Australian Government

Department of Health

RATIFIED PICO

Application 1600:

Genetic testing for inherited kidney disease (other than Alport syndrome)

Background

Whole-exome sequencing (WES) is a genome-wide testing approach that allows selective sequencing of the protein-coding regions of the genome, which are enriched for disease-associated variants. (1) To facilitate and simplify interpretation, WES analysis can be targeted using gene panels that focus on known causative genes for a renal phenotype (clinical presentation). (2)

This PICO includes two index populations and one population for cascade testing of first degree relatives of index patients. Testing of the cascade population will be specific to the genetic variant identified in the index patient.

- Where the index case is diagnosed with an autosomal dominant condition, cascade testing will identify non-carrier or affected status in an individual.
- Where the index case is diagnosed with an autosomal recessive condition, cascade testing will, depending on the relationship to the proband, identify either: heterozygous carriers, non-carriers or other homozygous (pre-clinically affected, or pre-diagnosed) cases.

Information included in this PICO was sourced from the Application Form and associated references, as well as EMBASE searches of population, epidemiology, intervention, comparator and outcome key words. HTA websites (NICE, CADTH, INAHTA and EUnetHTA) and the Cochrane database were searched for genetic testing for kidney disease however nothing relevant was identified. One Australian treatment guideline was identified for Autosomal Dominant Polycystic Kidney Disease; global treatment guidelines and consensus statements were drawn from Kidney Disease: Improving Global Outcomes (KDIGO). The Orphanet Report of prevalence and incidence of rare diseases was used to inform epidemiological estimates where no estimates were identified in the literature. The applicant noted that Orphanet is known to underestimate disease prevalence and the exact frequency of disease is often unknown.

PASC's First Consideration (December 2019)

PASC requested that the PICO be reframed by the assessment group, in line with two broad population groups that PASC has proposed (plus cascade testing). The applicant clarified that they were guided by the Department in inserting the initial seven populations in the original Draft PICO (with the knowledge that PASC would provide guidance on appropriate PICO structuring).

PASC advised that the revised PICO will need to RETURN to PASC (for ratification) before it can proceed to the Evaluation Sub-Committee (ESC).

PASC recommended that, upon revision and ratification of the PICO, it is appropriate for the assessment to follow the Clinical Utility Card (CUC) approach.

In response to PASC's consideration in December 2019, the applicant stated that they brought their initial proposal to the Department in August 2018, but were advised to submit the application with six or more categories, and PASC would decide the best approach for progression of the proposal. The applicant stated they also suggested that this non-Alport proposal (1600) could be progressed as an amendment to the Alport approval. The applicant was of the view that it is not sensible to have Alport syndrome listed as a separate group, in the context of all other disease groups being considered together.

PASC's Second Consideration (April 2020)

This application was reconsidered by PASC for a second time in April 2020. PASC's April 2020 advice is included in *italics,* distinguishing it from the advice provided during its first consideration in December 2019.

Summary of PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Please note: As per the Human Genome Variation Society (HGVS) recommendations (den Dunnen et al. 2016), the terms 'variant' and 'variants' should be (and has been) used to replace the outdated terms 'mutation', 'mutations' and 'mutated'.

POPULATION ONE – Cystic kidney disease

Component	Description
Patients	Clinically-affected individuals with clinical history strongly suggestive of inherited cystic kidney disease
Prior tests	Detailed medical and family history and static & dynamic renal imaging (e.g. ultrasound and CT scan, DMSA scan, DTPA scan). May also include oral glucose tolerance test for diabetes
Intervention	Testing for germline gene variants by whole genome sequencing in one or more of the genes causative for inherited cystic kidney disease
Comparator	No genetic testing (usual care), with diagnosis reliant on previous medical history, family history, and clinical criteria
Outcomes	• Safety (adverse events, harms of delayed diagnosis and passing on a genetic disease, misdiagnosis, missed diagnosis and incidental findings) • Clinical utility of genetic testing (change in clinical diagnosis, prognosis, management and reproductive choices) • Clinical effectiveness (Incidence of continued renal impairment, incidence of end-stage renal failure, need for dialysis or renal transplantation, cardiovascular disease-related mortality, incidence of kidney donation from a carrier relative) • Diagnostic performance of genetic testing (analytical sensitivity and specificity, rate of reanalysis, time taken to achieve result) • Clinical validity (diagnostic yield, prognostic value) • Health-related quality of life • Health care resource use (genetic testing, specialist consultations, diagnostic testing, treatment, genetic counselling, IVF). • Cost-effectiveness

The Department confirmed that 90% of ADPKD is germline, with the remainder being de novo variants (*https://ghr.nlm.nih.gov/condition/polycystic-kidney-disease#inheritance*). The PICO has been appropriately updated.

