Supplementary Material

Table of Contents

Appendix 1: Baseline characteristics of patients with suspected monogenic glomerular disease

	Total (N=87)
Characteristic	**number of patients (percent)**
Age at study entry, median (range)	35 (1 -72 years)
Age at study entry	
0-17 years	24
>=18 years	63
Age at first presentation to nephrology, median (range)	21 (7 months to 62 years)
Male	39 (44.8)
Ethnicity	
Caucasian	57 (65.5)
Asian	12 (13.8)
North African/Middle Eastern	5 (5.8)
Other[b]	11 (12.6)
Unknown	2 (2.3)
Dialysis	8 (9.2)
Transplant[a]	16 (18.4)
Parental consanguinity **(**self-reported**)**	3 (3.5)
Family history of renal disease	54 (67.5)
Extra renal manifestations	20 (23.0)
Clinical Diagnosis Subgroup	
Alport	43 (49.4)
Other Hematuria	5 (5.75)
Nephrotic Syndrome	39 (44.8)

[a]1 patient had a failed kidney transplant requiring dialysis (included in Dialysis)

[b]Other includes 4 patients with 'mixed' ethnicity, 2 patients from Sub-Saharan Africa. 2 Maori/Pacific Islander, 1 Other- Oceanian, 2 'People of the Americas'

Appendix 2

Detailed methods

The analysis drew upon a pragmatic, multicenter prospective study of 204 patients with suspected monogenic kidney disease who attended four tertiary public hospital sites in Melbourne, Australia[1] for exome sequencing via a multidisciplinary renal genetics clinic. Clinical data from the previously published cohort study was used to inform the model parameters, such as diagnostic yield and resource use. The full study design, methodology and clinical outcomes have been published previously[1]. In brief, the cohort study assessed the diagnostic utility and short-term clinical utility for patients with suspected monogenic kidney disease. Patients were recruited to one of four multidisciplinary renal genetic clinics (RGC) based at tertiary hospitals in Melbourne, Australia from July 2017 to September 2018 if they had suspected monogenic kidney disease as assessed by the multidisciplinary RGC team. Detailed data outlining results of previous diagnostic investigations, including biopsy were available and used to inform the cost-effectiveness analysis.

The economic evaluation drew upon primary diagnostic and clinical evidence of patients with suspected MKD that fell into one of the following clinical subgroups: Alport Syndrome (AS), nephrotic syndrome or other glomerular disease at the time of referral for genomic sequencing. These groups were selected because there was a well-defined diagnostic pathway[2,3] that is less heterogenous compared with other disease groups. Resource use for non-genomic investigations was informed by data from the cohort, in addition to current guidelines and published literature[2-7]. Based on current available evidence[2,7], the patient groups included in this study were deemed unlikely to have significant changes in management following test result, regardless of whether or not they had a molecular diagnosis.

This study was approved by the Human Research Ethics Committee at Melbourne Health (2016.224) and site-specific research governance approval was obtained from all participating hospitals. All patients or their guardians provided written informed consent for clinical ES and participation in the study.

Decision Model

A decision tree was used to model six diagnostic strategies which reflect current practice and recommended models of care based on other cohorts[8]: (1) non genomic investigations, (2) late gene panel followed by ES, (3) late ES, (4) early gene panel, (5) early gene panel followed by ES and (6) early ES (figure 1, supplementary figure 1). The model was developed in TreeAge Pro Healthcare 2020[9].

Standard diagnostic pathway

First, we considered non-genomic investigations (NGIs), as at the time of the study, genomic testing was not funded in the Australian healthcare system. In the previously described study[1], patients were categorized by clinical subgroup, depending on their presenting clinical features, and the suspected diagnosis at the time or referral to the RGC. All children with nephrotic syndrome had already failed to respond to at least 6-weeks of steroid therapy at the time of review. Given that most nephrology patients with hematuria and/or proteinuria have standard nephrology investigations, a team of eight nephrologists (including four who were not involved with the study) generated a NGI pathway for patients with glomerular disease. These pathways were based on standard order sets in the electronic medical record used at the study sites, published guidelines and literature[2-7]. Where there was debate regarding standard practice, this was resolved by discussion among the team. Investigations were divided into three tiers: 1) baseline investigations which established the clinical differential of glomerular disease and/or required prior to genomic testing, 2) complex non-invasive investigations, and 3) complex invasive investigations (Table 1). Supplementary appendix 2 provides details the costs of all investigations.

We mapped a diagnostic pathway that was standardized for all adults presenting with glomerular disease, and two pathways for children with glomerular disease (one for AS/other suspected glomerular disease, another for steroid resistant nephrotic syndrome, Table 1 and Supplementary appendix 2). Adult and pediatric patients were modelled separately to reflect differences in the diagnostic investigations performed. A team of nephrologists agreed that a reasonable mean biopsy rate in adults and children with glomerular disease was 70% and 80% respectively (range 50-100%). This rate was consistent with the biopsies that were either planned or already

performed in the cohort at study entry (68% in adults and 96% in children). A detailed list of assumptions for the modelled pathways can be found in supplementary appendix 3.

