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ARTICLE

Genomic testing for suspected monogenic kidney disease in children and adults: A health economic evaluation

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ABSTRACT

Purpose: To assess the relative cost-effectiveness of genomic testing compared with standard non-genomic diagnostic investigations in patients with suspected monogenic kidney disease from an Australian health care system perspective.

Methods: Diagnostic and clinical information was used from a national cohort of 349 participants. Simulation modelling captured diagnostic, health, and economic outcomes during a time horizon from clinical presentation until 3 months post-test results based on the outcome of cost per additional diagnosis and lifetime horizon based on cost per quality-adjusted life-year (QALY) gained.

Results: Genomic testing was Australian dollars (AU$) 1600 more costly per patient and led to an additional 27 diagnoses out of a 100 individuals tested, resulting in an incremental cost-effectiveness ratio of AU$5991 per additional diagnosis. Using a lifetime horizon, genomic testing resulted in an additional cost of AU$438 and 0.04 QALYs gained per individual compared with standard diagnostic investigations, corresponding to an incremental cost-effectiveness ratio of AU$10,823 per QALY gained. Sub-group analyses identified that the results were largely driven by the cost-effectiveness in glomerular diseases.

Conclusion: Based on established or expected thresholds of cost-effectiveness, our evidence suggests that genomic testing is very likely to be cost saving for individuals with suspected glomerular diseases, whereas no evidence of cost-effectiveness was found for non-glomerular diseases.

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Introduction

Chronic kidney disease is a global health burden with significant health care resource implications because of the substantial cost of dialysis and transplantation.[1,2] Obtaining a specific diagnosis in kidney disease patients is important, often affecting both prognosis and management. Steps toward achieving a diagnosis include biochemical investigations, imaging, and in select cases, a kidney biopsy for histological assessment.[3,4] Despite this, 5% to 15% of patients with end-stage kidney disease have unknown etiology.[5,6]

Genetic kidney disease (GKD), though rare, is estimated to account for 10% of adult and up to 40% of childhood nephropathy.[7,8] Genomic technologies are increasingly utilized in standard clinical care, especially as costs decline, while sequencing and analysis methods improve. Genomic testing has now been shown to be an effective diagnostic tool in several cohorts with suspected monogenic kidney disease,[9,10] with a diagnostic yield ranging 30% to 65%, depending on how patients are selected. Currently, the most well-recognized benefit of a genomic diagnosis in kidney disease patients is the potential avoidance of an invasive diagnostic kidney biopsy, which carries significant risks and expenses, particularly in children who require general anesthesia as part of the procedure.[11] Additional clinical benefits of genomic testing in kidney disease patients are being increasingly recognized,[9] with cohort studies demonstrating short-term changes in clinical management in patients with a confirmed genetic diagnosis. Some of these include changes in treatment strategy, changes in surveillance, reproductive implications, and facilitation of transplantation.[9]

Although the clinical benefits of genomic testing are well recognized by nephrologists, access to testing is not equitable. One of the main challenges is the high costs associated with sequencing, analysis, and additional consultation time,[9] and it is unclear whether these costs are currently justified. Therefore, to establish genomic testing as a reimbursed diagnostic tool in clinical practice, evidence for cost-effectiveness is needed. We previously published a cost-effectiveness study on exome sequencing with targeted analysis for one of the most common types of monogenic disease, glomerular disease.[11] We identified that using exome sequencing as a first-line test was cost saving in children. The current study aims to evaluate the relative cost-effectiveness of genomic testing (exome or genome sequencing) compared with standard non-genomic diagnostic investigations in a broad range of diagnostic groups with suspected monogenic kidney disease, while accounting for the possible long-term health and economic impacts of treatment changes from genomic diagnosis using a lifetime horizon.

Materials and Methods

Study design and participants

We evaluated the cost-effectiveness of genomic testing relative to non-genomic (standard) diagnostic investigations in children and adults suspected with 1 or more of the following 5 renal conditions: (1) glomerular disease (eg, Alport Syndrome, nephrotic syndrome, and glomerulopathy); (2) cystic disease (eg, autosomal dominant polycystic kidney disease, and ciliopathy); (3) congenital anomalies of kidney and urinary tract (CAKUT); (4) tubular disease (eg, tubulopathy and Gitelman Syndrome); and (5) complement disorders (eg, atypical hemolytic uremic syndrome). Clinical suspicion of these potential monogenic kidney diseases was identified by the treating nephrologists of the individual patients and then further assessed by referral to a multidisciplinary renal genetics service. We obtained the diagnostic and clinical information related to these conditions from the Australian Genomics Health Alliance (AGHA) KidGen Renal Genetics rare disease flagship project for which a cohort study protocol has been previously described,[12] national and international guidelines on the management of renal conditions[13-16] and clinical expertise, internal and external to the research team. More information about the AGHA KidGen flagship project cohort ($n = 349$) informing the diagnostic component of this analysis can be found in Supplemental Tables 1 and 2.[17] Ethical approval was granted from the Melbourne Health Human Research Ethics Committee as part of the AGHA protocol: HREC/16/MH/251. Informed written consent was obtained from the parents of study participants.

Economic evaluation

We developed a microsimulation model to estimate the costs, diagnostic and quality-adjusted life-year (QALY) outcomes associated with the genomic and non-genomic (standard) diagnostic strategies from an Australian health-care system perspective and based on the outcomes of cost per additional diagnosis and cost per QALY gained. Given the heterogeneity of non-genomic diagnostic pathways across the different renal conditions and between age groups, as well as corresponding variability in the diagnostic yield of genomic testing, we incorporated the characteristics of each individual within each of the suspected clinical groups into the model using tracker variables and assigned to each simulated individual through bootstrapping. We developed a health economic analysis plan and received approval from the research team before the analysis. The plan is available upon request.

