

Genetic counselling and testing for inherited glomerular kidney diseases: A single-centre experience

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Dear Editor,

The World Health Organization (WHO) has projected kidney diseases to become the fifth leading cause of mortality by the year 2040.¹ Singapore is no exception; it currently ranks fifth and second among countries with the highest incident and prevalent kidney failure rates, respectively.² As genetic causes contribute to 10–30% of chronic kidney disease (CKD), early detection can allow prompt institution of disease-modifying treatment, avert an arduous and expensive diagnostic odyssey, avoid potentially futile treatment (e.g. use of immunosuppressants in genetic podocytopathies) and guide surveillance for extra-renal manifestations (e.g. sensorineural hearing loss in Alport syndrome).³ A genetic diagnosis in the proband (i.e. first person identified within a family to receive genetic counselling or testing) can also facilitate cascade testing in family members for earlier diagnosis and interventions.

Historically, patients with suspected monogenic kidney diseases at the Singapore General Hospital (SGH) were referred to the genetics service in a physically distant children's hospital or the adult genetics service within the institution because there was no genetic kidney disease service (GKS) within its adult nephrology unit. Since March 2023, a nephrologist-led GKS was implemented in the nephrology unit as part of a nationwide genomics clinical implementation effort. The implementation team comprised 6 nephrologists with genetics interest (termed "genetic nephrologists") and 2 coordinators. This implementation team was part of the Renal Alliance for Precision Diagnosis in Singapore (RAPIDS), a multidisciplinary

and multi-institutional team of nephrologists, geneticists, genetic counsellors, bioinformaticians, coordinators and laboratory scientists.⁴ Genetic nephrologists received training, supervision and feedback to increase genetic knowledge and skills in the RAPIDS multidisciplinary collaboration.⁴ Patients with suspected monogenic glomerular disease were identified and referred by nephrologists in the department and from other hospitals. As Alport syndrome is the most common monogenic glomerular disease, and has high phenotypic variability and incomplete penetrance,⁶ the authors initiated a collaboration with the Ocular Genetics Service at the Singapore National Eye Centre (SNEC) to identify and refer patients who had classical ophthalmological features of monogenic kidney conditions (e.g. fleck retinopathy in Alport syndrome). Fig. 1 summarises the patient journey. Specific barriers at the centre were established with facilitators, and implementation strategies were adapted in an iterative process that considered feedback from the implementation team, referring nephrologists and patients by using the PRISM process model (Supplementary Table S1).⁵ The authors described the intervention (Supplementary Table S2), implementation study method (Supplementary Table S3–S5) and outcomes of adoption, utility and intent to sustain the service (Supplementary Table S6) according to the Standards for Reporting Implementation Studies (StaRI) checklist (Supplementary Table S7).

In total, 201 eligible patients were referred to the GKS. Twenty-eight of 35 nephrologists (80.0%) and 4 of 20 nephrology trainees (20.0%) from SGH referred 186 patients, while 5 nephrologists from other

