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A study protocol for comprehensive evaluation of clinical genomic testing in patients with suspected genetic kidney disease

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A study protocol for comprehensive evaluation of clinical genomic testing in patients with suspected genetic kidney disease

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ABSTRACT

Introduction

Recent advances in genomic technology have allowed better delineation of renal conditions, the identification of new kidney disease genes and subsequent targets for therapy. To date however, the utility of genomic testing in a clinically ascertained, prospectively recruited kidney disease cohort remains unknown. The aim of this study is to explore the clinical utility and cost effectiveness of genomic testing within a national cohort of patients with suspected genetic kidney disease who attend multidisciplinary renal genetics clinics.

Methods and Analysis

This is a prospective observational cohort study performed at 16 centres throughout Australia. Patients will be included if they are referred to one of the multidisciplinary renal genetics clinics and are deemed likely to have a genetic basis to their kidney disease by the multidisciplinary renal genetics team. The expected cohort consists of 360 adult and paediatric patients recruited by December 2018 with ongoing validation cohort who will be recruited until June 2020. The primary outcome will be the proportion of patients who receive a molecular diagnosis via genomic testing (diagnostic rate) compared to usual care. Secondary outcomes will include change in clinical diagnosis following genomic testing, change in clinical management following genomic testing, and the cost-effectiveness of genomic testing compared to usual care.

Ethics and dissemination

The project has received ethics approval from the Melbourne Health Human Research Ethics Committee as part of the Australian Genomics Health Alliance protocol: HREC/16/MH/251. All participants will provide informed consent for data collection and to undergo clinically relevant genetic/genomic testing. The results of this study will be published in peer-reviewed journals and will also be presented at national and international conferences.

STRENGTHS AND LIMITATIONS

- This is a prospectively conducted multicentre national study in which patient data will be captured in the real-world setting
- Patients will be recruited for clinically indicated genomic testing for suspected genetic kidney disorders
- Due to the heterogeneity of genetic testing availability in Australia, it will not be equitable or practical to have a concurrent control arm for comparison
- This study will contribute to the future research and clinical service redesign by establishing the utility of genomic testing in a kidney disease cohort from patient, clinician and health resource perspectives

INTRODUCTION

Genetic Kidney Disease (GKD) accounts for 10% of adults with chronic kidney disease (1), with a monogenic cause being identified in around 20% of those with early onset CKD (2). Recent advances in genomic sequencing have enabled rapid and cost-effective sequencing of large amounts of DNA (3) via massively parallel sequencing, otherwise known as next generation sequencing (NGS). This in turn has led to better delineation of GKD, the identification of new renal disease genes and subsequent targets for therapy(4). Moreover, the clinical implementation of genomic testing has increased the number of patients receiving a timely and accurate genetic diagnosis(5). NGS-based genetic testing has demonstrated a monogenic cause in 20% of patients with early onset chronic kidney disease (CKD), and almost 10% in an unselected cohort of 3000 adults with CKD(2, 6). A genomic diagnosis has many potential benefits including enabling targeted therapies(7-9), preventing the use of inappropriate treatments(10) and reducing the use of invasive diagnostic investigations such as renal biopsy. In addition to concluding a sometimes protracted diagnostic odyssey, a genomic diagnosis may also provide prognostic information, inform targeted surveillance for extra-renal complications and facilitate transplantation and reproductive planning. Despite these potential benefits, there is a paucity of comprehensive evaluations of clinical utility and health economic impact of genomic testing in kidney disease cohorts.

Multifaceted novel approaches are required to address the complexities of successfully implementing genomic technologies into clinical care. Diagnostic renal genetics clinics (RGC) apply a multidisciplinary team approach through collaboration between adult and paediatric nephrologists, clinical geneticists, genetic counsellors and diagnostic laboratory scientists. Whilst RGCs are operational in several countries, there is a lack of reported outcomes of this clinical model of care(5, 11).

The purpose of this study is to comprehensively determine the clinical utility and cost effectiveness of genomic testing in patients with suspected genetic kidney disease seen in a multidisciplinary RGC, and to compare this with their care and clinical diagnosis prior to referral. In addition, we aim to evaluate the value of a multidisciplinary RGC model from a patient perspective.

STUDY AIMS

1. To determine the proportion of patients with suspected GKD who obtain a positive diagnosis following genomic testing compared with their clinical diagnosis prior to testing
2. To determine the clinical impact of genomic testing at three months follow-up in a cohort of patients with suspected GKD and identify subgroups of patients more likely to have a clinical impact following genomic testing
3. To determine whether genomic testing in a cohort of patients with suspected GKD is cost effective compared to usual care, and to identify whether genomic testing is cost effective for specific subgroups
4. To provide access to further research genomics participation for patients with suspected genetic kidney disease who remain undiagnosed following clinical genomic testing
5. To determine patient preferences regarding a service delivery model for a dedicated renal genetics service
6. To determine the value of genomic testing in those with suspected GKD from a patient perspective

METHODS AND ANALYSIS

Study design

This prospective observational study will be undertaken at multiple Australian sites that provide multidisciplinary renal genetics services. There are 16 participating sites throughout Australia (Figure 1). Patients who are referred by their treating physician to these multidisciplinary renal genetics clinics will be recruited over 4 years (Figure 2). Due to the rare nature of GKD, and because genetic testing is performed as part of routine clinical care in most states/centres, it would not be equitable to have a control arm for this study. In order to enable determination of comparative clinical utility, planned diagnostic investigations will be nominated by the recruiting clinicians. In addition, data regarding any changes in management will be collected from the referring nephrologist at three months following the return of genomic testing results.

Recruitment of a baseline cohort of 360 participants occurred between 2017 and 2018 (Figure 3) and a further replication cohort will be recruited between 2019 and 2020. The replication

cohort will have the same data collected but will also include patients with a prior genomic diagnosis. These patients will not participate in evaluation surveys (described below). The cohort of patients is anticipated to be ethnically diverse with a broad spectrum of renal phenotypes, clinical diagnoses and severity of kidney disease. Patients seen in a multidisciplinary renal genetics clinic as part of standard clinical care will be invited to participate in the study if there is consensus of opinion by the clinic team that their kidney disease is likely genetic in origin. Patients with an existing molecularly confirmed genetic diagnosis and those with heterogeneous or complex diseases with a low or unlikely monogenic diagnosis rate by current genomic sequencing (such as isolated congenital abnormalities of the kidney and urinary tract (CAKUT)) (12) will be excluded in the baseline cohort. Patients who undergo only Sanger sequencing are excluded from the study. Patients who attend a RGC but do not undergo genetic testing through the clinic are also excluded from the study. This includes patients who decline clinically-indicated testing. Informed consent, both for clinical genomic testing and participation in the research study will be obtained by the nominated clinical geneticist, nephrologist or genetic counsellor at each site.

Participant Identifiers

All participants will be assigned a unique identifier for the purposes of this study at recruitment. Study data will be collected and managed using REDCap(13) electronic data capture tools hosted at Murdoch Children's Research Institute. Study investigators and other investigators, including the evaluation team, that are not involved in direct patient clinical care will receive all case details including results of genomic testing and demographic details, in a de-identified manner. Only the clinicians and scientists directly involved with patient care will know the identity of the patient DNA samples and be able to re-identify data associated with an individual study unique identifier.

Measures

Once consented to the study, baseline demographic information, clinical information, and detailed phenotypic information will be recorded by clinicians in REDCap. Demographic data including age, gender, ethnicity, and English language status will be captured for all recruited patients. Further demographic information will be captured in patient surveys. Clinical data include suspected clinical diagnosis, comorbidities and types of specialists previously seen. A detailed family history and pedigree will be collected to identify the number of probands and at-risk relatives presenting for assessment. Comprehensive

phenotypic information will also be collected including the presence of extra-renal features, renal impairment, urea and creatinine level, CKD stage, presence and details of hypertension, haematuria, proteinuria and biochemical/haematological abnormalities, results of imaging including ultrasound, CT and MRI, and results of renal biopsy if already performed. Data will also be collected regarding type of genomic test, outcomes of test and time taken to achieve diagnosis. Clinical diagnosis will be recorded as listed in the referral of each patient to a RGC, at the time of triaging for an RGC, prior to genomic testing and at the time of return of genomic testing results. This will enable comparison across multiple time points potentially leading up to a molecular genetic diagnosis.

Evaluation Surveys

Evaluation surveys will be distributed to be completed either online or on paper. Adult and proxy versions are available (parent for child). Participants are asked to complete the first survey at 2-3 weeks after attending the RGC and the second following their receipt of genomic test results. The surveys were developed based on existing surveys in use in the Melbourne Genomics Health Alliance.

The first survey (Table 1) captures additional demographic information and also includes questions about the experience of the consent process and views on the benefits of the multidisciplinary renal genetics clinic. The Genetic Counselling Outcomes Survey (14) is included in survey 1 and 2 to evaluate genetic counselling outcomes of the multidisciplinary clinic. Knowledge questions and a question on the likelihood of the test finding the cause of the kidney disease are included in survey 1 to gauge understanding. The first survey includes closed and open questions exploring hopes and expectations for testing. Willingness-to-pay questions designed specifically for this study are included in both surveys to gauge value. Validated multi-attribute quality of life instruments (SF-12 for adults and parents(15), CHU9D for children(16)) are included in surveys 1 and 2 to assess health related quality of life. The PedsQL(17) family impact module is included in survey 1 and 2 for parents to assess family impact. Both surveys include questions on family planning.

In addition to the measures described above, the second survey includes study-specific questions assessing understanding of the genomic results, impact this will have on the patient and their family and perceived value of genomic testing. The Decision Regret scale(18) is also included in survey 2.

Sequencing

Genomic sequencing will be undertaken and reported in clinically accredited laboratories. It is envisaged that these are likely to include but not be limited to the National Association of Testing Authorities accredited diagnostic laboratories at Children's Hospital at Westmead, Victorian Clinical Genetics Service, Genome.One, SA Pathology and PathWest. The specific clinical test requested for each participant will be selected by the treating clinician/s at the attending renal genetics clinic according to clinical indication. The spectrum of genomic testing that will be employed is anticipated to include targeted exome, whole exome and whole genome sequencing, including the application of virtual gene panels based on patient phenotype. When additional copy number variation assessment and/or variant confirmation is indicated, then multiplex ligation-dependent probe application, chromosomal microarray or Sanger sequencing may be undertaken in addition to genomic sequencing. The cost per test is expected to be AUD$1200 to AUD$2400 depending upon the specific test and diagnostic provider, with individual test costs to be ascertained directly. Further, each participant will have genomic sequencing performed once unless technical or sequence quality issues require re-sequencing to enable clinical reporting. Based on clinical indication, further analysis of disease or phenotype-specific virtual gene panels may occur, with any such sequence re-analysis being recorded.