Model structure

The decision-analytic model included a decision tree, which was used to simulate the costs and outcomes associated with the different diagnostic pathways, followed by Markov models, which simulated the clinical, health and economic consequences of diagnosis in the medical management of the renal condition. A graphical representation of the modeled pathways for genomic and standard diagnostic strategies is provided in the Supplemental Material (Supplemental Figure 1).

In the genomic testing pathway, individuals were offered a type of genomic analysis based on the clinical features and the results from Tier 1 testing, as implemented in the AGHA KidGen flagship project. Tier 1 testing includes full blood examination, urea electrolytes and creatinine, urinalysis, and microscopy, and urine protein: creatinine/albumin, renal tract ultrasound, liver function tests, and chromosomal microarray in all children and adult patients with CAKUT or with syndromic presentation. The types of genomic tests included exome or genome sequencing (ES/GS) with phenotype-driven analysis of relatively narrow virtual panels (eg, Tubulopathy) or much broader virtual panels (eg, Kidneyome or Mendeliome). Following genomic testing, further non-genomic investigations were still performed to clarify a genetic diagnosis (whether positive or negative). A positive diagnosis was considered when "pathogenic" or "likely pathogenic" variant(s) were identified in genes concordant with phenotype and mode of inheritance.

In the non-genomic (standard) diagnostic pathway, individuals went through a series of biochemical, imaging and/or biopsy tests (Tier 2 ± Tier 3; Supplemental Tables 4 and 5). This diagnostic pathway differed depending on the suspected kidney condition and whether individuals were children or adults. We developed the diagnostic pathways through an iterative clinical consensus process with a national group of representative nephrologists in Australia, internal and external to the research team. We assessed whether a clinical diagnosis was correct through the following process. Clinicians were asked to record the suspected clinical diagnosis at referral and before genomic testing. This was compared with the molecular diagnosis followed by testing. A clinical diagnosis was considered correct if the diagnosis at referral was the same as the molecular diagnosis following genomic testing, and if the suspected mode of inheritance entered at referral was also correct. If there was more than 1 differential diagnosis suspected, this was considered incorrect, based on the assumption that a molecular diagnosis resulted in clarification of the diagnosis and removed diagnostic and/or inheritance uncertainty.[11]

Following the diagnostic investigation, a proportion of patients could benefit from a management change. The benefit of treatment initiation following a genetic diagnosis largely lies in 3 types of patients: (1) patients with atypical autosomal dominant polycystic kidney disease (ADPKD) (ie, patients with a genetic diagnosis of ADPKD who had an incorrect prior clinical diagnosis; ADPKD is a type of cystic disease), (2) patients with a genetic diagnosis of Alport Syndrome (a type of glomerular disease) who had an incorrect prior clinical diagnosis and did not have presenting proteinuria, and (3) patients with atypical hemolytic uremic syndrome (aHUS; a type of complement disorder) who had a confirmed molecular diagnosis (Supplemental Tables 2 and 3). We simulated the long-term clinical management costs and outcomes for these individuals based on published evidence.[18-20] Given the lack of evidence for the natural history of aHUS, we developed 2 Markov models to simulate the disease progression of ADPKD and Alport Syndrome, with and without treatment, in the genomic testing and non-genomic diagnostic pathways respectively.

The Markov model for ADPKD contained 6 health states: chronic kidney disease (CKD) stage 1, CKD stage 2, CKD stage 3, CKD stage 4, kidney failure (KF), and death (Supplemental Figure 1).[21] The mean age of atypical ADPKD patients (at the time of diagnosis) was assumed to be 38 years for adults and 5 years for children with CKD stage 1, representing the average characteristics of the AGHA KidGen flagship project participants. The Markov model for Alport Syndrome had 3 health states: CKD stage 1-4, KF, and death. One health state was used to represent the 4 CKD stages before KF, given the lack of evidence for the disease progression through each stage of CKD in Alport Syndrome. The base case of Alport patients was 25-year-old adults and 11-year-old children with CKD stage 1, informed by the AGHA KidGen flagship project data.

Model parameters related to diagnostic pathways

The diagnostic cost of the genomic testing strategy comprised the cost of genomic testing, segregation tests, genetics consultations, and further non-genomic investigations as listed in Supplemental Table 6. The proportion of patients who had each type of genomic testing was drawn from the AGHA KidGen flagship project data: 19% genome sequencing with panel analysis, 53% had exome sequencing with panel analysis, 23% had exome sequencing with Kidneyome analysis as per PanelApp Australia https://panelapp.agha.umccr.org/panels/275/,[22] and 5% had exome sequencing with Mendeliome analysis as per PanelApp Australia https://panelapp.agha.umccr.org/panels/137/.[22] In the AGHA KidGen flagship project, 16 participants did not receive a genomic test. For the modelling purposes, we conservatively assumed that patients who only had Sanger sequencing (2.9%) have received exome sequencing panel, whereas patients who only had chromosome microarray or VNTR *MUC1* (1.7%) have received genome sequencing panel. The higher costs of the exome sequencing and genome sequencing were used in the model, while keeping the diagnostic rates at the lower level.