Genomic sequencing pathways

We modelled five genomic sequencing strategies to compare to NGIs (Figure 1). When modelling late integration of genomic sequencing, we assumed that the majority of patients (95%) with suspected monogenic kidney disease would still need to undergo genomic sequencing, given that a clinical diagnosis is not precise, even following renal biopsy (for example, even if the biopsy was diagnostic for AS, it would not determine the inheritance pattern, which is an important consideration for many clinical scenarios). In suspected AS, patients were modelled to undergo the 3 gene panel that is currently funded by the Australian healthcare system[10]. In other cases, gene panels included Renal Glomerular Disease (PanelApp Australia version 0.174, 60 genes), and Proteinuria (PanelApp Australia version 0.112, 55 genes) based on the currently available consensus diagnostic gene panels[11]. Procedures for ES, variant detection and filtering and analysis are already described[1]. In brief, the whole exome was sequenced, but variants in genes associated with the patient's specific disease category (e.g., glomerular disease) were evaluated using a tiered approach. If no variants were identified, analysis was expanded upto a maximum of 100 genes associated with glomerular kidney disease, depending on the patient's phenotype[12]. We assumed that a proportion of patients will still require some Tier 2 tests to clarify the genetic diagnosis, (whether positive or negative following genomic sequencing, see Figure 2, supplementary appendix 3).

First, we considered exhausting NGIs followed by panel testing ; if panel testing was non-diagnostic, ES would be performed as the final test. Second, we considered exhausting all NGIs followed by ES (Model 2). In Model 3, patients had early genomic sequencing (after Tier 1 tests), in the form of panel testing only, followed by ES in unresolved cases. In Model 4, patients had early panel testing only. Finally, in Model 5, we considered early ES following Tier 1 tests in all patients. Figure 1 summarizes the NGIs and five modelled strategies.

Cascade testing

We also considered the overall effect of subsequent cascade testing in family members of the proband. We only considered the benefit to family members of a molecularly diagnosed proband, who accepted cascade testing (supplementary figure 3). Using data from the cohort[1], we were able to ascertain the proportion of patients who were recommended cascade testing, how many members were offered cascade testing in those families, and the diagnostic rate in the family members based on the inheritance pattern of the probands (supplementary appendix 4). We assumed an uptake rate of 25% for cascade testing, on the basis of the following assumptions: 30% chance of having a genomic diagnosis, moderate severity of condition, no availability of preventative or treatment options, very likely to improve the process of medical care[13]. In NGIs (i.e. when cascade testing was not offered given there was no genetic diagnosis), we assumed that family members of those with suspected genetic kidney disease would have a better diagnostic yield than the proband (50%) when they became symptomatic, with less NGIs (as multiple affected family members would help identify the inheritance). We also assumed that patients who were found to have a genomic diagnosis following cascade testing would need additional surveillance for 10 years and included these costs in the analysis. All assumptions for the cascade testing pathway can be found supplementary appendix 4).

Costs

We calculated costs, by identifying resources that were used to provide a service related to the diagnostic test and assigning a value to each of those resources. We obtained the costs of biopsies from the hospital (Monash Medical Centre, Melbourne, Australia for adults and the Royal Children's Hospital, Melbourne, Australia for pediatric patients), and the Medicare Benefits Schedule[10], and testing laboratories for all other investigations. The cost of a diagnostic trial of medication was sourced from the Pharmaceutical Benefits Scheme[14]. All costs were in 2019 Australian dollars (1AUD = 0.73USD on 30/9/2019)[15]. We excluded costs related to nephrology reviews, as patients were still likely to have regular nephrology follow up regardless of the diagnostic approach. We also excluded the costs of baseline investigations that were required prior to referral for genomic testing (Tier 1 tests), as they were common across all five pathways, and therefore they do not affect the outcomes of the incremental cost-effectiveness

estimates in the analysis. The renal biopsy contributed to the bulk of diagnostic costs (supplementary appendix 2).

The cost of the genomic sequencing pathways included the cost of genomic sequencing, two genetics clinic consultations with a clinical geneticist and a genetic counselor and a proportion of Tier 2 tests. The cost of ES with targeted analysis of up to 100 genes was AU$1200, and the cost of the gene panels for all three subgroups was also AU$1200. The combined costs of initial and follow-up appointments with clinical geneticists/genetic counsellors were AU$820 and AU$330 respectively. Table 1 and supplementary appendix 2 describe details of items included in genomic pathways. For the cascade testing pathway, an annual discount rate of 5% was applied for costs[16].

Outcomes

Model outcomes included cost per successful diagnosis and the net benefit, which represents the difference between the monetary value of benefits and monetary value of costs. The diagnostic rates of the genomic sequencing strategies were sourced from the previously described cohort[1]. A positive molecular diagnosis was considered when a pathogenic or likely pathogenic variant/s were found according to current ACMG criteria[17]. Patients who could have been diagnosed from panel testing were determined by comparing the current available gene lists[11] (supplementary appendix 5) for each clinical subgroup to the pathological variant/s identified through ES. A diagnosis from the NGIs was considered correct if the diagnosis at referral was the same as the molecular diagnosis following ES, *and* if the suspected mode of inheritance entered prior to ES was also correct. If there was more than one differential diagnosis suspected, this was considered incorrect (ES resulted in clarification of the diagnosis and removed diagnostic uncertainty).