All participants will provide clinical consent for genomic testing and analysis will be restricted to the assessment of genes related to the condition of interest. Secondary findings unrelated to the presenting condition will not be reported in this study. Consent for participation in the research study will be attained separately, which includes options to consent to accessing the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits scheme (PBS), hospital and emergency data sets and data sharing in addition to study evaluation data collection. In addition, an optional consent will be obtained in order to share data and samples for use in ethically approved research outside of the study.

Health economic evaluation

A model-based economic evaluation will be conducted to assess the relative cost-effectiveness of implementing NGS in the diagnostic trajectory of patients with suspected GKD compared with usual care. A decision analytic model will be developed to estimate the expected costs and outcomes associated with diagnostic investigations and initial clinical

management over a time horizon of one year based on the outcomes of cost per additional diagnosis, cost per quality-adjusted life-year (QALY), and net monetary benefit. The analyses will be conducted from an Australian health care payer perspective. Depending on the impact of NGS testing on clinical management and the availability of published literature on long-term health outcomes following changes in management, long-term costs and effectiveness will also be modelled in the analysis. Deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the findings to plausible variations in key assumptions and analytical methods used, and to consider the broader issue of generalisability of the study's results. Cost-effectiveness acceptability curves will be generated to reflect decision uncertainty.

Study outcomes

The primary outcome will be the proportion of patients who receive a molecular diagnosis via genomic testing (diagnostic rate). Secondary outcomes will be change in clinical diagnosis following genomic testing, change in clinical management following genomic testing and cost-effectiveness of genomic testing compared to non-genomic diagnostic investigations. Survey outcomes will include the proportion of patients who preferred to be seen by the multidisciplinary team compared to those who prefer to be seen in individual clinics. In addition, the GCOS will be compared before and after testing and between those with a positive/negative genomic testing result.

Data analysis

Results on diagnostic and clinical utility will be expressed as frequencies and percentages for categorical variables and be compared using the chi-square test. Continuous non-normally distributed variables will be expressed as median (IQR) and compared using the Mann-Whitney test. Normally distributed continuous variables will be expressed as mean±SD and compared using the Student's t-test. Multivariable logistic regression will be performed to determine which variables may predict a positive genomic diagnosis, such as age of onset of CKD, aetiology of CKD, family history or presence of haematuria/proteinuria/cysts. This will help to develop professional guidelines regarding genomic testing in suspected GKD. In addition, the diagnostic rates between different genomic testing modalities will also be compared. The target sample size is 500 patients across both baseline and replication cohorts.

DISCUSSION

In this protocol, we describe the rationale and methods for a prospective observational study of a national cohort of patients with suspected genetic renal disease that are referred to multidisciplinary renal genetics clinics throughout Australia. The strengths of this study are the multicentre design, prospective data collection and a real-world clinical setting. The absence of a control arm is a limitation of this study however it was not feasible to randomize patients in this study for two reasons. Firstly due to the rare nature of kidney disease, and secondly given that genomic testing is clinically indicated and performed routinely in some participating states/centres, it would be unethical to deny genomic testing to some patients. Further those patients not receiving a genomic test after clinical assessment are likely to do so in a non-random fashion thus precluding their analysis as a true control group.

Genomic technologies have transformed the concept of precision medicine in many specialities, however the potential benefits in kidney medicine are yet to be demonstrated. Until now, the diagnostic utility of genomic testing has been assessed in a small number of patients or in a research context (19, 20). In addition, while studies which perform genomic sequencing in larger cohorts (6, 21) are emerging, detailed phenotypic information is not being collected and there remains a paucity of data on clinical outcomes. Importantly, these large-scale studies include patients with all types of chronic kidney disease and are thus powered to understand prevalence of GKD rather than to determine utility and yield in a cohort in which the clinician suspects genetic disease(6). Data on genomic sequencing in a real-world clinical environment at a national scale for a targeted population of patients with suspected GKD are lacking and the health economic impacts of genomic testing are not well understood or established(22). We believe that collecting such detailed information from a prospectively ascertained cohort will enable us to determine the diagnostic yield and comprehensive clinical utility, to inform future practice recommendations.

Results from this study will provide the opportunity to determine the clinical utility of genomic testing in a large cohort of patients, and further enable analysis of which subgroups of patients may benefit most. By assessing the clinical utility, cost effectiveness and implementation aspects of genomic testing in patients with kidney disease, the results of this study will inform patients, treating physicians and health services and define priorities for future trials. Collectively, this is anticipated to have significant impacts upon clinical practice and health service redesign.

FUNDING STATEMENT

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ETHICS AND DISSEMINATION

Ethics

Ethics approval for this project has been obtained by Australian Genomics Health Alliance as part of the research study Australian Genomics Health Alliance: Preparing Australia for Genomic Medicine and issued by Melbourne Health HREC/16/MH/251. Governance site specific approval for the project has been obtained for each of the participating clinic sites. All participants will provide informed consent for data collection and to undergo clinically relevant genetic/genomic testing.

Dissemination Plan

The main findings of this study will be published in peer-reviewed journals and will also be presented at national and international conferences. We will also issue reports of results of the study to the Australian Government, State/Territory Governments and health organizations in order to inform future policy and guidelines. This study will also contribute to the training and development of post-doctoral students.

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TABLES

Table 1. Summary of survey measures

Measure	Description	S1	S2
Demographics	Age, gender, marital status, education, income, number of dependents in household, postcode, private health insurance status.	X	
Patient reported outcomes measures	CHU9D[ref] and PEDS family impact[ref] for paediatric surveys OR SF-12 [ref] for adult surveys	X	X
Experience of the multidisciplinary clinic	Three study specific questions exploring advantages and disadvantages of multidisciplinary renal genetics clinics	X	X
Genetic counselling	24-item scale measuring outcomes of genetic counselling GCOS-24[ref]	X	X
Family planning	Four study specific questions addressing plans for another child, estimated recurrence of the kidney condition, concern about recurrence, interest in reproductive technologies (parent surveys only)	X	

Understanding	In survey 1, 8 study specific questions address participant understanding of: types of potential results (4 questions), potential familial implications (1 question), ways in which the data can be used (2) questions); number of genes examined (1 question). In survey 2, 2 study specific questions used to measure recall and understanding of result.	X	X
Willingness to pay (value)	Study specific questions included to establish a quantitative reference for the value placed on testing	X	X
Information provision	Study specific questions to assess participant perception about the way in which information (3 items – S1) and results (3 items – S2) were provided	X	X
Hopes/ Expectation	Eight study specific questions exploring participants reasons for agreeing to the test, rated on a 5 point scale as extremely unimportant to extremely important	X	
Likelihood	One study specific question to determine participant's perception of the likelihood testing will find the cause of the condition .	X	
Decision regret	5 item scale measuring distress or remorse after a (health care) decision [ref O'Connor]		X
Value of the test	Eleven study specific questions exploring the value to participants of having had the test rated on a 4 point scale as not valuable to extremely valuable or not applicable		X

Impact of the test	Two study specific questions asking about the impact of the test on family planning		X