The weighted mean cost of genomic testing and consultations was estimated at Australian dollars (AU$) 3,057 per proband. In the non-genomic (standard) diagnostic strategy, the Tier 2 and 3 tests involved in each kidney clinical group are listed in the online Supplemental Material (Tables S4 and S5). The unit costs of the diagnostic investigations were sourced from the Australia Medicare Benefits Schedule, Victorian Clinical Genetics Services, and other testing laboratories. The mean diagnostic costs for glomerular, cystic, CAKUT, tubular, and complement diseases were, respectively, estimated at AU$6,205, $315, $855, $325, and $546 in children and AU$1,945, $410, $194, $622, and $1532 in adults.

The diagnostic rates for the genomic testing and non-genomic (standard) diagnostic strategies were sourced from the AGHA KidGen flagship project data and were

specific to each clinical and age group (Supplemental Tables 7 and 8). The diagnostic yield of genomic testing in the overall cohort was 48%, ranging between 13% (complement disorders) to 56% (tubular disease).

Model parameters related to clinical pathways

According to the AGHA KidGen flagship project study, following genomic testing 8 (2.3%) individuals with a molecular diagnosis of ADPKD (Group 1) and 4 (1.1%) individuals with a molecular diagnosis of Alport syndrome diagnosis (Group 2) could benefit from a treatment change (Supplemental Tables 2 and 3). For Group 1, individuals were assumed to be eligible for Tolvaptan treatment if they were over the age of 18 years and had a rapid progression of the condition (ie, treatment starting from CKD stage 2). For Group 2, individuals were assumed to be eligible for ramipril treatment following the molecular diagnosis. These treatments were assumed to continue until KF or death. In the non-genomic (standard) pathway, these individuals were assumed to remain untreated and progressed at the rate of natural history because they would not have received an accurate diagnosis. The diagnostic costs of the 5 conditions and the incremental lifetime clinical management costs and QALY gains of these 12 (3.4%) patients were simulated, given that the long-term costs and outcomes between the 2 strategies are the same for the rest of the cohort. The parameters for simulating disease progression, treatment effects, mortality, costs, and health utilities were sourced from published evidence and established national sources.[18-20,23-30] These are listed in Supplemental Table 9. Detailed description of the methods used to incorporate these parameters into the model is provided in the online appendices.

Analyses

We validated the model following the recommendations from Good Research Practices in Modelling Task Force-7.[31] Model structures, assumptions and input parameters were reviewed and approved by leading clinicians, both internal and external to the research team, to ensure face validity and relevance across States and Territories in Australia. For internal validity, we verified the decision tree part of the model by manual calculation comparing models results against values used in developing the model. We validated the 2 Markov models by comparing the age of KF onset and treatment effect predicted from the model to published evidence.[20,32]

We conducted 2 incremental cost-effectiveness analyses using Monte Carlo microsimulation of 100,000 individuals. Analysis 1 simulated the costs and diagnostic outcomes of genomic testing and non-genomic (standard) diagnostic strategies using a time horizon from presentation to 3 months following test result. Analysis 2 used a lifetime horizon to simulate the costs related to the diagnostic and clinical pathways and associated QALY gains for the 2 strategies. We presented the results as cost per additional diagnosis (Analysis 1) and cost per QALY gained (Analysis 2). All costs were in 2020 AU$. We applied an annual discount rate of 5% in Analysis 2 as recommended in Australia.[33] We compared the incremental cost-effectiveness ratios (ICERs) with a willingness-to-pay (WTP) threshold of $50,000 per QALY gained to determine whether genomic testing was cost-effective.[34] We developed and analyzed the model using TreeAge Pro Healthcare 2020. We also conducted subgroup analyses for each clinical group and for individual adult and pediatric cohorts. We performed a probabilistic and a range of deterministic sensitivity analyses to test the robustness and generalizability of the cost-effectiveness results.

Results

Across the simulated GKD cohort in Analysis 1 (Table 1), the mean per patient cost of the non-genomic (standard) diagnostic strategy was AU$1537, with 21 out of 100 individuals being diagnosed. The genomic testing strategy was AU$1600 more costly per patient ($3137), while providing a diagnosis in 48 out of 100 individuals. Therefore, the mean ICER of genomic testing relative to the non-genomic (standard) strategy was AU$5991 per additional diagnosis. As shown in Table 1, genomic testing was more cost-effective in children, with an ICER of AU$1946 per additional diagnosis. The corresponding ICER in the adult cohort was AU$8766. Genomic testing was more cost-effective compared with non-genomic (standard) investigations in the glomerular disease group (Table 1), with an ICER of $533 per additional diagnosis. The corresponding ICER in the other groups ranged between $7,218 (tubular disease) and $18,576 (CAKUT) per additional diagnosis.

Including the long-term management costs of patients who may benefit from treatment initiation following a genetic diagnosis (Analysis 2), genomic testing resulted in an additional cost of AU$438 and 0.04 more QALYs per individual compared with the non-genomic (standard) diagnostic strategy, which corresponds to an ICER of AU$10,823 per QALY gained (Table 2). In children, genomic testing dominated the non-genomic (standard) diagnostic strategy because it was less costly and more effective. In adults, the ICER was estimated at AU$41,748 per QALY gained. Because the value of a genetic diagnosis, in terms of treatment change, was more relevant to the atypical ADPKD and some Alport syndrome patients who would have been incorrectly diagnosed with non-genomic (standard) investigations, the treatment benefits only fell into the glomerular and cystic disease groups. In the glomerular disease group, genomic testing was dominant because it led to a cost saving of AU$7355 per individual tested and 0.075 more QALYs gained relative to non-genomic (standard) diagnostic investigations (Table 2). The corresponding ICER in the cystic disease group was AU$283,597 per QALY gained because of the large annual treatment cost with Tolvaptan (AU$24,060). A breakdown of the cost-effectiveness results by condition and age group is provided in Supplemental Table 10.