There is ongoing debate on the use of the word ‘autosomal dominant AS’ for individuals with heterozygous *COL4A3* or *COL4A4* variants. For this analysis, we assumed that the referring diagnosis was correct if these patients were deemed to have ‘thin basement nephropathy’ or ‘AS’ at referral if the inheritance pattern was correct. This would give the most conservative estimate of the diagnostic utility of ES, and it is consistent with the most recently published expert consensus guidelines on AS[7].

Given that none of the children would have been correctly diagnosed in the NGIs pathway according to results from our cohort, in the base case analysis, we assumed that the diagnostic yield was 50% of the yield from NGIs in the adult cohort (we assumed that children may present earlier and have less specific features on investigations, including renal biopsy, compared to adults). This parameter was varied in the sensitivity analysis to reflect uncertainty of the diagnostic yield from NGIs in pediatric patients[18-20].

Two different approaches were used to estimate the incremental willingness to pay (WTP) of ES relative to NGIs. The first relied on a contingent valuation exercise whereby participants indicated their maximum WTP on a payment card (supplementary appendix 8). The payment card presented values ranging between (AU$500-8,000), with AU$500 increments, and included an open-ended question that enabled respondents to indicate a WTP that was not listed on the card. WTP data were analyzed using linear regression methods. Given that only 38 (44%) of participants responded to the WTP question, and without significant evidence that the WTP estimates differed between pediatric and adult participants, one WTP estimate was generated for the whole sample (Table 3). The second approach relied on an estimation of WTP using the compensating variation formula[21], based on the estimated marginal utilities reported in the study by Goranitis et al 2020[13], assuming a 30% chance of having a genomic diagnosis, moderate severity of condition, no availability of preventative or treatment options, and very likely chance of improving the process of patient's medical care. The outcome 'improving the process of patient's medical care' was described by evidence that were identified from a previous qualitative study[22]. Some of these well recognized benefits to improving patient care in the kidney context could include donor selection/reproductive planning/informing surveillance and prognostic information..

Economic Evaluation

An incremental cost-effectiveness analysis comparing genomic sequencing strategies to NGIs was performed. The probability of a correct diagnosis using genomic and non-genomic investigations were based on the outcomes of the previously published cohort study[1]. The economic evaluation was undertaken from the Australian health care system perspective, with a time horizon of 12 months (from presentation to three months following test result). The time

horizon was considered similar in both genomic and non-genomic arms, as although non-genomic investigations occur sequentially in a more protracted course, the results are returned faster compared to the standard turnaround time of 3-6 months for genomic results[1]. The costs of the NGIs, gene panel and ES pathways, the diagnostic yield for each pathway and the cost per diagnosis were calculated. The results are presented as incremental cost-effectiveness ratios (ICERs), defined as incremental cost per additional diagnosis, and the net monetary benefit. The base case analysis incorporated assumptions which are listed in supplementary appendix 3.

Sensitivity analyses were performed to test the robustness of the results. One-way sensitivity analyses were applied to assess the impact of varying the key cost and effectiveness parameters and assumptions over a range of values on the results and presented in a tornado diagram. With regards to the cascade testing pathway, sensitivity analyses were also performed to examine the effect of a higher rate (at 70% and 90%) of family members who are correctly diagnosed using the NGIs pathway. Probabilistic sensitivity analysis was conducted to explore the impact of joint uncertainty around model inputs (distribution of the model parameters is listed in supplementary appendix 6) using a second-order Monte Carlo simulation. Cost-effectiveness acceptability curves (CEAC) were plotted to present the probability of each intervention being cost-effective across a range of willingness to pay thresholds per additional diagnosis.

Appendix 3

Table 1: Costs of genomic sequencing and clinical consultations- adults and children

Item	Unit cost	Total cost	Source
Total cost of exome sequencing plus clinical consultation		2350	
Average cost of exome sequencing in cohort	1200.00		VCGS price list 2020
Clinical geneticist appointment (initial)	457.59		Stark et al., 2017
Clinical geneticist appointment (review)	366.07		Stark et al., 2017
Genetic counsellor appointment (initial)	183.96		Stark et al., 2017
Genetic counsellor appointment (review)	147.17		Stark et al., 2017
	1154.79		
Cost of a gene panel pathway		2350	
Cost of alport panel	1200.00		MBS item 73298
Clinical geneticist appointment (initial)	457.59		Stark et al., 2017
Clinical geneticist appointment (review)	366.07		Stark et al., 2017
Genetic counsellor appointment (initial)	183.96		Stark et al., 2017
Genetic counsellor appointment (review)	147.17		Stark et al., 2017

Table 1a: VCGS price list 2020

Exome	Cost
1-15 genes (Alport list)	$1,000
15-100 genes (glomerular and proteinuria lsits)	$1,200
101-200 genes	$1,800
201-400 genes (Kidneyome)	$2,400
>400 genes (Mendeliome)	$3,100

Table 2: Standard pathway, tier 2 costs: Adults with suspected glomerular diseases

