While short-read sequencing is typically limited to reads of 150–300 base pairs (bp), nanopore technology routinely generates reads exceeding 10 kilobases (kb). This enables the detection of large structural variations, such as insertions, deletions, and translocations that can be missed by short-read sequencing. Long-read sequencing allows for the spanning of entire genes, facilitating allele phasing, detection of compound heterozygosity, identification of full-length isoforms and splice variants, and the resolution of repetitive regions including tandem repeats and centromeric regions. Additionally, nanopore sequencing permits the direct sequencing of DNA without the need for reverse

transcription or amplification, preserving native molecules and enabling the detection of epigenetic modifications. Hence, while the high-throughput short-read sequencing is the first-line genetic test in our workflow, the lower throughput nanopore sequencing will complement and complete the evaluation. We will also develop a genetic kidney risk prediction model to better identify at-risk individuals for high-yield, cost-conscious testing. Such iterative modifications will further improve the implementation of genetic testing for monogenic kidney diseases.

While the realization of the benefits of precision medicine may take years, this project will inform the optimal referral and genetic testing strategy and guide policy decision-making for the future implementation of precision medicine in our local healthcare system. Globally, the mainstreaming of genetic testing via nephrologists-led genomic testing can improve access, provide knowledge of the monogenic kidney disease to formulate personalized treatment plans, and enable individuals to make informed choices regarding their health and family planning. By facilitating early detection and prevention strategies, mainstreaming genomic testing may reduce long-term healthcare expenses. The myriad benefits outweigh the potential risks when genomic testing is implemented responsibly. Additionally, the sharing of the anonymized clinical genetic test results on publicly accessible international databases will add to the diversity of genomic data where Asian, especially Southeast Asian, populations were under-represented [71]. In conclusion, this study will provide much-needed insights into implementing genetic testing in the clinical management of individuals with suspected and/or confirmed glomerular disease and improve healthcare through precision medicine.

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Statement of Ethics

This study was approved by the Institutional Ethics Review Committee, Domain Specific Review Boards, National Healthcare Group (2022/00108). Written informed consent for study participation and genetic testing will be obtained from the subjects and/or parents or legal guardians.

Conflict of Interest Statement

Cynthia Lim received honoraria from AstraZeneca, Boehringer Ingelheim, and Sebia. Jason Choo has received consulting fees from Novartis, Bayer, AstraZeneca, Boehringer Ingelheim, Pfizer, Nitto Denko ATC, GSK, and Baxter; speaker bureau fees from Abbott, Bayer, AstraZeneca, and Boehringer Ingelheim; participation on Data Safety Monitoring Boards for Novartis; and scientific grant funding from National Medical Research Council Singapore and Nitto Denko ATC and is the President of the Singapore Society of Nephrology and Medical Director of the National Kidney Foundation, Singapore; Gek Cher Chan received research funding from National University Health System and National Medical Research Council Singapore; Hui Zhuan Tan received honoraria from AstraZeneca, Boehringer Ingelheim, and Johnson & Johnson; Hui-Lin Chin has shares in Alamya Health; Jia Liang Kwek has received honoraria from AstraZeneca, Boehringer Ingelheim, Otsuka, Lien Centre for Palliative Care, Singapore Institute of Technology and Nanyang Polytechnic and research funding from the National Kidney Foundation, Singapore; and the remaining authors have no conflicts of interest to declare.

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Author Contributions

Cynthia Lim prepared the first draft, contributed to the revision, and approved the final manuscript; Ru Sin Lim, Jason Choo, Esther Huimin Leow, Gek Cher Chan, Yaochun Zhang, Hui-Lin Chin, Ee Shien Tan, Jeannette Goh, Naline Gandhi, Yong Hong Ng, Mya Than, Indra Ganesan, Siew Le Chong, Celeste Yap, Sing Ming Chao, Breana Cham, Sylvia Kam, Jiin Ying Lim, Irene Mok, Hui Zhuan Tan, Jia Liang Kwek, Tung Lin Lee, Ziyin Wang, Su Mein Goh, Regina Lim, See Cheng Yeo, Boon Wee Teo, and Yi Da contributed to the revision and approved the final manuscript; Jun Li Ng collated data, contributed to the revision, and approved the final manuscript; David Matchar conceptualized the study, contributed to the revision, and approved the final manuscript; Kar Hui Ng conceptualized the study, prepared the first draft, contributed to the revision, and approved the final manuscript. Artificial Intelligence was not used to prepare the manuscript, tables, or figures.

Data Availability Statement

The variants will be shared in ClinVar, National Library of Medicine (https://www.ncbi.nlm.nih.gov/clinvar/) after study completion. The other data obtained in this study will not be publicly available due to privacy and legal restrictions but are available from Kar Hui Ng on request and subject to institutional data-sharing policies.

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