The results of all deterministic sensitivity analyses conducted as part of Analyses 1 and 2 are shown in

Table 1 Analysis 1—Results based on the outcome of cost per additional diagnosis

Groups	Costs (AU$)	Diagnostic Yield (%)	Incremental Cost (AU$)	Incremental Yield (%)	Incremental Cost-Effectiveness Ratio
Genomic sequencing	3137	48	1600	27	5991
Standard diagnostic pathway	1537	21	-	-	-
Adults					
Genomic sequencing	3153	46	2003	23	8766
Standard diagnostic pathway	1150	23	-	-	-
Children					
Genomic sequencing	3099	52	689	35	1946
Standard diagnostic pathway	2410	16	-	-	-
Glomerular					
Genomic sequencing	3227	46	167	31	533
Standard diagnostic pathway	3059	14	-	-	-
Cystic					
Genomic sequencing pathway	3068	54	2686	23	11,834
Standard diagnostic pathway	382	32	-	-	-
CAKUT					
Genomic sequencing pathway	3064	25	2333	13	18,576
Standard diagnostic pathway	731	13	-	-	-
Tubular					
Genomic sequencing pathway	3117	56	2612	36	7218
Standard diagnostic pathway	505	20	-	-	-
Complement					
Genomic sequencing pathway	3061	13	1601	13	12,633
Standard diagnostic pathway	1460	0	-	-	-

AU$, Australian dollars; *CAKUT*, congenital anomalies of kidney and urinary tract.

Supplemental Table 11 in the online appendices. As shown in the cost-effectiveness acceptability curve of Figure 1, genomic testing would have over 95% probability of being cost-effective relative to non-genomic (standard) investigations only if decision maker's willingness to pay per additional diagnosis was greater than AU$8000 (Analysis 1). For the commonly cited threshold of willingness to pay per additional QALY is Australia (AU$50,000), the genomic testing strategy had 75% probability of being cost-effective relative to non-genomic (standard) investigations.

Discussion

In this study, we conducted 2 analyses from an Australian health care system perspective to evaluate the relative cost-effectiveness of genomic testing compared with non-genomic (standard) investigations in children and adults suspected with GKD. The first analysis (Analysis 1) assessed cost-effectiveness using a short time horizon, from clinical presentation up to 3 months post-test results because of the inherent uncertainty and limited data associated with long-term costs and outcomes in this context. The analysis estimated that the genomic testing group was AU$1600 more costly per individual tested, while leading to an additional 27 out of 100 individuals being diagnosed. The mean monetary value of the benefits generated from the test in patients with GKD has been estimated at AU$1879 ($1,427-$2,332) using a contingent valuation method and based on responses from 46 parents of children and 113 adult patients with GKD from the AGHA KidGen flagship project.[35] Using discrete choice experiment methods, the mean value of the benefits of testing in patients with glomerular diseases was estimated at AU$4400 ($4200-$4600) for children and AU$900 ($800-$1000) for adults,[36] resulting in a weighted average of AU$1880 based on a 72% adult and 28% children cohort composition.[11] Although these values may indicate that genomic testing is likely to be cost-beneficial across all participants with GKD, significant variations between the disease groups exist. Considering that the WTP for genomic testing was estimated at AU$1880, which resulted in an additional 27 diagnoses per 100 individuals tested, a WTP threshold of AU$6963 per additional diagnosis can be inferred. At this threshold of WTP, genomic testing had 65% probability of being cost-effective. The results, however, are largely driven by the cost-effectiveness of genomic testing for glomerular diseases and especially in children.

The second analysis (Analysis 2) used a lifetime horizon to simulate the implications of management changes following a genomic diagnosis on the cost and quality and quantity of life outcomes in a specific group of individuals suspected with glomerular or cystic disease. Considering that the commonly cited threshold of cost-effectiveness in Australia is AU$50,000 per QALY gained,[37] genomic testing had an ICER of $10,823 per QALY gained, and therefore is likely to be cost-effective, with 75% probability

Table 2 Analysis 2—Results based on the outcome of cost per quality-adjusted life-year (QALY) gained

Groups	Costs (AU$)	QALYs	Incremental Cost (AU$)	Incremental QALY	Incremental Cost-Effectiveness Ratio
Genomic sequencing	15,748	0.519	438	0.040	10,823
Standard diagnostic pathway	15,310	0.478	-	-	-
Adults					
Genomic sequencing	10,791	0.298	1175	0.028	41,748
Standard diagnostic pathway	9616	0.270	-	-	-
Children					
Genomic sequencing	26,946	1.017	−1228	0.068	Dominant
Standard diagnostic pathway	28,174	0.949	-	-	-
Glomerular					
Genomic sequencing	13,934	0.443	−7355	0.075	Dominant
Standard diagnostic pathway	21,289	0.368	-	-	-
Cystic					
Genomic sequencing pathway	23,344	0.839	7122	0.025	283,597
Standard diagnostic pathway	16,222	0.814	-	-	-
CAKUT[a]					
Genomic sequencing pathway	3064	0	2333	0	Dominated
Standard diagnostic pathway	731	0	-	-	-
Tubular[a]					
Genomic sequencing pathway	3,117	0	2612	0	Dominated
Standard diagnostic pathway	505	0	-	-	-
Complement[a]					
Genomic sequencing pathway	3061	0	1601	0	Dominated
Standard diagnostic pathway	1460	0	-	-	-

AU$, Australian dollars; *CAKUT*, congenital anomalies of kidney and urinary tract; *QALYs*, quality-adjusted life-years.