Glomerular Screen (attribute 90% of costs below)			
Test	Unit cost	Quantity	Cost
coagulation screen (INR, APTT, fibrinogen,)	27.85	1	27.85
calcium, magnesium, phosphate	13.65	1	13.65
lipid profile	11.65	1	11.65
HbA1C	16.8	1	16.8
repeat urine microscopy	20.55	1	20.55
repeat urine albumin to creatinine ratio	11.65	1	11.65
Hepatitis B serology	29.25	1	29.25
Hepatitis C serology	15.65	1	15.65
HIV serology	15.65	1	15.65
ANA	24.45	1	24.45
DsDNA	26.5	1	26.5
C3, C4	28.95	1	28.95
ANCA	34.55	1	34.55
Anti ENA	17.4	1	17.4
SPEP	32.9	1	32.9
serum FLC	59.6	1	59.6
Beta-2-microglobulin	20.1	1	20.1
Rheumatoid factor	11.3	1	11.3
cryoglobulins	20.75	1	20.75
anti-GBM antibody	34.55	1	34.55
ESR	7.85	1	7.85
CRP	9.7	1	9.7
ASOT	15.65	1	15.65
anti-Dnase	15.65	1	15.65
syphillis serology	15.65	1	15.65
anti-PLA2R AB*	17.35	1	17.35
LFT	17.7	1	17.7
Other			
opthalmology*only applicable for AS patients	155.6	1	155.6
audiology*only applicable for AS patients	155.6	1	155.6

Table 3: Standard pathway, tier 2 costs: Children with suspected Alport syndrome/other haematuria

Glomerular Screen (attribute 80% of costs below)			
Test	Unit cost	Quantity	Cost
coagulation screen	27.85	1	27.85
calcium, magnesium, phosphate	13.65	1	13.65
repeat urine microscopy	20.55	1	20.55
repeat urine albumin to creatinine ratio	11.65	1	11.65
Hepatitis B serology	29.25	1	29.25
Hepatitis C serology	15.65	1	15.65
HIV serology	15.65	1	15.65
ANA	24.45	1	24.45
DsDNA	26.5	1	26.5
C3, C4	28.95	1	28.95
ANCA	34.55	1	34.55
spot urine calcium: creatinine	11.65	1	11.65
Anti ENA	17.4	1	17.4
cryoglobulins	20.75	1	20.75
anti-GBM antibody	34.55	1	34.55
ESR	7.85	1	7.85
CRP	9.7	1	9.7
ASOT	15.65	1	15.65
anti-Dnase	15.65	1	15.65
Urine microscopy for parents (x2 and GP review x2)	20.55	2	41.1
Subtotal			
Other			
ophthalmology*only applicable for AS patients	155.6	1	155.6
audiology*only applicable for AS patients	155.6	1	155.6

Table 4: Standard pathway, tier 2 costs: Children with suspected steroid resistance nephrotic syndrome

Glomerular Screen (attribute 80% of costs below)			
Test	Unit cost	Quantity	Cost
Hb Electrophoresis (sickle cell disease)	96.6	1	96.6
HIV 1/2 serology	15.65	1	15.65
Hepatitis B serology	29.25	1	29.25
interferon gamma release assay for detection of latent TB	34.9	1	34.9
spot urine Ca/Creatinine ratio	11.65	1	11.65
repeat urine albumin creatinine ratio	11.65	1	11.65
CRP	9.7	1	9.7
INR, aPTT, fibrinogen, AT III	35.5	1	35.5
IgG	14.55	1	14.55
glucose	9.7	1	9.7
C3, C4	28.95	1	28.95
ANA	24.45	1	24.45
ultrasound abdomen	111.3	1	111.3

Table 5: Standard pathway, tier 3 costs for adults

Test	Unit cost	Quantity	Cost
renal biopsy[a]	1676.731	1	**1676.731**
if isolated hematuria[b]:			
CTKUB in 50%	385	1	385
urology review in 50% of patients	88.25	1	88.25
cystoscopy in 50% of patients	233.55	1	233.55
urine cytology (x3) in all patients	94.7	3	284.1

[a]based on 10 representative adult patients
[b]2 adults had isolated haematuria in cohort (0.03)

Table 6: Standard pathway, tier 3 costs for children with suspected Alport syndrome or other haematuria

Test	Unit cost	Quantity	Cost
renal biopsy[a]	5837.254	1	5837.254
if macrohaematuria present[b]			
urology review	88.25	1	88.25
doppler ultrasound of bladder and kidneys	169.5	1	169.5

[a]based on 10 representative paediatric patients
[b]4 children had isolated haematuria in cohort (0.17)

Table 7: Standard pathway, tier 3 costs for children with suspected steroid resistant nephrotic syndrome

Test	Unit cost	Quantity	Cost
renal biopsy[a]	5837.254	1	5837.254
Diagnostic trial of immunosuppression in 90% of patients)			
Drug cost[b]	1621.88	1	1621.88
Drug monitoring	208.80	1	208.80
Rituximab in 50% of patients who did not respond to tacrolimus	1246.71	2	2493.42
Drug cost[d]			
Baseline test required before rituximab[e]	1935.73	1	1935.73

[a]based on 10 representative paediatric patients
[b] tacrolimus 0.15mg/kg/day (average 20kg) for 6 months
[c]weekly tacrolimus trough for 4 weeks then 3 monthly (average 6 tests over 6 months)
[d]dose is 375mgx2, use 500mg/50ml vials x2
[e]includes 1x bone density scan, 1x ophthalmology review for cataracts, lymphocyte subsets at baseline and monthly (total 6), immunoglobulins- all 4 subclasses at baseline and monthly (total 6), bactrim 5mg/kg to maximum dose of 160/800mg 3x weekly