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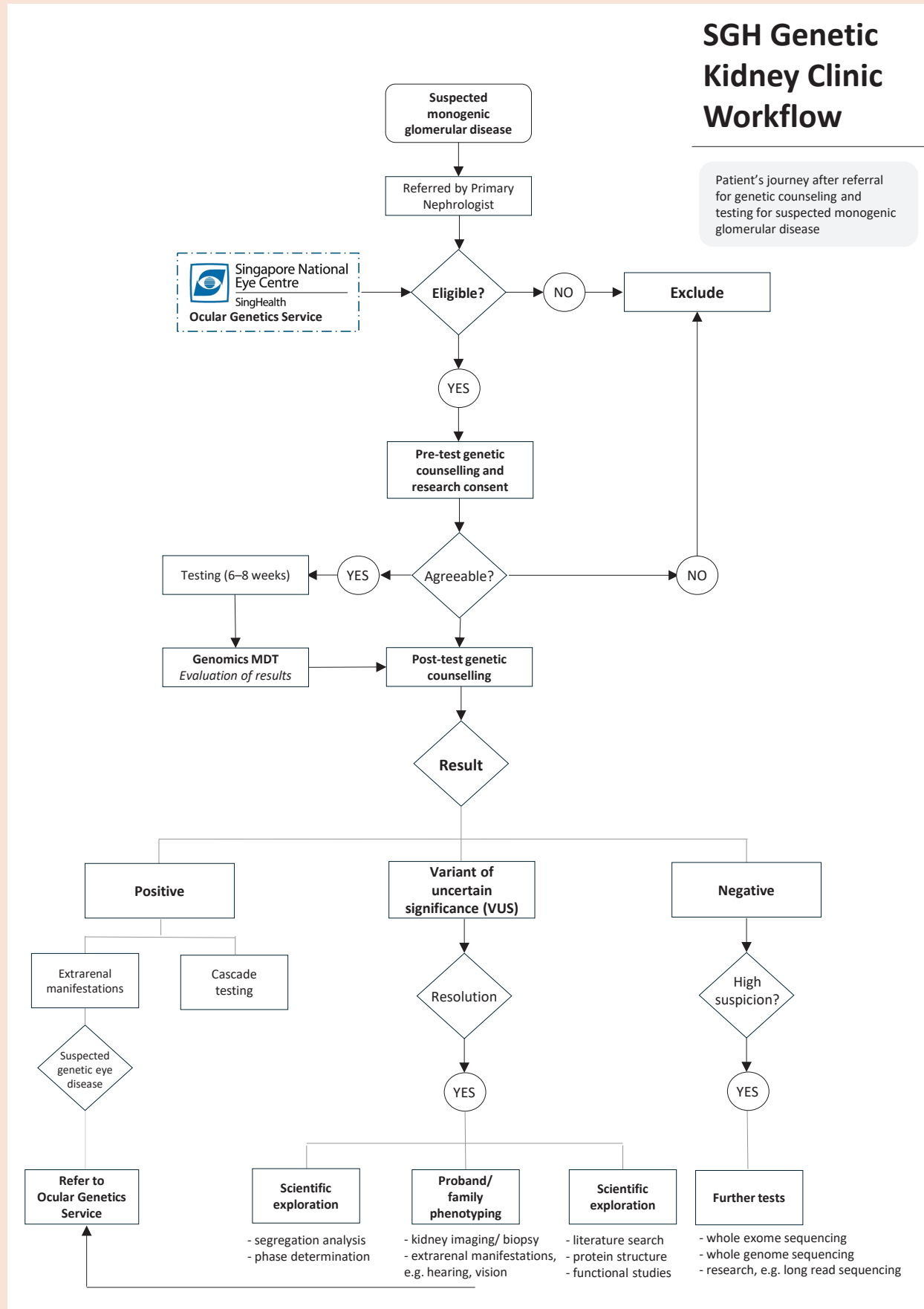
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Fig. 1. Patient journey.



institutions (2 public hospitals and 1 private hospital) referred 15 patients. Among 201 patients referred to the GKS, 109 (54.2%) consented to receive pre-test genetic counselling. Six patients declined testing and 2 withdrew consent after testing. Supplementary Table S8 shows the characteristics of the 101 patients who underwent genetic testing. The median age was 43 years (interquartile range 34.0–55.0) and 82.1% were Chinese. Most had a family history of kidney disease (75.2%). The most common indications for genetic testing were persistent albuminuria (60.4%), isolated haematuria (19.8%) and CKD Stage G3–G5 of unknown aetiology (19.8%).

The clinical genetics lab initially found that 13 patients (12.9%) had pathogenic variants that explained their kidney condition. The monthly genomic board variant curation meetings also determined that 18 (17.8%) patients had variants of uncertain significance (VUS) suspicious for pathogenicity. VUS resolution efforts undertaken included segregation analysis, family phenotyping, research tests such as functional studies and further genetic analysis (e.g. 10 patients [9.9%] had additional whole exome sequencing (WES). Subsequently, 8 additional patients (7.9%) had genetic diagnoses so that a total of 21 patients (20.8%) had genetic diagnoses. The most common genetic diagnosis was Alport syndrome (17/21 patients, or 81.0%). Supplementary Table S9 details the pathogenic variants and VUS of high pathogenic suspicion detected in the study cohort.