FIGURES

Figure 1. Participating Renal Genetics Clinics

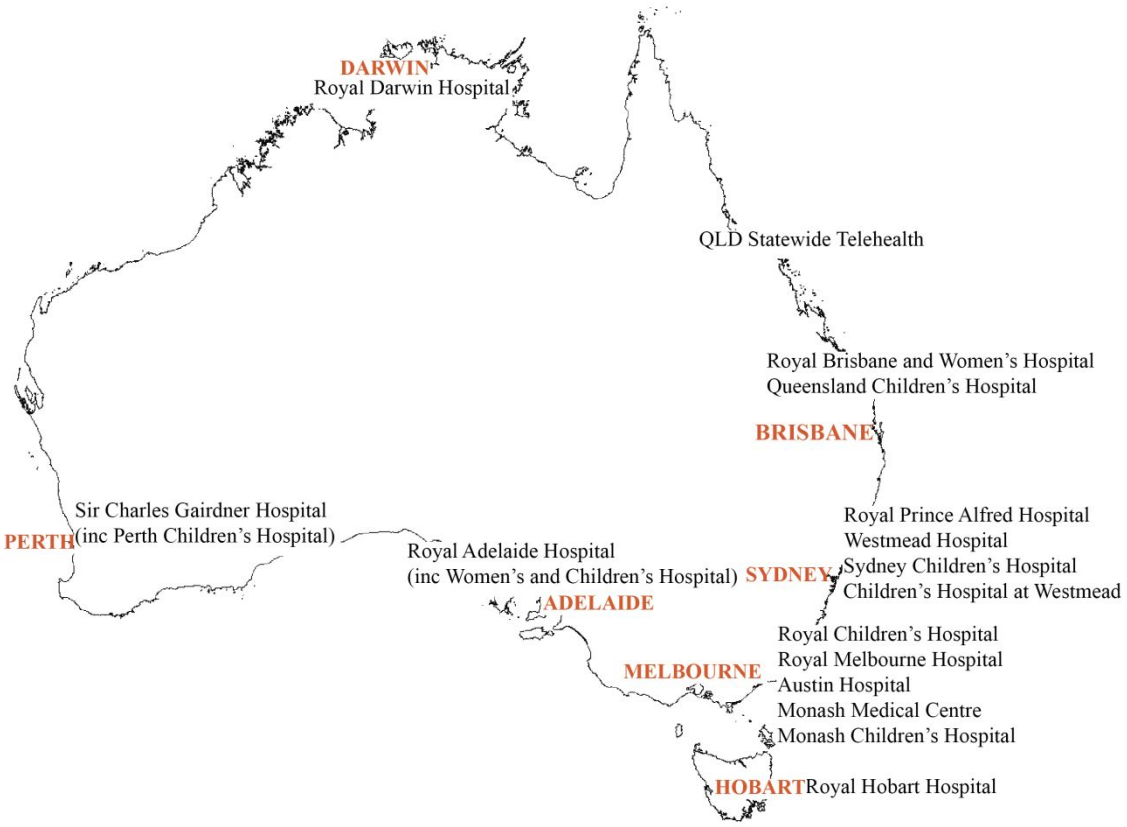
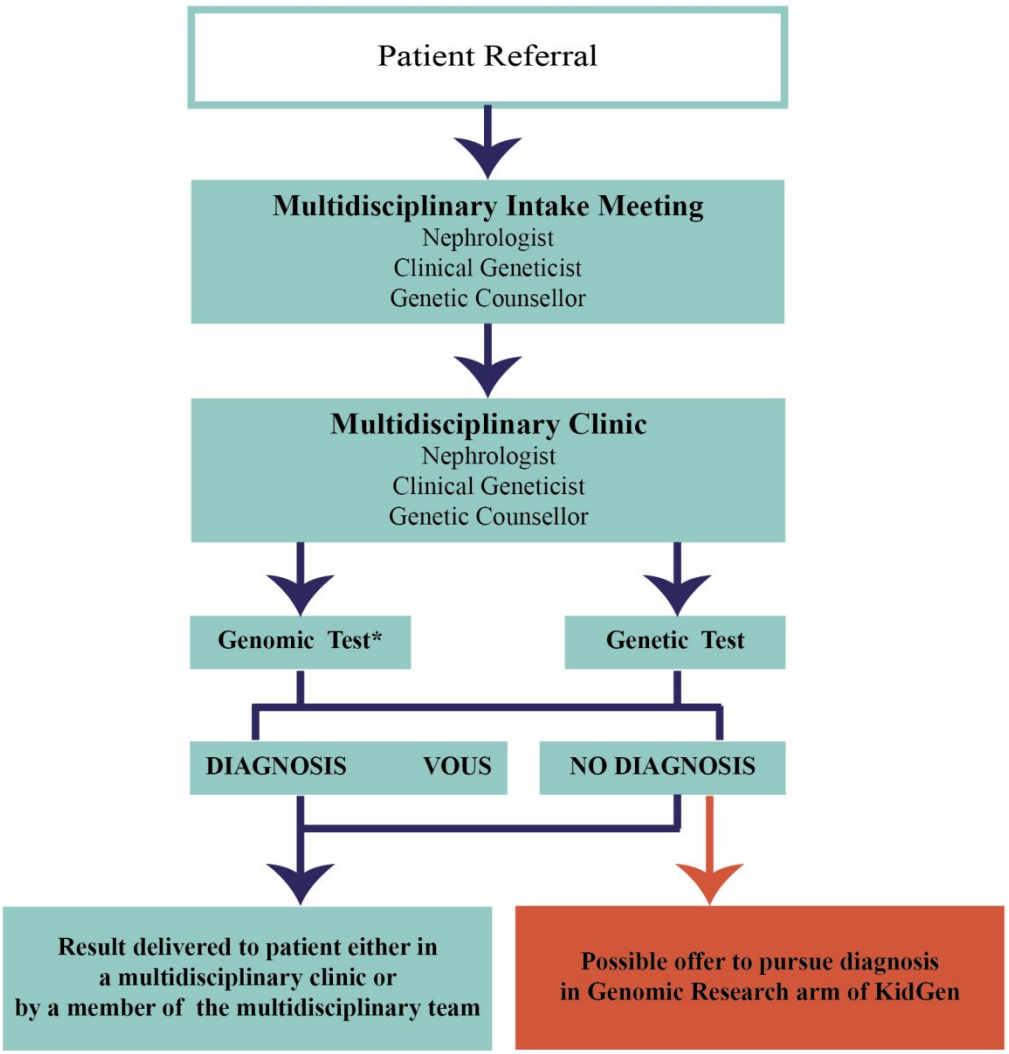
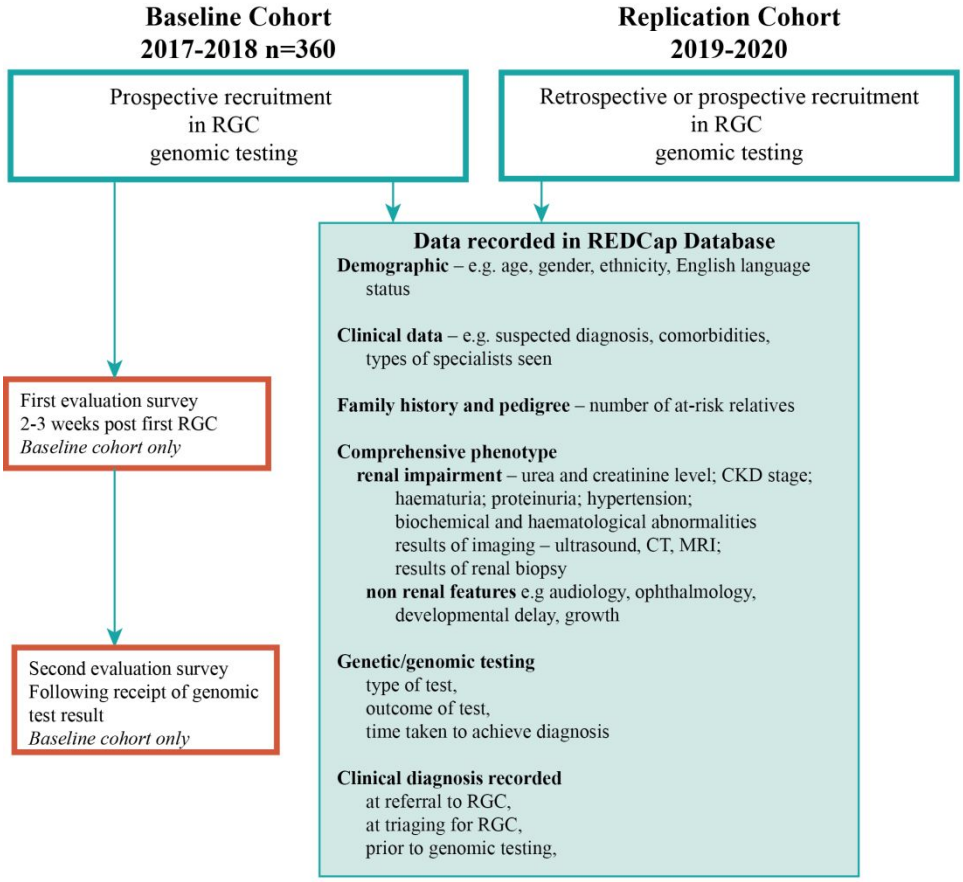


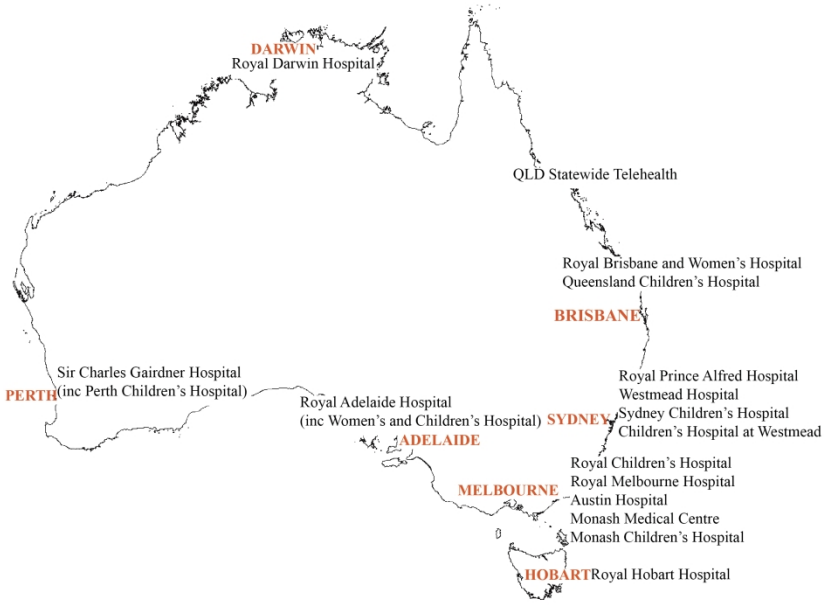
Figure 2. Patient flow within a KidGen Renal Genetics Clinic



*** Prior to reporting results may be interpreted at a MDT by clinicians and laboratory scientists.**

Figure 3. Recruitment workflow within the KidGen Renal Genetics Clinic network





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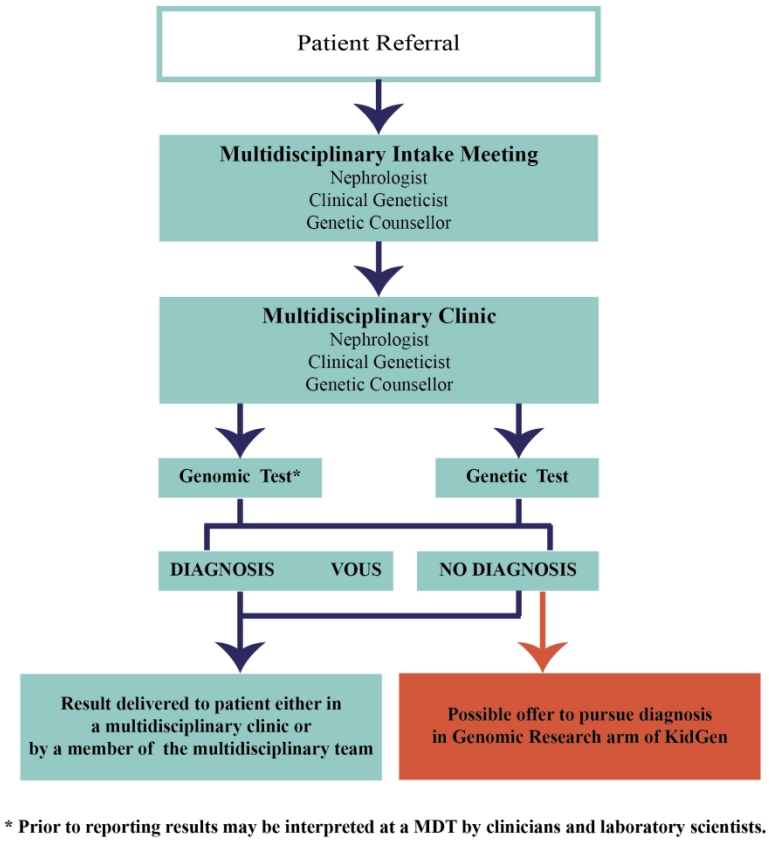

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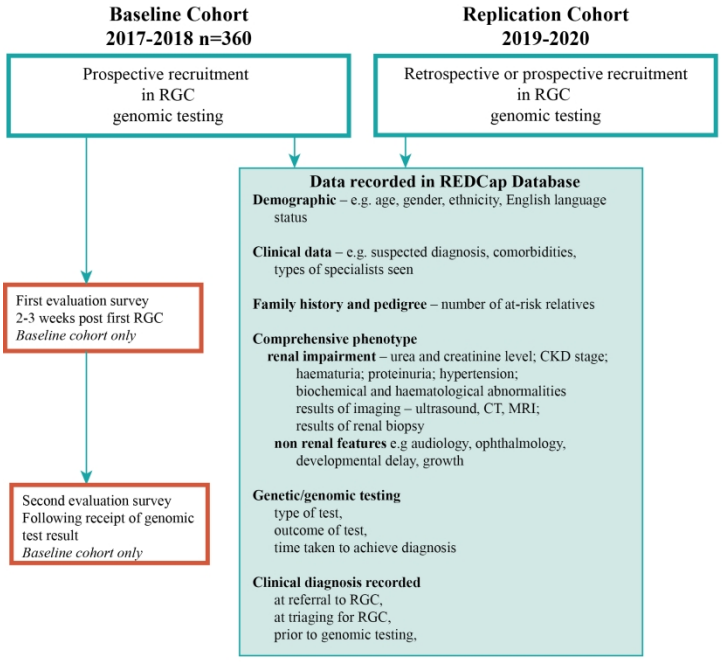

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A study protocol for comprehensive evaluation of clinical genomic testing in patients with suspected genetic kidney disease

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ABSTRACT

Introduction

Recent advances in genomic technology have allowed better delineation of renal conditions, the identification of new kidney disease genes and subsequent targets for therapy. To date however, the utility of genomic testing in a clinically ascertained, prospectively recruited kidney disease cohort remains unknown. The aim of this study is to explore the clinical utility and cost effectiveness of genomic testing within a national cohort of patients with suspected genetic kidney disease who attend multidisciplinary renal genetics clinics.