[a]For CAKUT, tubular diseases and complement disorders, only the diagnostic costs are included, which are same as in Table 1. Given the lack of evidence on the differential management change following a genomic or clinical diagnosis or evidence on the natural history of disease progression, the lifetime costs and QALY gains of the 2 pathways post testing were assumed to be same for these conditions and do not affect the incremental cost-effectiveness ratios.

of cost-effectiveness across the whole cohort (Figure 2). The cost-effectiveness, however, is driven by the health and economic benefits of genomic testing in patients with glomerular disease.

Evidence on the cost-effectiveness of genomics for GKD has been very limited, with only 1 study, led by Jayasinghe et al and our KidGen program,[11] evaluating targeted exome analysis as a diagnostic test in glomerular diseases. The study concluded that early application of exome sequencing with targeted analysis was effective for diagnosing monogenic glomerular disease, with substantial cost savings in children. The study, however, relied on evidence from a single state (Victoria) in Australia, a single GKD (ie, genetic glomerular disease), and time horizon from clinical presentation to 3 months following test result. Further, it was undertaken upon a subset (25%) of the KidGen flagship project cohort that has now been more fully and broadly analyzed here. Our work benefited from the use of national data across Australia, including participants from all states, the inclusion of multiple GKDs, and the use of a lifetime horizon, which enabled a consideration of the longer-term health and economic impacts of the test's clinical utility. Our findings confirmed the cost saving of genomic testing in children with glomerular diseases. The inclusion of longer-term health and economic impacts in this study provided evidence of cost-effectiveness also in adults with glomerular diseases. Our analysis highlighted that, although genomic testing may be cost-effective across individuals with GKD, decision uncertainty exists, with genomic testing expected to be about 65%-75% cost-effective. In addition, the main barrier to the argument that genomic testing for GKD is cost-effective is likely to be the extreme heterogeneity of cost-effectiveness for the different types of GKD, specifically glomerular disease compared with non-glomerular disease. The cost-effectiveness of genomic testing is largely driven by the health economic outcomes observed for glomerular diseases. Although genomic testing could be cost-effective in children with suspected cystic diseases, no evidence of cost-effectiveness was found for the other non-glomerular GKDs.

There are, however, limitations worth highlighting. Clinical practice in regard to non-genomic testing within the investigative tiers we have analyzed may vary between countries, although it is reflective of practice at the time of the study in Australia. Further, in this study, non-syndromic CAKUT and cases clearly meeting clinical diagnostic criteria for ADPKD were excluded. The dynamic nature of our evolving knowledge about gene-disease and variant-disease associations is, indeed, challenging but has benefited from the emergence of international guidelines and considerable efforts to harmonize interpretation at national and international level. Reclassifications of Likely Pathogenic variants to Variant

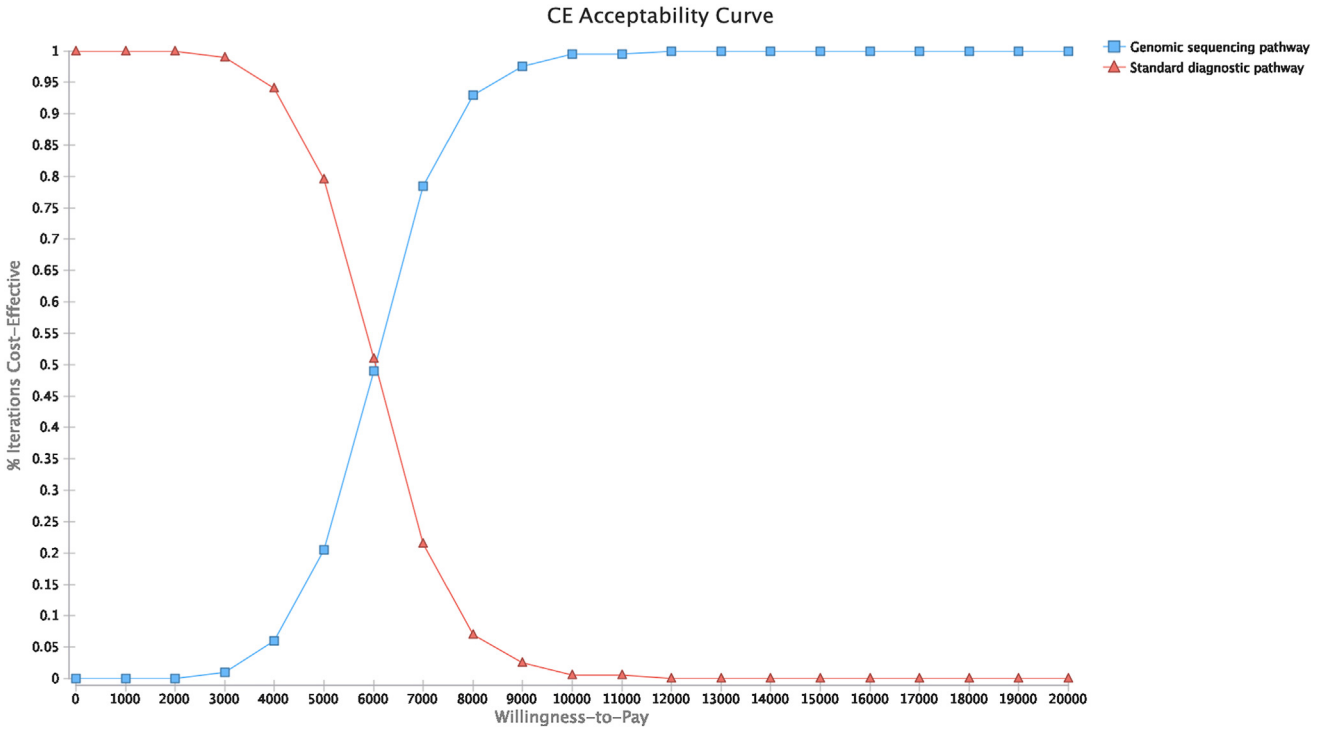

Figure 1 Cost-effectiveness acceptability curve – Analysis 1. Note: The graph plots the probability of genomic sequencing pathway or standard diagnostic pathway being cost-effective across a range of willingness to pay values per additional diagnosis.