The applicant advised that 90% of patients with multiple cysts have a variant in *PKD1* or *2* (i.e defines these patients as having ADPKD), which may be de novo. The other 10% are due to variants in other genes (e.g. *HNF1beta*, Alport genes, ARPKD, etc). The applicant confirmed there are specific treatments for ADPKD (tolvaptan), *HNF1beta* (sulphonylureas), and Alport syndrome (ACE inhibitors).

POPULATION TWO – Chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease)

Component	Description
Patients	Children aged under 18 years with chronic kidney disease excluding Alport syndrome & cystic kidney disease
Prior tests	Detailed medical and family history, with diagnostic pathology and imaging tests dependent on suspected clinical diagnosis.
Intervention	Testing for germline gene variants by whole genome sequencing in one or more of the genes causative for inherited chronic kidney disease
Comparator	No genetic testing (usual care), with diagnosis reliant on previous medical history, family history, and clinical criteria
Outcomes	Same as Population One

The applicant advised that this population is likely to represent all inherited renal diseases. Almost all inherited renal diseases may affect children, but can also present for the first time in adults. Given the lack of a discrete age separation for a particular genotype-phenotype relationship, the applicant cautions against only looking at children, especially given they may also be covered by the childhood syndromes application.

The applicant sought clarification on the following:

- Will adults only be tested if they have a child affected in their family?
- If a child has no features at the age of six (but the adult does), and that child only develops the disease at age 12, does this mean the adult needs to wait six years before testing?
- In relation to inherited nephrotic syndrome, nephrolithiasis and nephrocalcinosis are unlikely to be tested in children. Inherited renal stones usually occur only in adulthood.

POPULATION THREE - Cascade testing

The Application Form indicated that genetic testing is required to detect disease in family members of patients with aHUS, C3 glomerulopathy, cystic kidney disease, nephrolithiasis and nephrocalcinosis only. Given the inheritance pattern of both index populations discussed in this PICO, cascade testing is proposed for first degree biological relatives of an index patient with a known monogenic cause of chronic kidney disease.

Component	Description
Patients	First degree relatives of a patient with a known monogenic cause of inherited kidney disease.
Prior tests	Detailed medical and family history
Intervention	Testing for germline gene variants in one or more of the genes causative for inherited kidney disease.
Comparator	No genetic testing (usual care)
Outcomes	Same as Population One

POPULATION

PASC's First Consideration (December 2019)

PASC noted the complexity of the application, with seven diverse populations, including many rare conditions with likely limited data on testing (and uncertain patient numbers), as well as a cascade testing population (labelled as population 8).

The applicant confirmed that these conditions are rare (in that they occur in fewer than one in 2,000), but the prevalence of 1 in 100,000 is inaccurate. The applicant stated the problem has been difficulty with diagnosis (until now), with patients only being treated symptomatically. The applicant re-confirmed its statement at the PASC meeting, that six patients with suspected Gitelman syndrome have been seen at one centre in the past two years.

PASC queried the addition of patients with diseases of the adrenal glands in population 7, which the assessment group had added. PASC advised that adrenal gland disorders should be removed from this application, and the applicant agreed.

PASC noted the seven (six plus cascade testing) populations currently proposed, and acknowledged in its current form, this application would require seven evaluations (given they are all different conditions with different clinical claims). PASC proposed that the application be re-structured and simplified, focusing initially on two populations:

1. Cystic kidney disease (CKD);
2. Chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome and cystic disease).

The applicant stated they included all these groups, because they are analogous (similar) to Alport syndrome. The applicant sought clarification on whether the childhood syndromes proposal included these forms of renal disease.