Methods and Analysis

This is a prospective observational cohort study performed at 16 centres throughout Australia. Patients will be included if they are referred to one of the multidisciplinary renal genetics clinics and are deemed likely to have a genetic basis to their kidney disease by the multidisciplinary renal genetics team. The expected cohort consists of 360 adult and paediatric patients recruited by December 2018 with ongoing validation cohort of 140 patients who will be recruited until June 2020. The primary outcome will be the proportion of patients who receive a molecular diagnosis via genomic testing (diagnostic rate) compared to usual care. Secondary outcomes will include change in clinical diagnosis following genomic testing, change in clinical management following genomic testing, and the cost-effectiveness of genomic testing compared to usual care.

Ethics and dissemination

The project has received ethics approval from the Melbourne Health Human Research Ethics Committee as part of the Australian Genomics Health Alliance protocol: HREC/16/MH/251. All participants will provide informed consent for data collection and to undergo clinically relevant genetic/genomic testing. The results of this study will be published in peer-reviewed journals and will also be presented at national and international conferences.

STRENGTHS AND LIMITATIONS

- This is a prospectively conducted multicentre national study in which patient data will be captured in the real-world setting
- Patients will be recruited for clinically indicated genomic testing for suspected genetic kidney disorders, which may allow better generalizability of results
- Genomic testing is clinically indicated and performed routinely in some participating states/centres in Australia, and therefore it would be unethical to have a control arm for comparison as this would deny some patients of testing.
- This study will contribute to the future research and clinical service redesign by establishing the utility of genomic testing in a kidney disease cohort from patient, clinician and health resource perspectives

INTRODUCTION

Genetic Kidney Disease (GKD) accounts for 10% of adults with chronic kidney disease (1), with a monogenic cause being identified in around 20% of those with early onset chronic kidney disease (CKD) (2). Recent advances in genomic sequencing have enabled rapid and cost-effective sequencing of large amounts of DNA (3) via massively parallel sequencing, otherwise known as next generation sequencing (NGS). This in turn has led to better delineation of GKD, the identification of new renal disease genes and subsequent targets for therapy(4). Moreover, the clinical implementation of genomic testing has increased the number of patients receiving a timely and accurate genetic diagnosis(5). NGS-based genetic testing has demonstrated a monogenic cause in 20% of patients with early onset CKD, and almost 10% in an unselected cohort of 3000 adults with CKD(2, 6). A genomic diagnosis has many potential benefits including enabling targeted therapies(7-9), preventing the use of inappropriate treatments(10) and reducing the use of invasive diagnostic investigations such as renal biopsy. In addition to concluding a sometimes protracted diagnostic odyssey, a genomic diagnosis may also provide prognostic information, inform targeted surveillance for extra-renal complications and facilitate transplantation and reproductive planning. Despite these potential benefits, there is a paucity of comprehensive evaluations of clinical utility and health economic impact of genomic testing in kidney disease cohorts.

Multifaceted novel approaches are required to address the complexities of successfully implementing genomic technologies into clinical care. Diagnostic renal genetics clinics (RGC) apply a multidisciplinary team approach through collaboration between adult and paediatric nephrologists, clinical geneticists, genetic counsellors and diagnostic laboratory scientists. Whilst RGCs are operational in several countries, there is a lack of reported outcomes of this clinical model of care(5, 11).

The purpose of this study is to comprehensively determine the clinical utility and cost effectiveness of genomic testing in patients with suspected genetic kidney disease seen in a multidisciplinary RGC, and to compare this with their care and clinical diagnosis prior to referral. In addition, we aim to evaluate the value of a multidisciplinary RGC model from a patient perspective.

STUDY AIMS

1. To determine the proportion of patients with suspected GKD who obtain a positive diagnosis following genomic testing compared with their clinical diagnosis prior to testing
2. To determine the clinical impact of genomic testing after three months follow-up in a cohort of patients with suspected GKD and identify subgroups of patients more likely to have a clinical impact following genomic testing
3. To determine whether genomic testing in a cohort of patients with suspected GKD is cost effective compared to usual care, and to identify whether genomic testing is cost effective for specific subgroups
4. To provide access to further research genomics participation for patients with suspected genetic kidney disease who remain undiagnosed following clinical genomic testing
5. To determine patient preferences regarding a service delivery model for a dedicated renal genetics service
6. To determine the value of genomic testing in those with suspected GKD from a patient perspective

METHODS AND ANALYSIS

Study design

This prospective observational study will be undertaken at multiple Australian sites that provide multidisciplinary renal genetics services. There are 16 participating sites throughout Australia (Figure 1). Patients who are referred by their treating physician to these multidisciplinary renal genetics clinics will be recruited over 4 years (Figure 2). Patients may be referred for testing for a variety of reasons. These include confirmation of a suspected diagnosis, exclusion of differential diagnoses, clarification of mode of inheritance, and for obtaining the diagnosis where one is previously unknown. For this reason, it was not possible to include a control arm, as this would prevent some patients from undergoing their usual clinical care. . In order to enable determination of comparative clinical utility, planned diagnostic investigations will be nominated by the recruiting clinicians. In addition, data regarding any changes in management will be collected from the referring nephrologist at three months following the return of genomic testing results.

Recruitment of a baseline cohort of 360 participants occurred between 2017 and 2018 (Figure 3) and a further mutually exclusive replication cohort will be recruited between 2019 and 2020. The replication cohort will have the same data collected but will also include patients with a prior genomic diagnosis. These patients will not participate in evaluation surveys (described below) but will be evaluated against all other outcome measures in order to further identify patient, disease and sub-cohort clinical outcomes enabled by larger scale and longer time span observation. The cohort of patients is anticipated to be ethnically diverse with a broad spectrum of renal phenotypes, clinical diagnoses and severity of kidney disease. Patients seen in a multidisciplinary renal genetics clinic as part of standard clinical care will be invited to participate in the study if there is consensus of opinion by the clinic team that their kidney disease is likely genetic in origin. Patients without a clear clinical indication for prospective clinical genomic testing will be excluded in the baseline cohort, including an existing molecularly confirmed genetic diagnosis and those with heterogeneous or complex diseases with a low or unlikely monogenic diagnosis rate by current genomic sequencing (such as isolated congenital abnormalities of the kidney and urinary tract (CAKUT)) (12). Patients who undergo only Sanger sequencing are excluded from the study as this would not represent a genomic approach to clinical investigation and may instead represent clarification or segregation of an already identified familial variant. Patients who attend a RGC but do not undergo genetic testing through the clinic are also excluded from the study. This includes patients who decline clinically-indicated testing. Informed consent, both for clinical genomic testing and participation in the research study will be obtained by the nominated clinical geneticist, nephrologist or genetic counsellor at each site.

Participant Identifiers

All participants will be assigned a unique identifier for the purposes of this study at recruitment. Study data will be collected and managed using REDCap(13) electronic data capture tools hosted at Murdoch Children's Research Institute. Access to patient identifying details is restricted to clinicians providing care and to those who need contact details for evaluation purposes..

Measures

Once consented to the study, baseline demographic information, clinical information, and detailed phenotypic information will be recorded by clinicians in REDCap. Demographic data including age, gender, ethnicity, and English language status will be captured for all

recruited patients. Further demographic information will be captured in patient surveys. Clinical data include suspected clinical diagnosis, comorbidities and types of specialists previously seen. A detailed family history and pedigree will be collected to identify the number of probands and at-risk relatives presenting for assessment. Comprehensive phenotypic information will also be collected including the presence of extra-renal features, renal impairment, urea and creatinine level, CKD stage, presence and details of hypertension, haematuria, proteinuria and biochemical/haematological abnormalities, results of imaging including ultrasound, CT and MRI, and results of renal biopsy if already performed. Data will also be collected regarding type of genomic test, outcomes of test and time taken to achieve diagnosis. Clinical diagnosis will be recorded as listed in the referral of each patient to a RGC, at the time of triaging for an RGC, prior to genomic testing and at the time of return of genomic testing results. This will enable comparison across multiple time points potentially leading up to a molecular genetic diagnosis.

Patient and Public Involvement

The project was reviewed, edited and revised after in depth engagement with the Australian Genomic Health Alliance (AGHA) Consumer and Community Advisory group. Previous informal engagement with relevant representative local Australian kidney health patient organisations, including Polycystic Kidney Disease (PKD) Australia and Kidney Health Australia (KHA) also occurred. Results from this study will be published and be accessible to all patients on request.

Evaluation Surveys

Evaluation surveys will be distributed to be completed either online or on paper. Adult and proxy versions are available (parent for child). Participants are asked to complete the first survey at 2-3 weeks after attending the RGC at which they are offered and consent to testing, and the second following their receipt of genomic test results. The surveys were developed based on existing surveys in use in the Melbourne Genomics Health Alliance.

The first survey (Table 1) captures additional demographic information and also includes questions about the experience of the consent process and views on the benefits of the multidisciplinary renal genetics clinic. The Genetic Counselling Outcomes Survey (14) is included in survey 1 and 2 to evaluate genetic counselling outcomes of the multidisciplinary clinic. Knowledge questions and a question on the likelihood of the test finding the cause of

the kidney disease are included in survey 1 to gauge understanding. The first survey includes closed and open questions exploring hopes and expectations for testing. Willingness-to-pay questions designed specifically for this study are included in both surveys to gauge value. Validated multi-attribute quality of life instruments (SF-12 for adults and parents(15), CHU9D for children(16)) are included in surveys 1 and 2 to assess health related quality of life. The PedsQL(17) family impact module is included in survey 1 and 2 for parents to assess family impact. Both surveys include questions on family planning.

In addition to the measures described above, the second survey includes study-specific questions assessing understanding of the genomic results, impact this will have on the patient and their family and perceived value of genomic testing. The Decision Regret scale(18) is also included in survey 2.