Appendix 4
Model parameters and distributions

Description of parameter	Adults	Distribution	Children	Distribution
Proportion of patients with genetic kidney disease	0.37	Beta (23,40)	0.42	Beta(10,14)
Probability of diagnosis with ES in patients with genetic kidney disease	1.00		1.00	
Probability of diagnosis using gene panel testing in patients with genetic kidney disease	0.87	Beta (20,3)	0.80	Beta(8,2)
Probability of receiving a correct clinical diagnosis from NGIs in patients with GKD	0.52	Beta (12,11)	0.40	Beta(4,6)
Probability of receiving a correct suspected inheritance pattern from NGIs in patients with GKD and correct clinical diagnosis	0.42	Beta (5,7)	0.24	Beta(2.5,8.0)
Proportion of patients who have biopsy	0.70	Beta (44.1,18.9)	0.80	Beta(10.8,2.7)
Proportion of patients with isolated haematuria	0.03	Beta (2,61)		
Proportion with isolated macrohaematuria among AS and glom (other) patients			0.22	Beta(4,14)
Proportion of patients with Alport phenotype	0.44	Beta (28,35)	0.63	Beta(15,9)
Proportion of patients with nephrotic phenotype	0.52	Beta (33,30)	0.25	Beta(6,18)
Proportion of patients with 'other glomerular disease' phenotype	0.03	Beta (2,6)	0.13	Beta(3,21)
Proportion of Tier 2 tests ordered	0.90	Beta (28.6,3.2)	0.80	Beta(10.7,2.7)
Proportion of children with steroid resistant nephrotic syndrome who have immunosuppression trial			0.90	Beta(28.6,3.2)
Proportion of patients with Alport genetic diagnosis in GKD patients	0.74	Beta (17,6)	0.80	Beta(8,2)
Proportion of patients who have gene panel/ES in late GS following Tier 3 tests	0.95	Beta (14.0,0.7)	0.95	Beta(14.6,0.7)
Proportion of patients who may still require Tier 2 tests in early GS following a positive diagnosis from GS	0.50	Beta (4.5,4.5)	0.20	Beta(2.7,10.7)
Proportion of patients who may still require Tier 2 and 3 tests in early GS following a negative diagnosis from GS	0.80	Beta (6.3,1.6)	1 in nephrotic, 0.6 in AS	Beta(5.1,2.2)

Appendix 5

Table 1: Assumptions for parameters included in cascade testing pathway

assumption	result	comment
Genomic pathway		
probands from the cohort that would be recommended to undergo cascade testing	22 (probability =0.67)	based on this cohort, see Table 4 for details
the number of family members that would be offered cascade testing	2.2	Based on mean number of family members that may benefit (this entered by the clinicians for each of these 22 patients)
uptake rate of cascade testing by family member	0.25	
probability of positive genomic diagnosis in family member of proband with genetic kidney disease	0.44	mean probability based on inheritance patterns of cohort, see Table 2
average years of additional surveillance required by family member who tests positive on cascade testing	10 years	assumption (conservative)
annual cost of surveillance	average of $878 over 10 years	average cost per patient over 10 years, includes 5% discount rate per year, see 'surveillance costs' for details.
Non-genomic investigations still required in family members who undergo cascade testing	tier 1 tests	family members will still require tier 1 investigations if they become symptomatic (see main manuscript)
Standard pathway		
proportion of family members for investigation once symptomatic	1	assumption (most conservative)
proportion of family members who become symptomatic in childhood	0.2	assumption (conservative)
cost of non-genomic investigations in family member	average of $1350 per family member	same cost as per NGIs in proband, but only 50% biopsy rate
proportion of patients who would be correctly diagnosed using NGIs among family members with monogenic kidney disease	0.5	similar to overall diagnostic rate from cohort, when diagnosis was considered correct if same diagnosis entered (but did not need correct inheritance) sensitivity analysis performed for higher diagnostic rates (0.7 and 0.9) of NGIs in family members

Table 2: Details of families and conditions in the cohort which were used to model cascade testing pathway

Conditions in the cohort recommended for cascade testing	number of patients	proportion of positive family members	mean
X-Linked dominant Alport syndrome	12	0.5	0.27
X-Linked recessive Dent Disease	2	0.25	0.02
Autosomal dominant tubulointerstitial kidney disease	1	0.5	0.02
Autosomal recessive Alport syndrome	1	0.25	0.01
Autosomal recessive nephrotic syndrome	1	0.25	0.01
Autosomal dominant hypoparathyroidism, sensorineural deafness, and renal dysplasia	1	0.5	0.02
Autosomal dominant glomerulopathy with fibronectin deposits	1	0.5	0.02
Autosomal dominant tuberous sclerosis	1	0.5	0.02
Autosomal recessive interstitial nephritis, karyomegalic	1	0.25	0.01
Autosomal dominant angiopathy, hereditary, with nephropathy, aneurysms, and muscle cramps	1	0.5	0.02