The applicant advised that children are adequately covered by genetics departments, but the adult population is missing out, especially those with less common conditions. The applicant added that children's groups could include nephrotic syndrome, because this may present in childhood.

The applicant reiterated that they included all six groups at the recommendation of the Department, at a meeting in August 2018. The view was that, given the time it had taken to get approval for Alport syndrome, an application for only one disease group seemed inefficient. The applicant is concerned that patient groups who are not vocal, are missing out on services.

PASC acknowledged that, using the two (simplified) broad populations will exclude some (rare) conditions from the application. However, PASC advised that the application needs to include conditions (causing renal impairment) that have sufficient data to demonstrate safety, clinical effectiveness and cost effectiveness. PASC considered that, for rare conditions, a linked exemplar to the facilitator (e.g. ADPKD) could be a reasonable approach.

The applicant advised that sufficient data could take years to obtain, adding that these conditions cannot currently be accurately diagnosed because of lack of genetic testing. The applicant stated they are concerned about Australian patients potentially waiting 10 years for funded genetic testing, and that Australia is 10 years behind the United Kingdom.

PASC's Second Consideration (April 2020)

PASC noted that:

- *the previous 7 categories were remodelled into 2 populations (2 main items proposed plus items for data re-interrogation and cascade testing)*
- *nephrolithiasis is now included with the paediatric group, although it is very rare in children*
- *there are no additional data on the likely accurate size of the test population, which is required to establish the size of the test population and consequently the financial impact of testing. Data from the KidGen project may provide such information.*

Inherited kidney disease

Chronic Kidney Disease (CKD) is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. (3) There are five (5) stages of kidney disease: early stages (1 and 2) are usually asymptomatic, middle stages (3 and 4) are often symptomatic from the primary kidney disease (but can have secondary signs and symptoms) as kidney function slows and the amount of urea and creatinine in the blood increases, and end stage renal failure (ESRF, stage 5) where a patient requires dialysis or a kidney transplant to stay alive. (4)

Chronic kidney disease can be the result of diabetes, high blood pressure, diet and lifestyle factors, and inherited disease. Approximately 30% of chronic kidney disease can currently be attributed to an inherited monogenic cause, where a single gene variant is known to cause disease. (5) Three modes of inheritance are recognised: X-linked dominant, autosomal recessive and autosomal dominant. The incidence of de novo variant (which occurs after fertilisation) varies by disease type, and will have an impact on the extent of cascade testing required.

The applicant advised that the de novo variant rate is usually 10%, which means that parents and siblings are not affected, but offspring are likely to be.

The Application Form contained six index populations: aHUS or C3 glomerulopathy; steroid-resistant nephrotic syndrome; cystic kidney disease; renal tubular defects; nephrolithiasis and nephrocalcinosis; and rare inherited causes of renal tract or adrenal gland disease. A seventh population (cascade testing for first degree relatives of index patients) was also proposed.

The revised PICO (post December 2019 PASC) contains two index populations: cystic kidney disease (CKD) and chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease).

The third population relates to cascade testing, and includes biological relatives of patients diagnosed with monogenic causes of inherited kidney disease.

PASC noted the predicted number of tests (2,000 per year) was very uncertain and based on the population with end-stage renal failure. PASC noted it is plausible that the item could be used in patients before progression to ESRF, and that a population estimate including these patients should be presented accordingly.

PASC considered the size of population three (cascade testing) is required to provide further information on the financial implications of testing - What is the proportion of patients, and number of patients, from populations 1 and 2 who are expected to have a variant which requires cascade testing?

The applicant acknowledged that the true prevalence of patients with inherited kidney disease remains unknown. The Applicant stated that approximately 25,000 people are on renal replacement therapy in Australia and estimated that inherited kidney disease is the cause in about 30% of those patients, corresponding to 7,500 patients overall.