Sequencing

Genomic sequencing will be undertaken and reported in clinically accredited laboratories. It is envisaged that these are likely to include but not be limited to the National Association of Testing Authorities accredited diagnostic laboratories at Children's Hospital at Westmead, Victorian Clinical Genetics Service, Genome.One, SA Pathology and PathWest. The specific clinical test requested for each participant will be selected by the treating clinician/s at the attending renal genetics clinic according to clinical indication. The spectrum of genomic testing that will be employed is anticipated to include targeted exome, whole exome and whole genome sequencing, including the application of virtual gene panels based on patient phenotype. When additional copy number variation assessment and/or variant confirmation is indicated, then multiplex ligation-dependent probe application, chromosomal microarray or Sanger sequencing may be undertaken in addition to genomic sequencing. The cost per test is expected to be AUD$1200 to AUD$2400 depending upon the specific test and diagnostic provider, with individual test costs to be ascertained directly. Further, each participant will have genomic sequencing performed once unless technical or sequence quality issues require re-sequencing to enable clinical reporting. Based on clinical indication, further analysis of disease or phenotype-specific virtual gene panels may occur, with any such sequence re-analysis being recorded.

All participants will provide clinical consent for genomic testing and analysis will be restricted to the assessment of genes related to the condition of interest. In this instance,

analysis will be limited to a predefined gene list of 360 genes related to nephropathy((19). Secondary findings unrelated to the presenting condition will not be reported in this study. Consent for participation in the research study will be attained separately, which includes options to consent to accessing the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits scheme (PBS), hospital and emergency data sets and data sharing in addition to study evaluation data collection. The MBS and PBS are listings of all medical services and medicines subsidised by the Australian government, respectively. In addition, an optional consent will be obtained in order to share data and samples for use in ethically approved research outside of the study.

Health economic evaluation

An economic evaluation will be conducted to assess the incremental cost-effectiveness of NGS compared with usual care in patients with suspected kidney disease. A microsimulation model of disease progression will be developed to estimate the lifetime costs and outcomes associated with usual care and NGS. The analysis will be conducted from an Australian healthcare system perspective in line with recommended practices(20-22), and based on the outcomes of cost per additional diagnosis, cost per quality-adjusted life-year (QALY), and net monetary benefit.

Hospital patient-level resource use and cost data will be acquired for each study participant to cost the diagnostic and short-term medical management in the NGS arm. The additional per-patient diagnostic investigations that could potentially be incurred in the usual care pathway will be identified based on a review of national and international guidelines on the diagnosis of suspected kidney disease and clinical expertise from each of the 16 participating centres across Australia. The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) will be used to undertake a survival analysis of CKD patients. Parametric and non-parametric methods will be used to estimate transition probabilities for key endpoints including; all-cause mortality, initiation of dialysis and transplantation. This will allow for the development of evidence-based transition probabilities while controlling for patient-specific factors such as age, gender, treatment pathways and disease status. Unit costs associated with these endpoints and related treatments will be drawn from established national sources (23-25). A microsimulation will be used to capture the costs and benefits associated with earlier renal replacement therapy and delayed dialysis from the introduction of NGS. To accurately

model the implications, registry-derived transition probabilities will be adjusted, on the basis of published evidence (26), to reflect the impact of new treatment pathways following NGS.

For the cost-utility analysis, participants responses to the SF-12 measure will initially be used to generate utilities at baseline prior to NGS and following the return of NGS findings. A review of the literature will be undertaken to complement these estimates with evidence from secondary sources, such as utilities for chronic kidney disease (27) and renal transplantation (28). The cost-benefit analysis will rely on a contingent valuation exercise that was undertaken to understand the personal value of NGS to the families. Deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the findings to plausible variations in key assumptions around costs, outcomes and transition probabilities, and to consider the broader issue of generalisability of the study's results. Cost-effectiveness acceptability curves will be generated to reflect decision uncertainty.

Study outcomes

The primary outcome will be the proportion of patients who receive a molecular diagnosis via genomic testing (diagnostic rate). Secondary outcomes will be change in clinical diagnosis following genomic testing, change in clinical management following genomic testing and cost-effectiveness of genomic testing compared to non-genomic diagnostic investigations. Survey outcomes will include the proportion of patients who preferred to be seen by the multidisciplinary team compared to those who prefer to be seen in individual clinics. In addition, the GCOS will be compared before and after testing and between those with a positive/negative genomic testing result.

Data analysis

Results on diagnostic utility and clinical implications will be expressed as frequencies and percentages for categorical variables and be compared using the chi-square test. Continuous non-normally distributed variables will be expressed as median (IQR) and compared using the Mann-Whitney test. Normally distributed continuous variables will be expressed as mean±SD and compared using the Student's t-test. Multivariable logistic regression will be performed to determine which variables may predict a positive genomic diagnosis, such as age of onset of CKD, aetiology of CKD, family history or presence of haematuria/proteinuria/cysts. This will help to develop professional guidelines regarding genomic testing in suspected GKD. In addition, the diagnostic rates between different

genomic testing modalities will also be compared. The target sample size is 500 patients across both baseline and replication cohorts.

DISCUSSION

In this protocol, we describe the rationale and methods for a prospective observational study of a national cohort of patients with suspected genetic renal disease that are referred to multidisciplinary renal genetics clinics throughout Australia. The strengths of this study are the multicentre design, prospective data collection and a real-world clinical setting. The absence of a control arm is a limitation of this study however it was not feasible to randomize patients in this study for two reasons.. Firstly, genomic testing is clinically indicated and performed routinely in most participating states/centres, and it would therefore be unethical to deny genomic testing to some patients where it is clinically indicated and current standard of care. Secondly, feedback from patient representatives, the community and genetic counsellors highlighted that it was unacceptable to deny testing to some patients for the purpose of a control arm.. Further those patients not receiving a genomic test after clinical assessment are likely to do so in a non-random fashion thus precluding their analysis as a true control group.

Genomic technologies have transformed the concept of precision medicine in many specialities, however the potential benefits in kidney medicine are yet to be demonstrated. Until now, the diagnostic utility of genomic testing has been assessed in a small number of patients or in a research context (29, 30). In addition, while studies which perform genomic sequencing in larger cohorts (6, 31) are emerging, detailed phenotypic information is not being collected and there remains a paucity of data on clinical outcomes. Importantly, these large-scale studies include patients with all types of chronic kidney disease and are thus powered to understand prevalence of GKD rather than to determine utility and yield in a cohort in which the clinician suspects genetic disease(6). Data on genomic sequencing in a real-world clinical environment at a national scale for a targeted population of patients with suspected GKD are lacking and the health economic impacts of genomic testing are not well understood or established(32). We believe that collecting such detailed information from a prospectively ascertained cohort will enable us to determine the diagnostic yield and comprehensive clinical implications, to inform future practice recommendations.

To our knowledge, this is the first time that a structured, objective and minimally bias approach is undertaken to measure the outcomes of genomic testing in kidney disease. Results from this study will provide the opportunity to determine the clinical implicationsof genomic testing in a large cohort of patients, and further enable analysis of which subgroups of patients may benefit most. Furthermore, due to the pragmatic nature of this study, these results more likely to be replicated in a clinical environment. By assessing the utility, cost effectiveness and implementation aspects of genomic testing in patients with kidney disease, the results of this study will inform patients, treating physicians and health services and define priorities for future trials. Collectively, this is anticipated to have significant impacts upon clinical practice and health service redesign.

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ETHICS AND DISSEMINATION

Ethics

Ethics approval for this project has been obtained by Australian Genomics Health Alliance as part of the research study Australian Genomics Health Alliance: Preparing Australia for Genomic Medicine and issued by Melbourne Health HREC/16/MH/251. Governance site specific approval for the project has been obtained for each of the participating clinic sites. All participants will provide informed consent for data collection and to undergo clinically relevant genetic/genomic testing.

Dissemination Plan

The main findings of this study will be published in peer-reviewed journals and will also be presented at national and international conferences. We will also issue reports of results of the study to the Australian Government, State/Territory Governments and health organizations in order to inform future policy and guidelines. This study will also contribute to the training and development of post-doctoral students.

CONTRIBUTOR SHIP STATEMENT

KJ contributed to the design of the study and drafted the manuscript. CQ and AJM (Andrew John Mallett) conceived the project and obtained funding for the clinical flagships and research study, made substantial contributions to the design of the study and were major contributors in drafting the manuscript. LW and ZS undertook significant project design and data management elements, provided specific design elements around outcome analysis and were major contributors in drafting the manuscript. IG, YW and MM provided specific design elements around health economic analysis. SB provided specific implementation design elements. AM (Amali Mallawaarachchi), HM, RF, AC, MS, MJ, PK and CP contributed to regionalised study design and implementation. All authors contributed to the drafting of the manuscript, read and approved the final manuscript. In addition to the authors listed, the broader KidGen Collaborative scientific, clinical and diagnostic membership had input into this protocol.

COMPETING INTERESTS: No, there are no competing interests for any author

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TABLES

Table 1. Summary of survey measures

Measure	Description	S1	S2
Demographics	Age, gender, marital status, education, income, number of dependents in household, postcode, private health insurance status.	X	
Patient reported outcomes measures	CHU9D[ref] and PEDS family impact[ref] for paediatric surveys OR SF-12 [ref] for adult surveys	X	X
Experience of the multidisciplinary clinic	Three study specific questions exploring advantages and disadvantages of multidisciplinary renal genetics clinics	X	X
Genetic counselling	24-item scale measuring outcomes of genetic counselling GCOS-24[ref]	X	X
Family planning	Four study specific questions addressing plans for another child, estimated recurrence of the kidney condition, concern about recurrence, interest in reproductive technologies (parent surveys only)	X	

Understanding	In survey 1, 8 study specific questions address participant understanding of: types of potential results (4 questions), potential familial implications (1 question), ways in which the data can be used (2) questions); number of genes examined (1 question). In survey 2, 2 study specific questions used to measure recall and understanding of result.	X	X
Willingness to pay (value)	Study specific questions included to establish a quantitative reference for the value placed on testing	X	X
Information provision	Study specific questions to assess participant perception about the way in which information (3 items – S1) and results (3 items – S2) were provided	X	X
Hopes/ Expectation	Eight study specific questions exploring participants reasons for agreeing to the test, rated on a 5 point scale as extremely unimportant to extremely important	X	
Likelihood	One study specific question to determine participant's perception of the likelihood testing will find the cause of the condition .	X	
Decision regret	5 item scale measuring distress or remorse after a (health care) decision [ref O'Connor]		X
Value of the test	Eleven study specific questions exploring the value to participants of having had the test rated on a 4 point scale as not valuable to extremely valuable or not applicable		X

Impact of the test	Two study specific questions asking about the impact of the test on family planning		X