Table 3: Surveillance cost for family members who are diagnosed via cascade testing

surveillance costs					
tests	Unit cost	Source	Quantity	Duration (y)	Cost
annual					
urine albumin to creatinine ratio	11.65	MBS Item 66503	1	10	93.99
Urea, Electrolytes, Creatinine	17.7	MBS Item 66503	1	10	142.80
general practitioner review[a]	38.2	MBS Item 66503	1	9	269.99
one off					
Full Blood Examination	16.95	MBS Item 65070	1		16.95
nephrology review	155.6	MBS Item 110	1		155.60
					172.55
one off (only in family members with confirmed Alport syndrome)					
ophthalmology	155.6	MBS Item 110	1		155.60
audiology	155.6	MBS Item 110	1		155.60

[a] from second year onwards

Appendix 6: Refer to separate excel document

Appendix 7. Supplementary Tables: Results of deterministic sensitivity analysis

Parameter description	Adults			Children		
	Base case	Range in SA	ICER	Base case	Range in SA	ICER
Base Case			$5,450			dominant (-$3,230)
Cost of biopsy	$1,677	$1,500 - $3,350	$3439 to $5669	$5,837	$3,000 - $8,750	-$6887 to $332
Cost of ES	$1,200	$800 - $3,100	$4056 to $12106	$1,200	$800 - $3,100	-$4291 to $1810
Cost of gene panel	$1,200	$600 - $1,500	$4208[a] to $5456	$1,200	$600 - $1,500	-$3230 to $3292[b]
Cost of genetics clinic appointment	$1,155	$330 - $1,670	$2569 to $7258	$1,155	$330 - $1,670	-$5418 to -$1864
Proportion of patients with genetic kidney disease	0.37	0.18-0.55 (± 50%)	$3234 to $12253	0.42	0.21-0.63 (± 50%)	-$3598 to -$2158
Probability of receiving a correct clinical diagnosis from NGIs in patients with GKD	0.52	0.52-0.78 (+50%)	$5451 to $6326	0.40	0.4-0.6 (+50%)	-$3409 to -$3230
Probability of receiving a correct suspected inheritance pattern from standard care in patients with GKD and correct clinical diagnosis	0.42			0.24		
Proportion of patients who have biopsy	0.70	0.5 - 1	$4589 to $6034	0.80	0.5 - 1	-$5062 to -$481
Proportion of patients with Alport phenotype	0.44			0.63	0.4-0.8	-$3406 to -$2937
Proportion of Tier 2 tests ordered	0.90	0.5-1	$5375 to $5780	0.80	0.5-1	-$3393 to -$2985
Proportion of children with nephrotic syndrome who have immunosuppression trial				0.90	0.5-1	-$3388 to -$2595
Proportion of patients who have gene panel/ES in late GS following Tier 3 tests	0.95	0.5-1	$5456 to $5456	0.95	0.5-1	-$3230 to -$3230
Proportion of patients who may still require Tier 2 tests in early GS following a positive diagnosis from GS	0.50	0-0.7	$5126 to $5588	0.20	0-0.5	-$3305 to -$3117

Proportion of patients who may still require Tier 2 and 3 tests in early GS following a negative diagnosis from GS	0.80	0.2-0.9	$3176 to $5836	0.7 (1 in nephrotic, 0.6 in AS)	0.2-0.9	-$7843 to -$1384

Parameter description	**Scenario analysis**	
	Test value	ICER
Cost of biopsy	$1,749 with 6.5% complication rate in adults; $6,283 with 5% complication rate in children	$5,369 in adults; early ES is still dominant in children (-$3,790)
Probability of receiving a correct clinical diagnosis from NGIs in patients with GKD	0.8 in children (same dx rate as in adult)	early ES is still dominant in children (-$3,610)
Probability of receiving a correct suspected inheritance pattern from NGIs in patients with GKD and correct clinical diagnosis	1 in adults and children (correct clinical dx as correct diagnosis in NGIs)	$8,927 in adults; early ES is still dominant in children (-$4,870)
Proportion of patients who may still require Tier 2/3 tests in early GS following a positive diagnosis from GS	no patient with diagnosis on ES requires further Tier 2 testing, and 20% of patients with negative diagnosis on ES patients will still require further Tier2 and 3 tests	$2,847 in adult; early ES is dominant in children (-$7,918)

GKD: Genetic kidney disease
SA: Sensitivity Analysis
ES: Exome sequencing
AS: Alport syndrome
ICER: Incremental cost effectiveness ratio, comparing ES to non-genomic investigations, unless otherwise specified
[a]comparing early gene panel to non-genomic investigations
[b]comparing early ES to early gene panel

Appendix 8
PAYMENT CARD WILLINGNESS TO PAY QUESTION (FROM PATIENT SURVEY)

We are interested to know the value that you place on the answers that may come from genomic testing.

Suppose that the genomic test provides you with more certain answers about the cause of the condition, which may be important for your decision to have (more) children, and the future family planning of your children, and may rarely provide information that will help with treatment. Now suppose that you live in a country like the United States where people have to pay for their test.

Please indicate the MAXIMUM amount you would be willing to pay for this genomic test. Note: you will not be asked to actually pay for the test in this study.

What is the <u>MOST</u> you would be prepared to pay for this genomic test?