POPULATION ONE – Cystic kidney disease

Cystic kidney disease is characterised by the formation of renal cysts that disrupt the structure of the nephron (6). Extrarenal features may include brain developmental defects, retinal degeneration, skeletal deformities, facial dimorphism, laterality defects, and congenital heart disease, depending on the causative pathological variant (7). Estimates of prevalence vary by disease subtype. Table 1 summarises the prevalence estimates for cystic kidney disease *(As noted by the Applicant, these separation estimates by diagnosis may be an underestimate of the total burden of managing all consequences of chronic renal disease).*

Table 1 Estimated prevalence of cystic kidney disease subtypes from peer-reviewed literature, and total number of reported Australian hospital separations by diagnosis

Disease/Syndrome	Estimated prevalence from literature – total (per 100,000)	Estimated Australian prevalence – adults (8) (per 100,000)	Australian hospital separations (9)
Autosomal dominant polycystic kidney disease (ADPKD)	25 to 200 (10)	6.09	85[a]
Autosomal recessive polycystic kidney disease (ARPKD)	5 (11)	-	18[b]
Medullary cystic kidney disease (MCKD)	0.2 (12)	0.72	65[c]
HNF1B variant-related diseases	Rare (11)	-	n.a
Nephronophthisis (NPHP)	2 (11)	0.10	n.a
Tuberous sclerosis complex (TSC)	0.7 to 3.8 (13)	0.24	n.a
Renal coloboma syndrome	180 cases (14)	-	n.a

Notes: a, ICD-10 code Q61.2; b, ICD-10 code Q61.1; c, ICD-10 code Q61.5; n.a., not applicable – no ICD-10 diagnosis code identified for this condition

Genetic testing for cystic kidney disease is proposed for clinically affected individuals with suspected inherited cystic kidney disease, to make a genetic diagnosis and thus inform prognosis and treatment.

The applicant advised that ADPKD is thought to affect between one in 500 and one in 1,000 individuals, and that this is the prevalence taught to medical students. The applicant advised that the other causes represent fewer than 10% of all cystic kidney disease.

Rationale

In an effort to simplify the PICO, the rationale for cystic kidney disease has been re-structured to show disease characteristics in a table, with separate paragraphs for the diagnostic relevance of genetic testing and management. Around 90% of the causes of cystic renal disease are ADPKD, with variants in *PKD1* or *PKD2*. The other 10% are due to variants in other genes (usually *HNF1beta*, Alport genes, etc).

Almost 100 genes have been described as causative of inherited cystic kidney disease (5). Identifying the variant gene, type of variant, and mode of inheritance of cystic kidney disease, informs prognosis, treatment, and genetic counselling requirements. Table 2 (below Figure 1 below) summarises the phenotype-genotype relationships in various cystic kidney diseases.

In most cases, molecular genetic testing can detect a pathogenic variant known to cause a rare disease that is otherwise difficult (or impossible) to diagnose. A study by Bullich et al (2018) using a cystic kidney-disease gene panel identified causative genetic variants in 78% of patients with cystic kidney disease. (6) The diagnostic yield was 72% in paediatric patients and 80% in adult patients. Figure 1 compares the clinical suspicion and definitive molecular diagnosis of 207 patients presenting with cystic kidney disease. The clinical diagnosis was confirmed in 129 patients, changed in 3 patients, and a diagnosis was made in 29 patients referred with prenatal or unspecified cystic kidney disease. No known disease-causing genetic variant was identified in the remaining 46 patients. Excluding prenatal patients, molecular testing resulted in a change in the clinical diagnosis for 4% (7/176) of the tested population.