FIGURES

Figure 1. Participating Renal Genetics Clinics

Figure 2. Patient flow within a KidGen Renal Genetics Clinic

Figure 3. Recruitment workflow within the KidGen Renal Genetics Clinic network

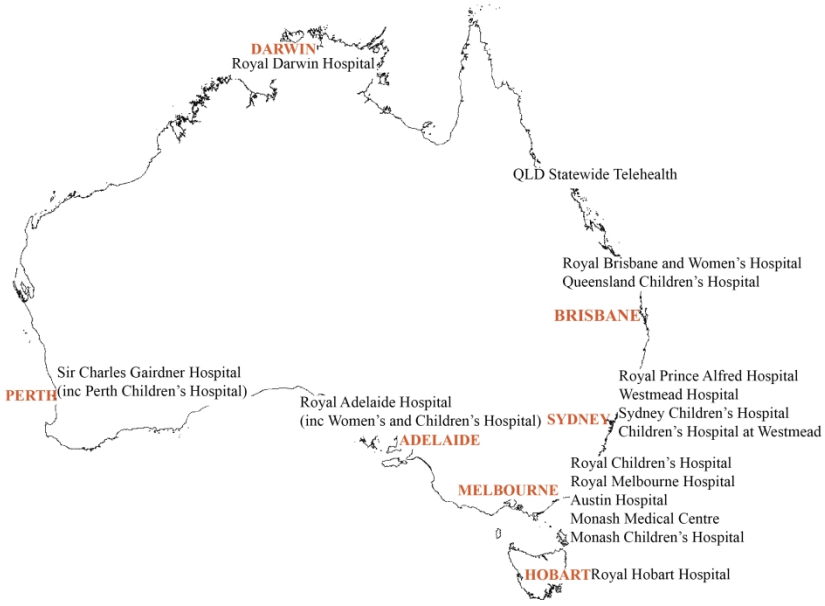

Figure 1. Participating Renal Genetics Clinics

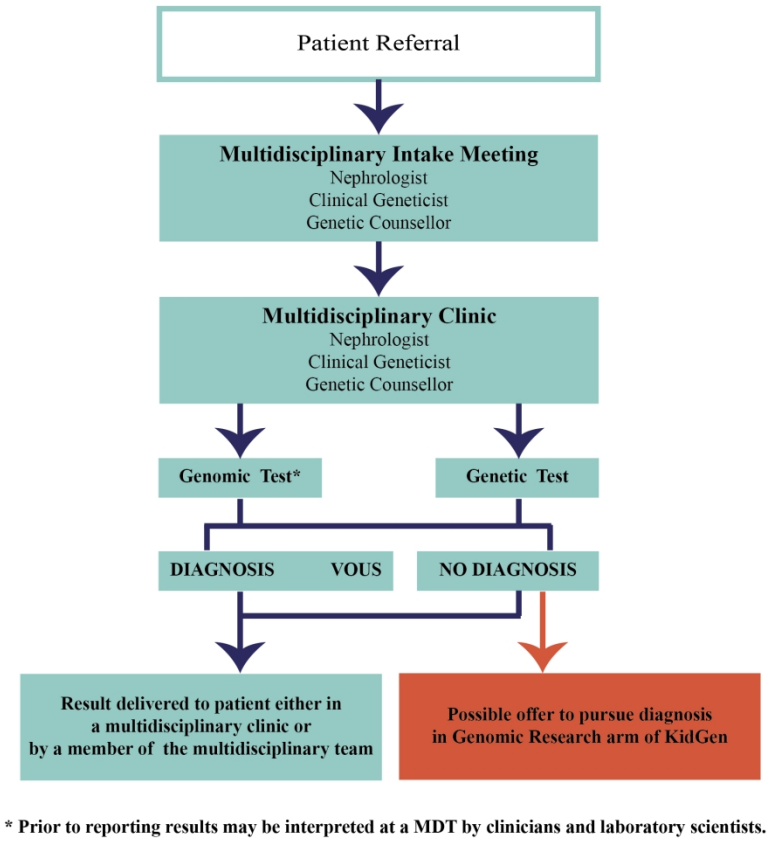

Figure 2. Patient flow within a KidGen Renal Genetics Clinic

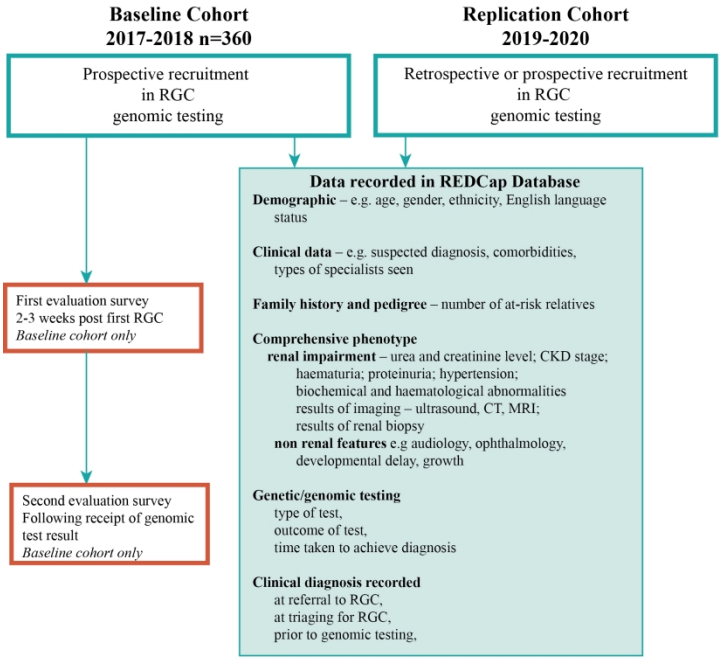

Figure 3. Recruitment workflow within the KidGen Renal Genetics Clinic network

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The comprehensive evaluation of a prospective Australian patient cohort with suspected genetic kidney disease undergoing clinical genomic testing- a study protocol

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The comprehensive evaluation of a prospective Australian patient cohort with suspected genetic kidney disease undergoing clinical genomic testing- a study protocol

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ABSTRACT

Introduction

Recent advances in genomic technology have allowed better delineation of renal conditions, the identification of new kidney disease genes and subsequent targets for therapy. To date however, the utility of genomic testing in a clinically ascertained, prospectively recruited kidney disease cohort remains unknown. The aim of this study is to explore the clinical utility and cost effectiveness of genomic testing within a national cohort of patients with suspected genetic kidney disease who attend multidisciplinary renal genetics clinics.

Methods and Analysis

This is a prospective observational cohort study performed at 16 centres throughout Australia. Patients will be included if they are referred to one of the multidisciplinary renal genetics clinics and are deemed likely to have a genetic basis to their kidney disease by the multidisciplinary renal genetics team. The expected cohort consists of 360 adult and paediatric patients recruited by December 2018 with ongoing validation cohort of 140 patients who will be recruited until June 2020. The primary outcome will be the proportion of patients who receive a molecular diagnosis via genomic testing (diagnostic rate) compared to usual care. Secondary outcomes will include change in clinical diagnosis following genomic testing, change in clinical management following genomic testing, and the cost-effectiveness of genomic testing compared to usual care.

Ethics and dissemination

The project has received ethics approval from the Melbourne Health Human Research Ethics Committee as part of the Australian Genomics Health Alliance protocol: HREC/16/MH/251. All participants will provide written informed consent for data collection and to undergo clinically relevant genetic/genomic testing. The results of this study will be published in peer-reviewed journals and will also be presented at national and international conferences.

STRENGTHS AND LIMITATIONS

- This is a prospectively conducted multicenter national study in which patient data will be captured in a pragmatic clinical setting
- Patients will be recruited for clinically indicated genomic testing for suspected genetic kidney disorders, which may allow better generalizability of results
- Genomic testing is clinically indicated and performed routinely in some participating states/centres in Australia, and therefore it would be unethical to have a control arm for comparison as this would deny some patients of testing.
- This study will contribute to the future research and clinical service redesign by establishing the utility of genomic testing in a kidney disease cohort from patient, clinician and health resource perspectives

INTRODUCTION

Genetic Kidney Disease (GKD) accounts for 10% of adults with chronic kidney disease (1), with a monogenic cause being identified in around 20% of those with early onset chronic kidney disease (CKD) (2). Recent advances in genomic sequencing have enabled rapid and cost-effective sequencing of large amounts of DNA (3) via massively parallel sequencing, otherwise known as next generation sequencing (NGS). This in turn has led to better delineation of GKD, the identification of new renal disease genes and subsequent targets for therapy(4). Moreover, the clinical implementation of genomic testing has increased the number of patients receiving a timely and accurate genetic diagnosis(5). NGS-based genetic testing has demonstrated a monogenic cause in 20% of patients with early onset CKD, and almost 10% in an unselected cohort of 3000 adults with CKD(2, 6). A genomic diagnosis has many potential benefits including enabling targeted therapies(7-9), preventing the use of inappropriate treatments(10) and reducing the use of invasive diagnostic investigations such as renal biopsy. In addition to concluding a sometimes protracted diagnostic odyssey, a genomic diagnosis may also provide prognostic information, inform targeted surveillance for extra-renal complications and facilitate transplantation and reproductive planning. Despite these potential benefits, there is a paucity of comprehensive evaluations of clinical utility and health economic impact of genomic testing in kidney disease cohorts.

Multifaceted novel approaches are required to address the complexities of successfully implementing genomic technologies into clinical care. Diagnostic renal genetics clinics (RGC) apply a multidisciplinary team approach through collaboration between adult and paediatric nephrologists, clinical geneticists, genetic counsellors and diagnostic laboratory scientists. Whilst RGCs are operational in several countries, there is a lack of reported outcomes of this clinical model of care(5, 11).

The purpose of this study is to comprehensively determine the clinical utility and cost effectiveness of genomic testing in patients with suspected genetic kidney disease seen in a multidisciplinary RGC, and to compare this with their care and clinical diagnosis prior to referral. In addition, we aim to evaluate the value of a multidisciplinary RGC model from a patient perspective.

STUDY AIMS

1. To determine the proportion of patients with suspected GKD who obtain a positive diagnosis following genomic testing compared with their clinical diagnosis prior to testing
2. To determine the clinical impact of genomic testing after three months follow-up in a cohort of patients with suspected GKD and identify subgroups of patients who are more likely to have a clinical impact following genomic testing
3. To determine whether genomic testing in a cohort of patients with suspected GKD is cost effective compared to usual care, and to identify whether genomic testing is cost effective for specific subgroups
4. To provide access to further research genomics participation for patients with suspected genetic kidney disease who remain undiagnosed following clinical genomic testing
5. To determine patient preferences regarding a service delivery model for a dedicated renal genetics service
6. To determine the value of genomic testing in those with suspected GKD from a patient perspective

METHODS AND ANALYSIS

Study design

This prospective observational study will be undertaken at multiple Australian sites that provide multidisciplinary renal genetics services. There are 16 participating sites throughout Australia (Figure 1). Patients who are referred by their treating physician to these multidisciplinary renal genetics clinics will be recruited over four years (Figure 2). Patients may be referred for testing for a variety of reasons. These include confirmation of a suspected diagnosis, exclusion of differential diagnoses, clarification of mode of inheritance, and for obtaining the diagnosis where one is previously unknown. For this reason, it was not possible to include a control arm, as this would prevent some patients from undergoing their usual clinical care.. In order to enable determination of comparative clinical utility, planned diagnostic investigations will be nominated by the recruiting clinicians. In addition, data regarding any changes in management will be collected from the referring nephrologist at three months following the return of genomic testing results.