of Uncertain Significance/Likely Benign/Benign classifications are extremely rare. A 3-year study of the ClinVar database identified that only 2.16% of Likely Pathogenic variants were reclassified, and of those, around 80% were reclassified to Pathogenic status.[38] We adopted a health care system perspective, as recommended by MSAC in Australia and other HTA bodies internationally, but rare diseases commonly involve significant societal costs, for example, out-of-pocket expenses and productivity impacts for caring responsibilities, as well as for patients' absenteeism and presenteeism.[39] Inclusion of such societal costs could have improved the cost-effectiveness estimates for genomic testing. Although the inclusion of the longer-term implications of genomic diagnosis is valuable,[40] limited data availability meant that certain assumptions had to be made. For example, in the ADPKD Markov model, the transition probabilities and treatment effect were assumed to be the same in adults and children, although the values were derived from a study in adult patients. Also, in the Alport Markov model, the transitions between each of the CKD stages could not have been modeled, and instead a single health state was assumed to represent CKD stages 1 to 4. However, our modelling incorporated uncertainty in parameters and comprehensive deterministic and probabilistic sensitivity analyses were conducted to reinforce the generalizability of our findings.

In conclusion, our study assessed the relative cost-effectiveness of genomic testing for suspected childhood- and adult-onset genetic kidney conditions compared with non-genomic (standard) diagnostic investigations from an Australian health care system perspective. The study relied on evidence from a large national cohort in Australia, comprising children and adults suspected with 1 or more of the following GKDs: monogenic glomerular disease, cystic disease, CAKUT, tubular disease, and complement disorders. We further performed analyses by age and clinical subgroups, with decision uncertainty being effectively incorporated. On average, genomic testing could be argued as cost-effective across individuals suspected with GKD. Subgroup analyses identified that genomic testing was cost saving for individuals with suspected glomerular diseases, whereas no evidence of cost-effectiveness was found for non-glomerular diseases, potentially apart from childhood cystic diseases and only potentially in Analysis 1. These findings support a clear and evidence-based proposition for the implementation of genomic testing for glomerular GKD in clinical practice. No clear evidence of cost-effectiveness was identified for non-glomerular diseases, but the evidence-base for these conditions is very scarce, and our study may not have been powered enough to identify significant differences in the health economic outcomes of genomic testing for these conditions. In the rapidly evolving paradigm of genetic diagnosis and therapy, the value proposition of genomic testing for non-glomerular diseases may change. Within the paradigm of value-based health care, we suggest that equitable access and implementation for genomic testing for GKD be considered in the contest of evolving evidence and be supported by clinician education and training.