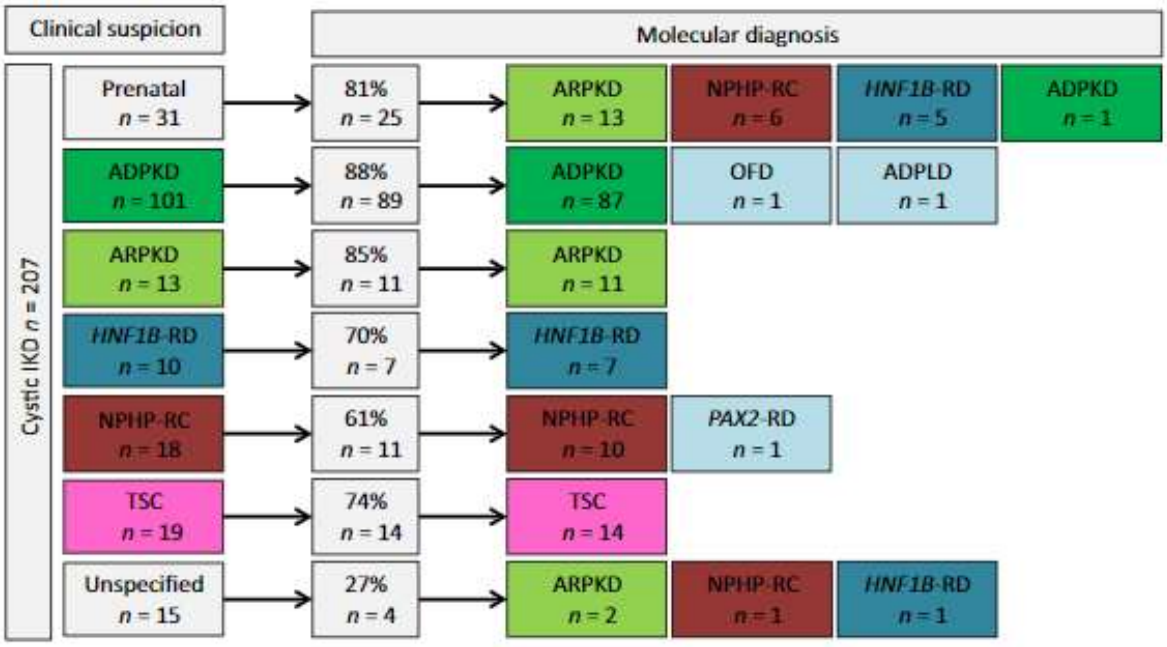

Figure 1 Variant detection rate and resulting molecular diagnosis for cystic kidney disease (from Bullich et al 2018)
Notes: Patients with a prenatal presentation were referred for testing with an unspecified clinical diagnosis.
Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; ARPKD, autosomal recessive polycystic kidney disease; HNF1B-RD, *HNF1B* related disease; NPHP-RC, nephronophthisis-related ciliopathies; OFD, oral-facial-digital syndrome; PAX2-RD, *PAX2* related disease TSC, tuberous sclerosis complex

The applicant clarified that 'tuberous sclerosis complex' is seen more in paediatric populations. In adult populations, medullary cystic kidney disease and Alport variants are more often observed.

Management of cystic kidney disease varies depending on disease subtype. Management of ADPKD includes interventions to decrease cyst growth, and minimise cardiovascular morbidity and intraglomerular hypertension (10). Tolvaptan is a disease modifying drug indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with chronic kidney disease stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease (28). Treatments for ARPKD focus on treatment of symptoms (e.g. ACE inhibitors for hypertension). Detection of an *HNF1B* variant facilitates screening and management of extra-renal manifestations, particularly maturity-onset diabetes of youth. Although there is currently no cure for NPHP, an early diagnosis through genetic testing informs disease progression and treatment options, including early learning of Braille to cope with vision loss (29). Targeted treatment with sirolimus and everolimus is thought to be effective in patients with *TSC1* or *TSC2* variants. (13) Accurate diagnosis of renal coloboma syndrome guides monitoring and management of ophthalmological and renal complications.

Diagnosis of the genetic cause of cystic kidney disease facilitates the delivery of appropriate treatment and/or management of the disease. Approximately 2-5% of patients with ADPKD present with an early and severe phenotype indistinguishable from ARPKD (6). Without genetic testing it is difficult to differentiate MCKD types 1 and 2, rendering the patient prognosis unclear and the time to ESRF uncertain. Early diagnosis of cystic kidney disease may also obviate the need for further diagnostic tests, including liver function tests for *HNF1B*-related disease and renal biopsy for NPHP (29).