Recruitment of a baseline cohort of 360 participants occurred between 2017 and 2018 (Figure 3) and a further mutually exclusive replication cohort will be recruited between 2019 and 2020. The replication cohort will have the same data collected but will also include patients with a prior genomic diagnosis. These patients will not participate in evaluation surveys (described below) but will be evaluated against all other outcome measures in order to further identify patient, disease and sub-cohort clinical outcomes enabled by larger scale and longer time span observation. The cohort of patients is anticipated to be ethnically diverse with a broad spectrum of renal phenotypes, clinical diagnoses and severity of kidney disease. Patients seen in a multidisciplinary renal genetics clinic as part of standard clinical care will be invited to participate in the study if there is consensus of opinion by the clinic team that their kidney disease is likely genetic in origin. Patients without a clear clinical indication for prospective clinical genomic testing will be excluded in the baseline cohort, including an existing molecularly confirmed genetic diagnosis and those with heterogeneous or complex diseases with a low or unlikely monogenic diagnosis rate by current genomic sequencing (such as isolated congenital abnormalities of the kidney and urinary tract (CAKUT)) (12). Patients who undergo only Sanger sequencing are excluded from the study as this would not represent a genomic approach to clinical investigation and may instead represent clarification or segregation of an already identified familial variant. Patients who attend a RGC but do not undergo genetic testing through the clinic are also excluded from the study. This includes patients who decline clinically-indicated testing. Written informed consent, both for clinical genomic testing and participation in the research study will be obtained by the nominated clinical geneticist, nephrologist or genetic counsellor at each site.

Participant Identifiers

All participants will be assigned a unique identifier for the purposes of this study at recruitment. Study data will be collected and managed using REDCap(13) electronic data capture tools hosted at Murdoch Children's Research Institute. Access to patient identifying details is restricted to clinicians providing care and to those who need contact details for evaluation purposes.

Measures

Once consented to the study, baseline demographic information, clinical information, and detailed phenotypic information will be recorded by clinicians in REDCap. Demographic data including age, gender, ethnicity, and English language status will be captured for all

recruited patients. Further demographic information will be captured in patient surveys. Clinical data include suspected clinical diagnosis, comorbidities and types of specialists previously seen. A detailed family history and pedigree will be collected to identify the number of probands and at-risk relatives presenting for assessment. Comprehensive phenotypic information will also be collected including the presence of extra-renal features, renal impairment, urea and creatinine level, CKD stage, presence and details of hypertension, haematuria, proteinuria and biochemical/haematological abnormalities, results of imaging including ultrasound, CT and MRI, and results of renal biopsy if already performed. Data will also be collected regarding type of genomic test, outcomes of test and time taken to achieve diagnosis. Clinical diagnosis will be recorded as listed in the referral of each patient to the RGC, at the time of triaging for the RGC, prior to genomic testing and at the time of return of genomic testing results. This will enable comparison across multiple time points potentially leading up to a molecular genetic diagnosis.

Patient and Public Involvement

The project was reviewed, edited and revised after in depth engagement with the Australian Genomic Health Alliance (AGHA) Consumer and Community Advisory group. Previous informal engagement with relevant representative local Australian kidney health patient organisations, including Polycystic Kidney Disease (PKD) Australia and Kidney Health Australia (KHA) also occurred. Results from this study will be published and be accessible to all patients on request.

Evaluation Surveys

Evaluation surveys will be distributed to be completed either online or on paper. Adult and proxy versions are available (parent for child). Participants are asked to complete the first survey at 2-3 weeks after attending the RGC at which they are offered and consent to testing, and the second following their receipt of genomic test results. The surveys were developed based on existing surveys in use in the Melbourne Genomics Health Alliance.

The first survey (Table 1) captures additional demographic information and also includes questions about the experience of the consent process and views on the benefits of the multidisciplinary renal genetics clinic. The Genetic Counselling Outcomes Survey (14) is included in survey 1 and 2 to evaluate genetic counselling outcomes of the multidisciplinary clinic. Knowledge questions and a question on the likelihood of the test finding the cause of

the kidney disease are included in survey 1 to gauge understanding. The first survey includes closed and open questions exploring hopes and expectations for testing. Willingness-to-pay questions designed specifically for this study are included in both surveys to gauge value. Validated multi-attribute quality of life instruments (SF-12 for adults and parents(15), CHU9D for children(16)) are included in surveys 1 and 2 to assess health related quality of life. The PedsQL(17) family impact module is included in survey 1 and 2 for parents to assess family impact. Both surveys include questions on family planning.

In addition to the measures described above, the second survey includes study-specific questions assessing understanding of the genomic results, impact this will have on the patient and their family and perceived value of genomic testing. The Decision Regret scale(18) is also included in survey 2.

Sequencing

Genomic sequencing will be undertaken and reported in clinically accredited laboratories. It is envisaged that these are likely to include but not be limited to the National Association of Testing Authorities accredited diagnostic laboratories at Children's Hospital at Westmead, Victorian Clinical Genetics Service, Genome.One, SA Pathology and PathWest. The specific clinical test requested for each participant will be selected by the treating clinician/s at the attending renal genetics clinic according to clinical indication. The spectrum of genomic testing that will be employed is anticipated to include targeted exome, whole exome and whole genome sequencing, including the application of virtual gene panels based on patient phenotype. When additional copy number variation assessment and/or variant confirmation is indicated, then multiplex ligation-dependent probe application, chromosomal microarray or Sanger sequencing may be undertaken in addition to genomic sequencing. The cost per test is expected to be AUD$1200 to AUD$2400 depending upon the specific test and diagnostic provider, with individual test costs to be ascertained directly. Further, each participant will have genomic sequencing performed once unless technical or sequence quality issues require re-sequencing to enable clinical reporting. Based on clinical indication, further analysis of disease or phenotype-specific virtual gene panels may occur, with any such sequence re-analysis being recorded.

All participants will provide written clinical consent for genomic testing and analysis will be restricted to the assessment of genes related to the condition of interest. In this instance,

analysis will be limited to a predefined gene list of 360 genes related to nephropathy((19). Secondary findings unrelated to the presenting condition will not be reported in this study. Written informed consent for participation in the research study will be attained separately, which includes options to consent to accessing the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits scheme (PBS), hospital and emergency data sets and data sharing in addition to study evaluation data collection. The MBS and PBS are listings of all medical services and medicines subsidised by the Australian government, respectively. In addition, an optional written consent will be obtained in order to share data and samples for use in ethically approved research outside of the study.

Health economic evaluation

An economic evaluation will be conducted to assess the incremental cost-effectiveness of NGS compared with usual care in patients with suspected kidney disease. A microsimulation model of disease progression will be developed to estimate the lifetime costs and outcomes associated with usual care and NGS. The analysis will be conducted from an Australian healthcare system perspective in line with recommended practices(20-22), and based on the outcomes of cost per additional diagnosis, cost per quality-adjusted life-year (QALY), and net monetary benefit.

Hospital patient-level resource use and cost data will be acquired for each study participant to cost the diagnostic and short-term medical management in the NGS arm. The additional per-patient diagnostic investigations that could potentially be incurred in the usual care pathway will be identified based on a review of national and international guidelines on the diagnosis of suspected kidney disease and clinical expertise from each of the 16 participating centres across Australia. The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) will be used to undertake a survival analysis of CKD patients. Parametric and non-parametric methods will be used to estimate transition probabilities for key endpoints including; all-cause mortality, initiation of dialysis and transplantation. This will allow for the development of evidence-based transition probabilities while controlling for patient-specific factors such as age, gender, treatment pathways and disease status. Unit costs associated with these endpoints and related treatments will be drawn from established national sources (23-25). A microsimulation will be used to capture the costs and benefits associated with earlier renal replacement therapy and delayed dialysis from the introduction of NGS. To accurately

model the implications, registry-derived transition probabilities will be adjusted, on the basis of published evidence (26), to reflect the impact of new treatment pathways following NGS.

For the cost-utility analysis, participants responses to the SF-12 measure will initially be used to generate utilities at baseline prior to NGS and following the return of NGS findings. A review of the literature will be undertaken to complement these estimates with evidence from secondary sources, such as utilities for chronic kidney disease (27) and renal transplantation (28). The cost-benefit analysis will rely on a contingent valuation exercise that was undertaken to understand the personal value of NGS to the families. Deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the findings to plausible variations in key assumptions around costs, outcomes and transition probabilities, and to consider the broader issue of generalisability of the study's results. Cost-effectiveness acceptability curves will be generated to reflect decision uncertainty.

Study outcomes

The primary outcome will be the proportion of patients who receive a molecular diagnosis via genomic testing (diagnostic rate). Secondary outcomes will be change in clinical diagnosis following genomic testing, change in clinical management following genomic testing and cost-effectiveness of genomic testing compared to non-genomic diagnostic investigations. Survey outcomes will include the proportion of patients who preferred to be seen by the multidisciplinary team compared to those who prefer to be seen in individual clinics. In addition, the GCOS will be compared before and after testing and between those with a positive/negative genomic testing result.

Data analysis

Results on diagnostic utility and clinical implications will be expressed as frequencies and percentages for categorical variables and be compared using the chi-square test. Continuous non-normally distributed variables will be expressed as median (IQR) and compared using the Mann-Whitney test. Normally distributed continuous variables will be expressed as mean±SD and compared using the Student's t-test. Multivariable logistic regression will be performed to determine which variables may predict a positive genomic diagnosis, such as age of onset of CKD, aetiology of CKD, family history or presence of haematuria/proteinuria/cysts. This will help to develop professional guidelines regarding genomic testing in suspected GKD. In addition, the diagnostic rates between different

genomic testing modalities will also be compared. The target sample size is 500 patients across both baseline and replication cohorts.

DISCUSSION

In this protocol, we describe the rationale and methods for a prospective observational study of a national cohort of patients with suspected genetic renal disease that are referred to multidisciplinary renal genetics clinics throughout Australia. The strengths of this study are the multicentre design, prospective data collection and a real-world clinical setting. The absence of a control arm is a limitation of this study however it was not feasible to randomize patients in this study for two reasons. Firstly, genomic testing is clinically indicated and performed routinely in most participating states/centres, and it would therefore be unethical to deny genomic testing to some patients where it is clinically indicated and current standard of care. Secondly, feedback from patient representatives, the community and genetic counsellors highlighted that it was unacceptable to deny testing to some patients for the purpose of a control arm. Further those patients not receiving a genomic test after clinical assessment are likely to do so in a non-random fashion thus precluding their analysis as a true control group.