A. $500
B. $1000
C. $1500
D. $2000
E. $2500
F. $3000
G. $3500
H. $4000
I. $4500
J. $5000
K. $5500
L. $6000
M. $6500
N. $7000
O. $7500
P. $8000
Q. Other (please specify): $……
R. I would NOT be willing to pay for this genomic test

If you **WOULD NOT** be willing to pay for this genomic test, please tell us why:

a) The information is of no value to me and my family ☐
b) Someone else should pay for it (e.g. the Government) ☐
c) I cannot afford it ☐
d) Other (please specify) ☐:
…….

Appendix 9

Estimated willingness to pay for exome sequencing over standard non genomic investigations, using two methods: contingent valuation data and the marginal utility estimates from a published discrete choice experiment.

WILLINGNESS TO PAY (AU$)		**95% confidence interval**
Contingent valuation exercise		
overall	1400	845-1990
Discrete choice experiment		
pediatric mean	4400	4200-4600
pediatric median	3700	3300-4100
adult mean	900	800-1000
adult median	770	740-800

*note: results for pediatric and adult in the contingent valuation exercise were similar and therefore have been combined.

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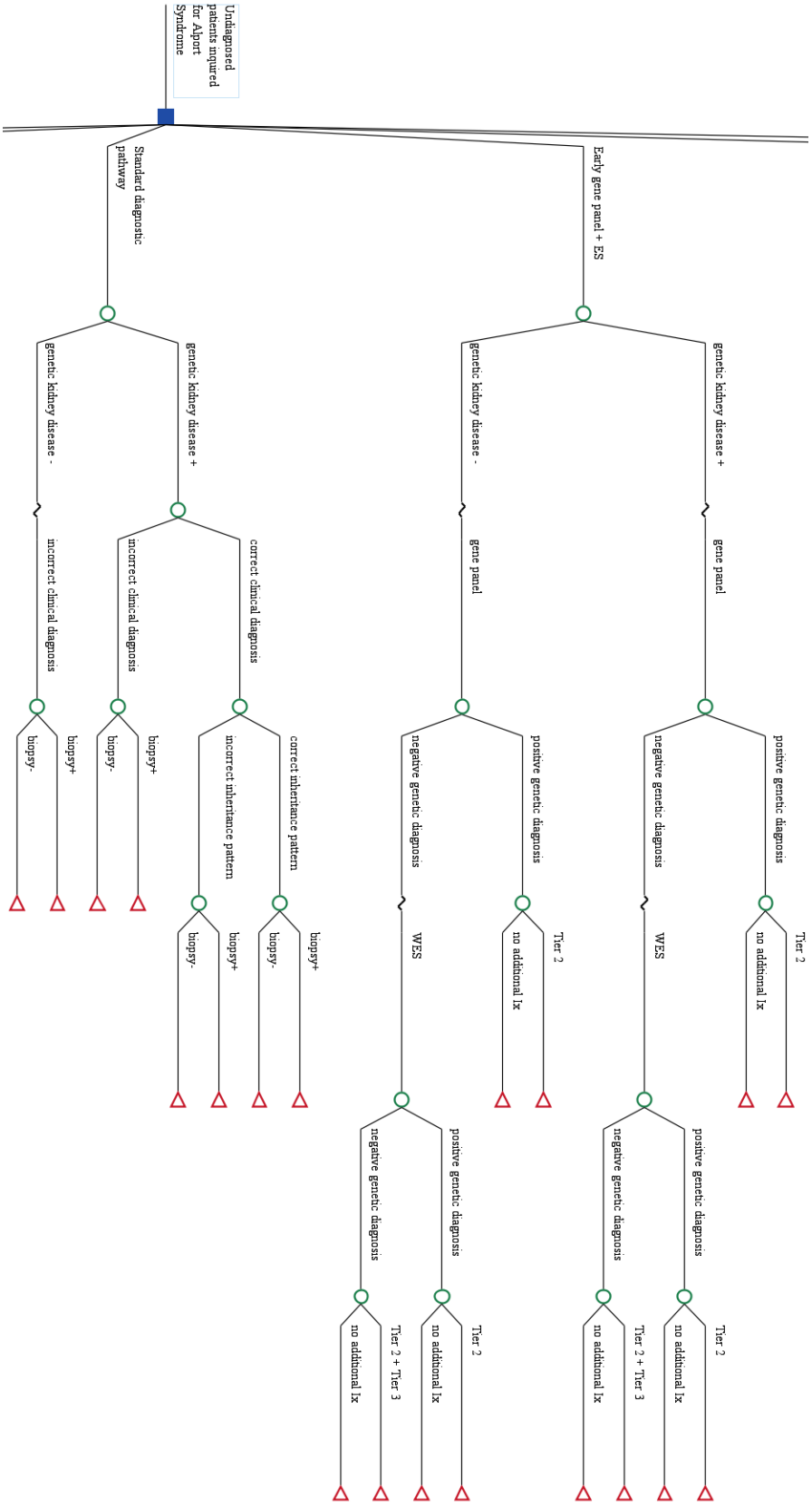
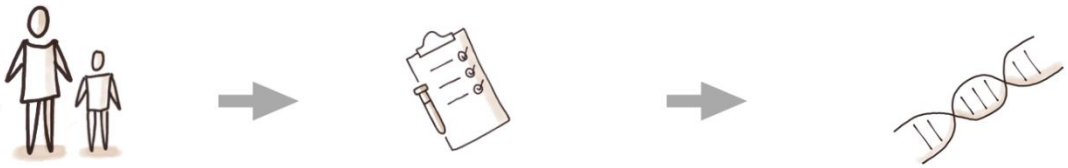
Supplementary Figure 1