Table 2 Clinical presentation, causative genes, mode of inheritance and diagnostic yield for genetic testing in cystic kidney disease

Disease	Renal features	Extra-renal features	Chronic Kidney Disease and mortality	Inheritance	Causative genes	Genetic diagnostic yield
Autosomal dominant polycystic kidney disease (ADPKD)	Numerous bilateral renal cysts that grow exponentially through adult life (10)	Arterial hypertension, urinary tract infections, liver cysts, cerebral aneurysms, heart valve insufficiency (10)	Progressive renal impairment leading to ESRF in fourth to sixth decade of life (15)	AD	*PKD1, PKD2* (10)	88% (6) 90% (10)
Autosomal recessive polycystic kidney disease (ARPKD)	Bilateral renal cystic renal enlargement and chronic kidney disease that generally presents in the perinatal period (6) (16)	Pulmonary hypoplasia, severe portal hypertension, hyponatremia, cholangitis, and hypersplenism	Many patients progress to ESRF in first decade of life (17)	AR	*PKHD1*	85% (6)
Medullary cystic kidney disease (MCKD) (Type 1)	Expanded urinary ducts in the corticomedullary boundary areas, diffuse tubulointerstitial nephritis with tubular atrophy, interstitial fibrosis, and inflammatory cell infiltration (18)	Hyperuricaemia, polyuria, polydipsia, anaemia and gout (19)	ESRF during fifth to sixth decade of life (20) (18)	AD	*MUC1*	NR
Medullary cystic kidney disease (MCKD) (Type 2)	Same as MCKD Type 1 (18)	Same as MCKD Type 1 (19)	ESRF during in the third decade of life (18)	AD	*UMOD*	NR
HNF1B-related disease	Similar to MCKD and largely non-specific. Renal cyst and diabetes syndrome, also known as maturity-onset diabetes mellitus of the young type 5 (21)	Diabetes mellitus, abnormal liver function, exocrine pancreatic failure, and genital tract abnormalities (21)	Disease may manifest from prenatal stage to mild symptoms in the elderly (22) Disease progression in adults is slow (21)	AD	*HNF1b*	70% (6)
Nephronophthisis (NPHP)	Normal or small-sized kidneys, increased renal echogenicity, and loss of cortico-medullary differentiation (7)	Retinal degeneration, liver fibrosis, and cerebellar vermis aplasia (16)	Median age of CKD is 13 years (16)	AR	*NPHP1* to *NPHP9* (16)	61% (6)
Tuberous sclerosis complex (TSC)	80% of patients have renal lesions (23)	Benign tumours in multiple organ systems (23). Skin lesions, seizures, intellectual deficit, heart tumours (24)	Shares features with ADPKD but progresses faster to ESRF (23)	AD	*TSC1* and *TSC2* (25)	74% (6) 85% (25)
Renal coloboma syndrome	92% of patients have renal disease, including renal hypodysplasia, vesicoureteral reflux, renal cysts, and multicystic dysplastic kidneys (26)	77% of patients have ophthalmological abnormalities. Other features include hearing loss, seizures, genitourinary anomalies, and intellectual disability (26)	Average age of ESRF 19.5 years (26)	AD	*PAX2* (27)	23% (27)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ESRF, end stage renal failure; NR, not reported

POPULATION TWO - Chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease)

Chronic kidney disease that manifests during childhood is often caused by congenital abnormalities of the kidneys and urinary tract (CAKUT), steroid-resistant nephrotic syndrome (SRNS), chronic glomerulonephritis, complement-mediated disorders and renal cystic ciliopathies, which together account for approximately 70% of paediatric CKD (29). Table 3 summarises the causes and genetic diagnosis of early onset kidney disease, defined as chronic kidney disease manifesting before 25 years of age. Paediatric patients with renal cystic ciliopathies (cystic kidney disease) are excluded from Population Two as they are already included in Population One. *PASC agreed that children with renal cystic ciliopathies should be excluded from Population 2.*

A 2013 study by the Australian and New Zealand Paediatric Nephrology Association estimated the overall prevalence of inherited kidney disease in children at 706 per 100,000, with Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT) and steroid resistant nephrotic syndrome (SRNS) the most frequent causes of CKD. (30)

The applicant confirmed that CAKUT is the commonest cause of inherited kidney failure in children. The applicant also advised it is often difficult to tell the difference between genes responsible for SRNS and those responsible for steroid sensitive nephrotic syndrome.