Genomic technologies have transformed the concept of precision medicine in many specialities, however the potential benefits in kidney medicine are yet to be demonstrated. Until now, the diagnostic utility of genomic testing has been assessed in a small number of patients or in a research context (29, 30). In addition, while studies which perform genomic sequencing in larger cohorts (6, 31) are emerging, detailed phenotypic information is not being collected and there remains a paucity of data on clinical outcomes. Importantly, these large-scale studies include patients with all types of chronic kidney disease and are thus powered to understand prevalence of GKD rather than to determine utility and yield in a cohort in which the clinician suspects genetic disease(6). Data on genomic sequencing in a real-world clinical environment at a national scale for a targeted population of patients with suspected GKD are lacking and the health economic impacts of genomic testing are not well understood or established(32). We believe that collecting such detailed information from a prospectively ascertained cohort will enable us to determine the diagnostic yield and comprehensive clinical implications, to inform future practice recommendations.

To our knowledge, this is the first time that a structured, objective and minimally bias approach is undertaken to measure the outcomes of genomic testing in kidney disease. Results from this study will provide the opportunity to determine the clinical implications of genomic testing in a large cohort of patients, and further enable analysis of which subgroups of patients may benefit most. Furthermore, due to the pragmatic nature of this study, these results more likely to be replicated in a clinical environment. By assessing the utility, cost effectiveness and implementation aspects of genomic testing in patients with kidney disease, the results of this study will inform patients, treating physicians and health services and define priorities for future trials. Collectively, this is anticipated to have significant impacts upon clinical practice and health service redesign.

FUNDING STATEMENT

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ETHICS AND DISSEMINATION

Ethics

Ethics approval for this project has been obtained by Australian Genomics Health Alliance as part of the research study Australian Genomics Health Alliance: Preparing Australia for Genomic Medicine and issued by Melbourne Health HREC/16/MH/251. Governance site specific approval for the project has been obtained for each of the participating clinic sites. All participants will provide written informed consent for data collection and to undergo clinically relevant genetic/genomic testing.

Dissemination Plan

The main findings of this study will be published in peer-reviewed journals and will also be presented at national and international conferences. We will also issue reports of results of the study to the Australian Government, State/Territory Governments and health organizations in order to inform future policy and guidelines. This study will also contribute to the training and development of post-doctoral students.

CONTRIBUTOR SHIP STATEMENT

KJ contributed to the design of the study and drafted the manuscript. CQ and AJM (Andrew John Mallett) conceived the project and obtained funding for the clinical flagships and research study, made substantial contributions to the design of the study and were major contributors in drafting the manuscript. LW and ZS undertook significant project design and data management elements, provided specific design elements around outcome analysis and were major contributors in drafting the manuscript. IG, YW and MM provided specific design elements around health economic analysis. SB provided specific implementation design elements. AM (Amali Mallawaarachchi), HM, RF, AC, MS, MJ, PK and CP contributed to regionalised study design and implementation. All authors contributed to the drafting of the manuscript, read and approved the final manuscript. In addition to the authors listed, the broader KidGen Collaborative scientific, clinical and diagnostic membership had input into this protocol.

COMPETING INTERESTS: No, there are no competing interests for any author

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TABLES

Table 1. Summary of survey measures

Measure	Description	S1	S2
Demographics	Age, gender, marital status, education, income, number of dependents in household, postcode, private health insurance status.	X	
Patient reported outcomes measures	CHU9D[ref] and PEDS family impact[ref] for paediatric surveys OR SF-12 [ref] for adult surveys	X	X
Experience of the multidisciplinary clinic	Three study specific questions exploring advantages and disadvantages of multidisciplinary renal genetics clinics	X	X
Genetic counselling	24-item scale measuring outcomes of genetic counselling GCOS-24[ref]	X	X
Family planning	Four study specific questions addressing plans for another child, estimated recurrence of the kidney condition, concern about recurrence, interest in reproductive technologies (parent surveys only)	X	

Understanding	In survey 1, 8 study specific questions address participant understanding of: types of potential results (4 questions), potential familial implications (1 question), ways in which the data can be used (2) questions); number of genes examined (1 question). In survey 2, 2 study specific questions used to measure recall and understanding of result.	X	X
Willingness to pay (value)	Study specific questions included to establish a quantitative reference for the value placed on testing	X	X
Information provision	Study specific questions to assess participant perception about the way in which information (3 items – S1) and results (3 items – S2) were provided	X	X
Hopes/ Expectation	Eight study specific questions exploring participants reasons for agreeing to the test, rated on a 5 point scale as extremely unimportant to extremely important	X	
Likelihood	One study specific question to determine participant's perception of the likelihood testing will find the cause of the condition .	X	
Decision regret	5 item scale measuring distress or remorse after a (health care) decision [ref O'Connor]		X
Value of the test	Eleven study specific questions exploring the value to participants of having had the test rated on a 4 point scale as not valuable to extremely valuable or not applicable		X

Impact of the test	Two study specific questions asking about the impact of the test on family planning		X

FIGURES

Figure 1. Participating Renal Genetics Clinics

Figure 2. Patient flow within a KidGen Renal Genetics Clinic

Figure 3. Recruitment workflow within the KidGen Renal Genetics Clinic network

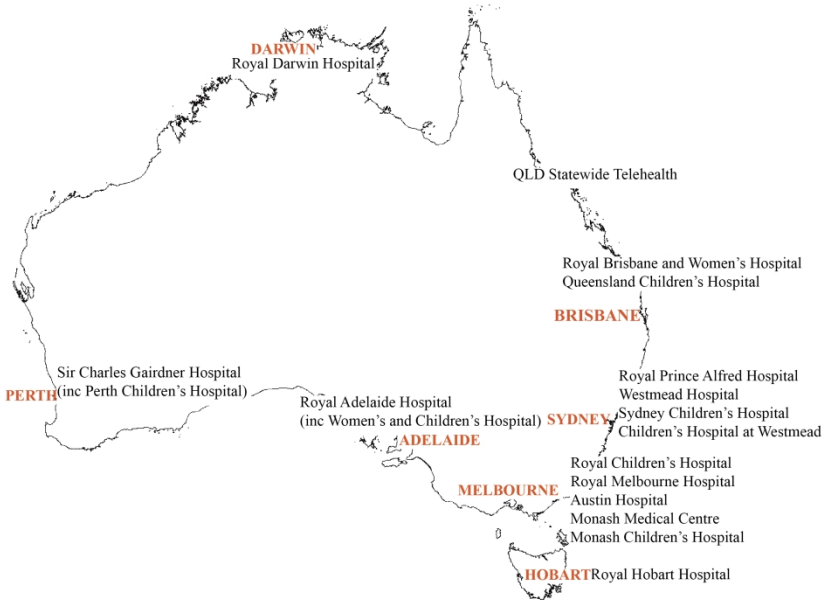

Figure 1. Participating Renal Genetics Clinics

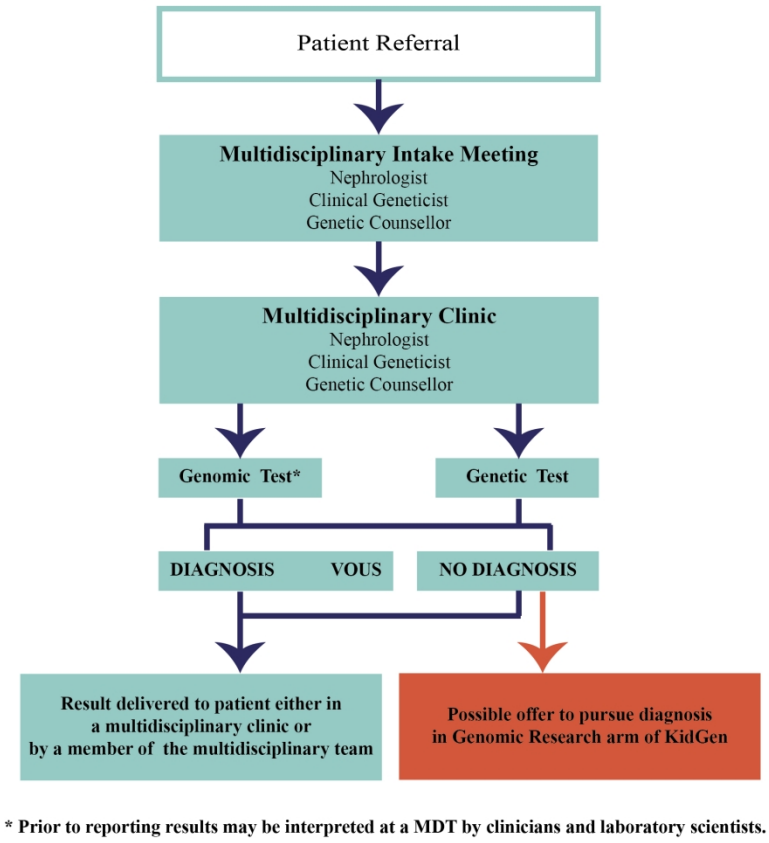

Figure 2. Patient flow within a KidGen Renal Genetics Clinic

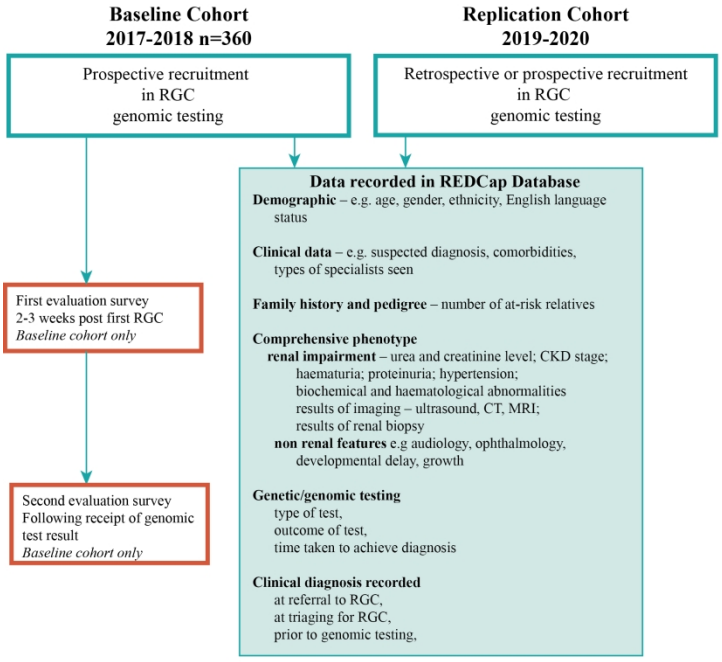

Figure 3. Recruitment workflow within the KidGen Renal Genetics Clinic network