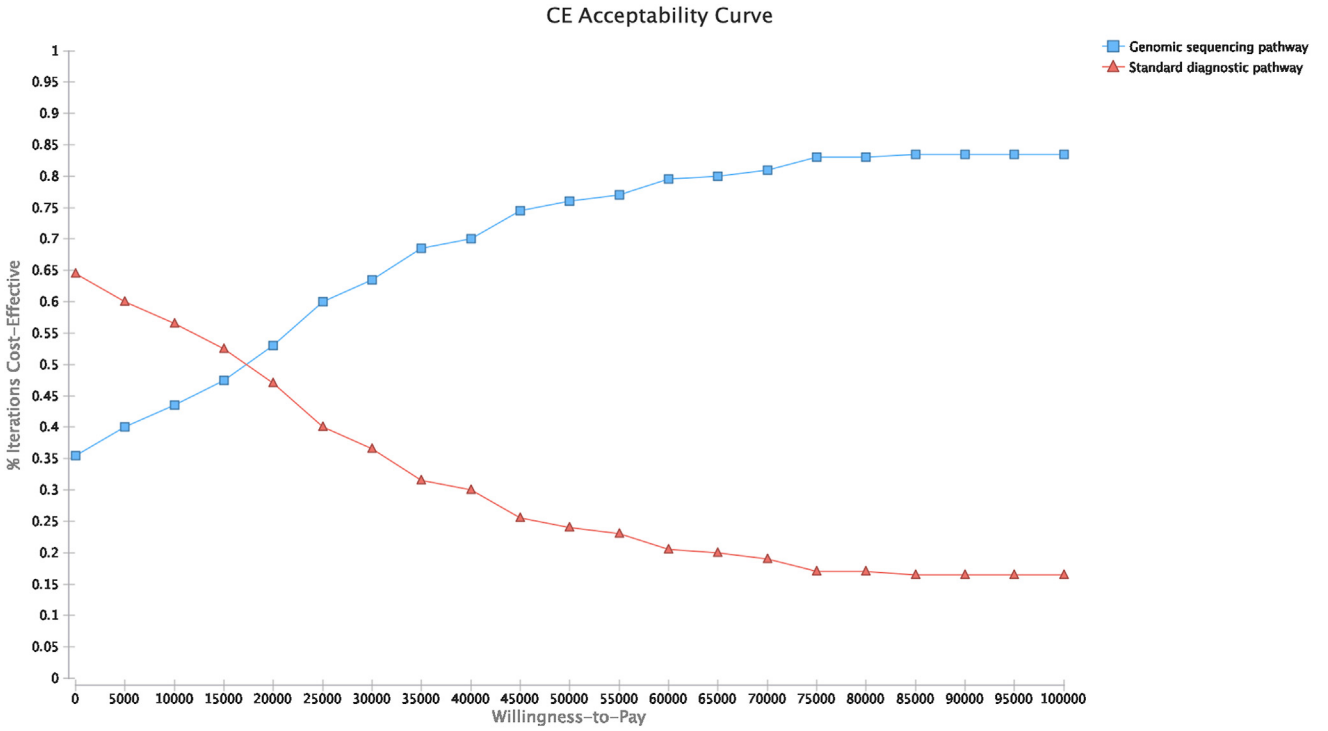

Figure 2 Cost-effectiveness acceptability curve – Analysis 2. Note: The graph plots the probability of genomic sequencing pathway or standard diagnostic pathway being cost-effective across a range of willingness to pay values per QALY gain.

Data Availability

All relevant data are listed within the paper and its supporting information files.

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Ethics Declaration

Ethical approval was granted from the Melbourne Health Human Research Ethics Committee (approval HREC/16/MH/251), which served as the central research ethics committee for this study as part of the overarching AGHA protocol. This included specific approval for this cohort study and this health economic analysis within that cohort study. Informed written consent was obtained from all participants including their parents or legal guardians as

required. All clinical data collected were de-identified and the study adhered to the principles set out in the Declaration of Heslinki. Because the potential for organ transplant recipients to participate was enabled, the clinical study also complied with the Declaration of Istanbul.

Conflict of Interest

Andrew J. Mallett received grants from Medical Research Future Fund, Sanofi-Genzyme, and Queensland Technology Futures Fund, and support for attending meetings from Otsuka Australia, holds leadership role in KidGen Collaborative, RACP Foundation, and Townsville Hospital & Health Service, and has other non-financial interests in Sanofi, Reata, and Dicerna. Hugh McCarthy received grant from Royal Australasian College of Physicians. Peter G. Kerr received a grant from NHMRC (Australia) and payment for presentations and manuscript writing from Astra Zeneca, participates on REDUCCTION Trial Data Safety Monitoring Board, and holds the Treasurer role in ANZ Society of Nephrology. All other authors declare no conflicts of interest.

Additional Information

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References

1. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. *Nephrol Dial Transplant*. 2012;27(suppl_3):iii73-iii80. https://doi.org/10.1093/ndt/gfs269
2. Saran R, Robinson B, Abbott KC, et al. US renal data system 2017 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2018;71(3):A7.
3. Fiorentino M, Bolignano D, Tesar V, et al. Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies. *Nephrol Dial Transplant*. 2017;32(1):97-110. http://doi.org/10.1093/ndt/gfw070
4. Hogan JJ, Mocanu M, Berns JS. The native kidney biopsy: update and evidence for best practice. *Clin J Am Soc Nephrol*. 2016;11(2):354-362. http://doi.org/10.2215/CJN.05750515
5. Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). ANZDATA 44th annual report. Adelaide, Australia: ANZDATA; 2021.
6. UK Renal Registry. United Kingdom Renal Registry 23rd annual report. Bristol, United Kingdom: United Kingdom Kidney Association; 2021.
7. Mann N, Braun DA, Amann K, et al. Whole-exome sequencing enables a precision medicine approach for kidney transplant recipients. *J Am Soc Nephrol*. 2019;30(2):201-215. http://doi.org/10.1681/ASN.2018060575
8. Chen J, Lin F, Zhai Y, et al. Diagnostic and clinical utility of genetic testing in children with kidney failure. *Pediatr Nephrol*. 2021;36(11):3653-3662. http://doi.org/10.1007/s00467-021-05141-5
9. Jayasinghe K, Stark Z, Kerr PG, et al. Clinical impact of genomic testing in patients with suspected monogenic kidney disease. *Genet Med*. 2021;23(1):183-191. http://doi.org/10.1038/s41436-020-00963-4
10. Tanudisastro HA, Holman K, Ho G, et al. Australia and New Zealand renal gene panel testing in routine clinical practice of 542 families. *npj Genom Med*. 2021;6(1):20. http://doi.org/10.1038/s41525-021-00184-x
11. Jayasinghe K, Wu Y, Stark Z, et al. Cost-effectiveness of targeted exome analysis as a diagnostic test in glomerular diseases. *Kidney Int Rep*. 2021;6(11):2850-2861. http://doi.org/10.1016/j.ekir.2021.08.028
12. Jayasinghe K, Stark Z, Patel C, et al. Comprehensive evaluation of a prospective Australian patient cohort with suspected genetic kidney disease undergoing clinical genomic testing: a study protocol. *BMJ Open*. 2019;9(8):e029541. http://doi.org/10.1136/bmjopen-2019-029541
13. Ahn W, Bomback AS. Approach to diagnosis and management of primary glomerular diseases due to podocytopathies in adults: core curriculum 2020. *Am J Kidney Dis*. 2020;75(6):955-964. http://doi.org/10.1053/j.ajkd.2019.12.019
14. Savige J, Ariani F, Mari F, et al. Expert consensus guidelines for the genetic diagnosis of Alport syndrome. *Pediatr Nephrol*. 2019;34(7):1175-1189. http://doi.org/10.1007/s00467-018-3985-4
15. Stevens PE, Levin A. Kidney Disease: improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158(11):825-830. http://doi.org/10.7326/0003-4819-158-11-201306040-00007
16. Trautmann A, Vivarelli M, Samuel S, et al. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome. *Pediatr Nephrol*. 2020;35(8):1529-1561. http://doi.org/10.1007/s00467-020-04519-1