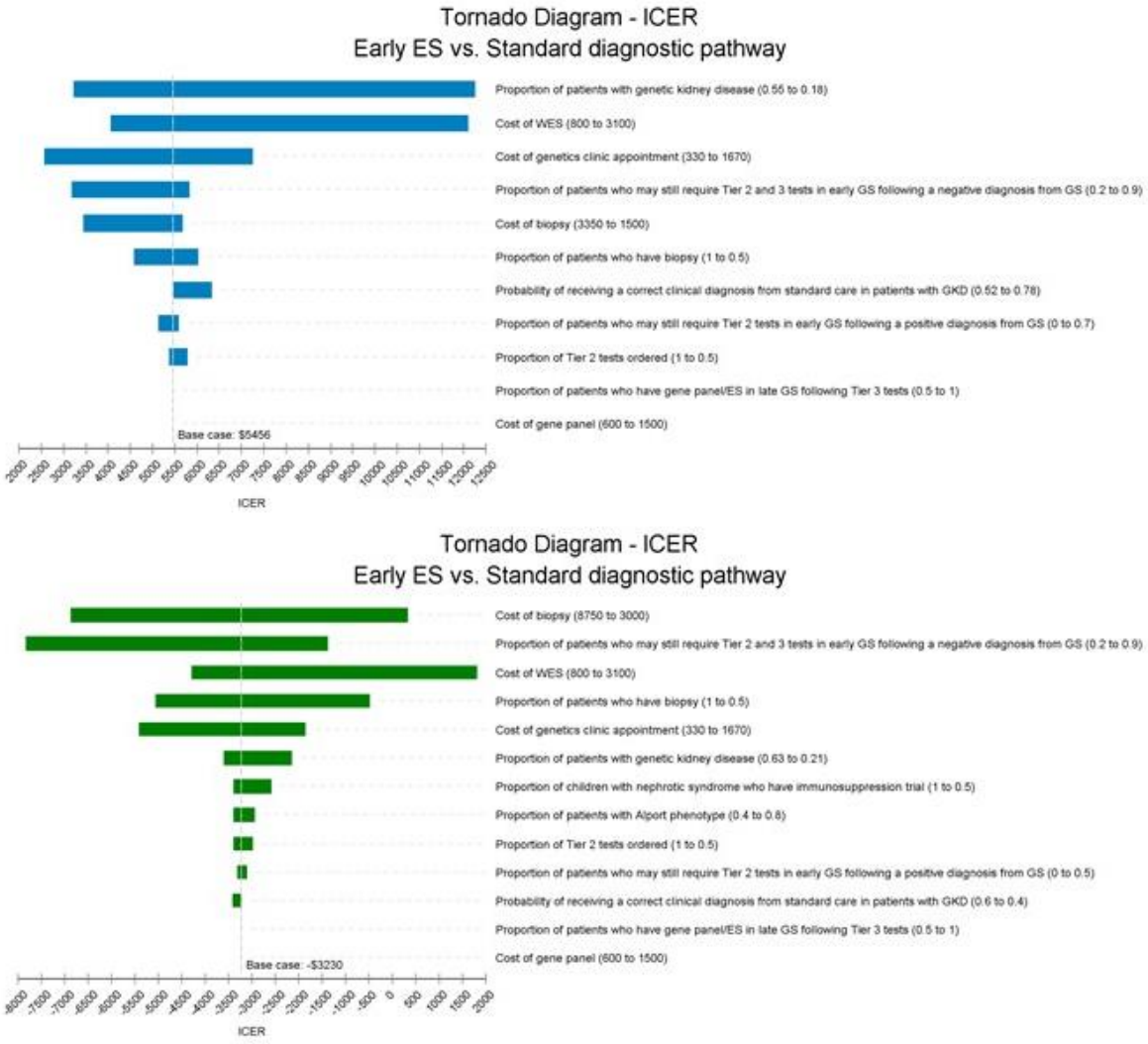
Supplementary Figure 2

Mary has a suspected diagnosis of Alport syndrome based on standard clinical investigations. She has a 5-year-old son and he becomes symptomatic with haematuria and proteinuria at age 15. His clinician ordered standard investigations and his nephrologist considered whether a kidney biopsy was appropriate in this situation.



Mary has a suspected diagnosis of Alport syndrome. She undergoes genomic sequencing, confirming that she has XLD Alport syndrome. Her 5-year-old, asymptomatic, son is subsequently offered cascade testing which confirmed XLD AS. Following this he was referred to a nephrologist and screened for proteinuria and haematuria annually and had audiology and ophthalmology assessments.

Supplementary figure 3



CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	4
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	4
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	4, 5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	See supplementary appendix 1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	6
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	6
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	4
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	4
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	4.5
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	See supplementary appendix 1
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	See supplementary material
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	8
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	7
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	See supplementary material
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	9-13
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	13
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	(3

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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