The initial diagnostic yield was considerably low, at 12.9%. This may be because only adult patients with glomerular disease phenotypes were recruited, while higher yield is associated with younger age and cystic kidney phenotypes.⁷ This may also reflect the paucity of genomic data from Asian populations.⁸ However, with the VUS resolution efforts carried out by the multidisciplinary RAPIDS collaboration, the authors were able to clinch genetic diagnoses for additional patients, and increased the yield to 20.8%. This has implications on medical management, cascade testing and family planning for the patients. Future analyses from the adult and paediatric centres participating in RAPIDS will provide more information on the clinical utility of genetic testing for monogenic kidney diseases.

Supplementary Table S10 shows that most nephrologists who responded to the survey were aware of the GKS and supported the service. Thus, many patients with suspected monogenic glomerular diseases were referred for genetic testing within the first 21 months of the GKS implementation (Supplementary Fig. S1), especially from the genetic nephrologists (Supplementary Figs. S2 and S3). However, only half of the patients agreed to receive pre-test

genetic counselling. Concerns regarding the adverse impact of a genetic diagnosis on insurability might have reduced the uptake of genetic counselling.⁹ At present, there is no legislation in Singapore to prevent genetic discrimination against employability and insurability. In addition, while genetic testing was fully covered by research funding in the study, the authors foresee that cost will be a barrier to future as there is no government subsidy nor insurance cover for genetic testing for kidney diseases in Singapore.⁹ In June 2025, Singapore's Ministry of Health (MOH) launched the national Familial Hypercholesterolaemia (FH) genetic testing programme where testing will be subsidised for eligible Singapore citizens and Permanent Residents, who can also utilise their MediSave (i.e. Singapore's national medical savings scheme) to offset the cost.¹⁰ MOH also disallowed life insurers from using genetic results from the FH programme for insurance underwriting.¹⁰ Similar healthcare policy and financing changes can encourage uptake of genetic testing for monogenic kidney diseases in the GKS.

In summary, implementing the GKS is feasible. While there continue to be barriers to the uptake of genetic testing, ongoing efforts to address them will improve adoption and access to genetic testing.

Supplementary Materials

Supplementary Table S1. Barriers and facilitators described according to the Practical, Robust Implementation and Sustainability Model (PRISM) domains with corresponding implementation strategies according to the Expert Recommendations for Implementing Change (ERIC) taxonomy.

Supplementary Table S2. Intervention and implementation strategies according to the Template for Intervention Description and Replication (TIDieR).

Supplementary Table S3. Implementation of study methodology.

Supplementary Table S4. Inclusion and exclusion criteria for probands and types of genetic tests.

Supplementary Table S5. List of genes tested for suspected inherited glomerular kidney disease.

Supplementary Table S6. Implementation outcomes of adoption, utility and intent to maintain the service.

Supplementary Table S7. Standards for Reporting Implementation Studies (StaRI) checklist.

Supplementary Table S8. Characteristics of patients who underwent genetic testing.

Supplementary Table S9. Genes detected with pathogenic/likely pathogenic variants and variants of uncertain significance (VUS) of high pathogenic suspicion.

Supplementary Table S10. The Normalization of Complex Interventions – Measure Development (NoMAD) survey responses at 12 months after implementation of the genetic kidney disease service.

Supplementary Figure S1. Number of referrals for genetic counselling and testing per quarter.

Supplementary Figure S2. Box plots of referrals per nephrologist from genetic nephrologist compared with non-genetic nephrologists.

Supplementary Figure S3. Box plots of referrals per nephrologist from genetic versus non-genetic nephrologists per quarter.

Ethics statement

All participants provided written informed consent for participation in the study, which included data collection and genetic testing. The study was conducted in accordance with the Declaration of Helsinki and approved by the National Healthcare Group's Domain Specific Review Board (2022/00108).

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. All authors have no conflicts of interest to declare.

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