17. Jayasinghe KC, Quinlan C, Mallett AJ. Australian genomics and Melbourne genomics renal genetics flagships, collaborative; tK. Nationwide diagnostic yield of clinical genomics in patients with suspected genetic kidney disease (FR-PR070). *J Am Soc Nephrol*. Vol 302019:60.
18. Torres VE, Higashihara E, Devuyst O, et al. Effect of tolvaptan in autosomal dominant polycystic kidney disease by CKD stage: results from the TEMPO 3: 4 trial. *Clin J Am Soc Nephrol*. 2016;11(5):803-811. http://doi.org/10.2215/CJN.06300615
19. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med*. 2017;377(20):1930-1942. http://doi.org/10.1056/NEJMoa1710030
20. Gross O, Licht C, Anders HJ, et al. Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. *Kidney Int*. 2012;81(5):494-501. http://doi.org/10.1038/ki.2011.407
21. Johnson CA, Levey AS, Coresh J, Levin A, Lau JGL, Eknoyan G. Clinical practice guidelines for chronic kidney disease in adults: part 1. Definition, disease stages, evaluation, treatment, and risk factors. *Am Fam Physician*. 2004;70(5):869-876.
22. Stark Z, Foulger RE, Williams E, et al. Scaling national and international improvement in virtual gene panel curation via a collaborative approach to discordance resolution. *Am J Hum Genet*. 2021;108(9):1551-1557. http://doi.org/10.1016/j.ajhg.2021.06.020
23. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296-1305. http://doi.org/10.1056/NEJMoa041031
24. Australian Bureau of Statistics. Life Tables, States, Territories and Australia; 2016-20182019.
25. Wyld ML, Lee CM, Zhuo X, et al. Cost to government and society of chronic kidney disease stage 1-5: a national cohort study. *Intern Med J*. 2015;45(7):741-747. http://doi.org/10.1111/imj.12797
26. Cass A, Chadban S, Gallagher M. The Economic Impact of End-Stage Kidney Disease in Australia: Projections to 2020. *Kidney Health Australia*; 2010:1-68.
27. ANZDATA registry [42nd report], Chapter 2. Prevalence of Renal Replacement Therapy for End Stage Kidney Disease. Adelaide, Australia: Australia and New Zealand Dialysis and Transplant Registry; 2019.
28. Eriksson D, Karlsson L, Eklund O, et al. Health-related quality of life across all stages of autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2017;32(12):2106-2111. http://doi.org/10.1093/ndt/gfw335
29. Radford J, Kitsos A, Stankovich J, et al. Epidemiology of chronic kidney disease in Australian general practice: National Prescribing Service MedicineWise MedicineInsight dataset. *Nephrology (Carlton)*. 2019;24(10):1017-1025. http://doi.org/10.1111/nep.13537
30. Gorodetskaya I, Zenios S, Mcculloch CE, et al. Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney Int*. 2005;68(6):2801-2808. http://doi.org/10.1111/j.1523-1755.2005.00752.x
31. Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–7. *Med Decis Making*. 2012;32(5):733-743. http://doi.org/10.1177/0272989X12454579
32. Erickson KF, Chertow GM, Goldhaber-Fiebert JD. Cost-effectiveness of tolvaptan in autosomal dominant polycystic kidney disease. *Ann Intern Med*. 2013;159(6):382-389. http://doi.org/10.7326/0003-4819-159-6-201309170-00004
33. Pharmaceutical Benefits Advisory Committee (PBAC). Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee. In: Australian Department of Health and Ageing, ed. Canberra, Australia2016.
34. Wang S, Gum D, Merlin T. Comparing the ICERs in medicine reimbursement submissions to NICE and PBAC-does the presence of an explicit threshold affect the ICER proposed? *Value Health*. 2018;21(8):938-943. http://doi.org/10.1016/j.jval.2018.01.017
35. Meng Y, Clarke PM, Goranitis I. The value of genomic testing: a contingent valuation across six child- and adult-onset genetic conditions. *Pharmacoeconomics*. 2022;40(2):215-223. http://doi.org/10.1007/s40273-021-01103-9
36. Goranitis I, Best S, Christodoulou J, Stark Z, Boughtwood T. The personal utility and uptake of genomic sequencing in pediatric and adult conditions: eliciting societal preferences with three discrete choice experiments. *Genet Med*. 2020;22(8):1311-1319. http://doi.org/10.1038/s41436-020-0809-2
37. Harris AH, Hill SR, Chin G, Li JJ, Walkom E. The role of value for money in public insurance coverage decisions for drugs in Australia: a retrospective analysis 1994-2004. *Med Decis Making*. 2008;28(5):713-722. http://doi.org/10.1177/0272989X08315247
38. Harrison SM, Rehm HL. Is "likely pathogenic" really 90% likely? Reclassification data in ClinVar. *Genome Med*. 2019;11(1):72. http://doi.org/10.1186/s13073-019-0688-9
39. Dragojlovic N, van Karnebeek CDM, Ghani A, et al. The cost trajectory of the diagnostic care pathway for children with suspected genetic disorders. *Genet Med*. 2020;22(2):292-300. http://doi.org/10.1038/s41436-019-0635-6
40. Belsey J, Chaihorsky L, Currie G, Goranitis I, Marshall D. Global data access for solving rare disease: a health economics value framework. http://www3.weforum.org/docs/WEF_Global_Data_Access_for_Solving_Rare_Disease_Report_2020.pdfWEF. In: ed2020.