Table 3 Causes and genetic diagnosis of early onset CKD

Diagnostic Group	Indication to run a gene panel	Proportion of cases of early onset CKD	Number of known causative genes	Proportion of cases caused by known pathological variants
CAKUT	CAKUT evident by renal imaging	49.1%	36	17%
SRNS	SRNS	10.4%	39	30%
Chronic glomerulonephritis	Evidence of proteinuria and haematuria	8.1%	10	20%
Renal cystic ciliopathies[a]	Increased echogenicity on renal ultrasound or ≥ 2 renal cysts	5.3%	95	70%
aHUS	Microangiopathic haemolytic anaemia, thrombocytopaenia and acute kidney injury	2.0%	9	60%
Nephrolithiasis or nephrocalcinosis	Known stone disease or nephrocalcinosis	1.6%	30	21%
Other	Other indications of genetic disease	23.5%	Unknown	Unknown

Reproduced from Vivante and Hildebrandt (2016) (29)

Abbreviations: aHUS, atypical Haemolytic Uraemic Syndrome; CAKUT, Congenital Abnormalities of the Kidney and Urinary Tract; SRNS, steroid resistant nephrotic syndrome.

[a] renal cystic ciliopathies are excluded from Population 2 but included in this table to demonstrate the proportion of early onset CKD attributable to each cause.

Genetic testing for chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease) is proposed for clinically affected individuals with kidney disease of suspected genetic origin, to make a diagnosis and thus inform prognosis and treatment.

The applicant advised there is also an urgent need to test for aHUS in adults.

Rationale

There are currently over 100 identified genetic kidney disorders and 450 monogenic causes of CKD, explaining approximately 30% of cases of paediatric chronic kidney disease (5) (30). The diagnostic yield from genetic testing varies depending on the disorder, from 17% of CAKUT cases up to 70% for childhood onset cases of cystic kidney disease and renal tubular disorders (5) (29).

Inherited kidney disease encompasses a range of disorders, with multiple genes contributing to specific disease phenotypes and single gene variants, causing multiple clinical presentations (2). In addition, a range of syndromes with renal associations and known causative genes (e.g. Gitelman syndrome) together account for a significant proportion of inherited kidney disease (30). Age of onset, progression to ESRF, and mortality vary by disease subgroup and diagnosis.

Patients aged under 18 years with chronic kidney disease may present with a range of clinical features and family histories due to the heterogeneous nature of inherited kidney disease. Genetic testing can be used to confirm a suspected diagnosis of a specific disorder or syndrome and clarify or exclude differential diagnoses (31). A definitive diagnosis may reduce the need for further investigations and surveillance and provide prognostic information and guide surveillance of extra-renal manifestations (31).

Management of chronic kidney disease in children will vary by disease subtype. Common treatments include surgical intervention, medical management and blood pressure control. Targeted treatments are available for some conditions including aHUS and Fabry disease. Lithotripsy (extracorporeal shock-wave therapy) may be used to treat nephrolithiasis and nephrocalcinosis. A definitive diagnosis will guide appropriate management of chronic kidney disease and may delay the onset of ESRF necessitating dialysis and renal transplant.

A potential gene panel list was drafted for Population 2, which contains 183 genes known to cause inherited kidney disease (other than cystic kidney disease). Genes known to cause Alport Syndrome are included in the draft panel as they are also associated with focal segmental glomerulosclerosis (FSGS, a subtype of steroid resistant nephrotic syndrome). All the genes listed have diagnostic utility; some also have predictive and prognostic utility. The applicant advises that the composition of the panel is generally acceptable. Although this panel is for children, genetic testing has demonstrated that many of the genes are affected in both children and adults. There is some overlap, with one gene associated with multiple phenotypes, for instance genes that affect kidney development can also cause haematuria or FSGS.

POPULATION THREE - Cascade testing

A genetic diagnosis in the index patient guides cascade screening to exclude disease in at-risk family members and identify currently asymptomatic disease in affected relatives, which in turn facilitates early treatment and avoids inappropriate kidney donation.

The Application Form stated that cascade testing is required to detect disease in the family members of patients with aHUS, C3 glomerulopathy, cystic kidney disease, nephrolithiasis and nephrocalcinosis. Given the inheritance pattern of the index populations discussed in this PICO, cascade testing is proposed for first degree biological relatives of an index patient with a known monogenic cause of chronic kidney disease.

Prior tests

Genetic testing should be reserved for individuals with a strong clinical suspicion of inherited kidney disease after clinical examination and a detailed medical and family history.

All patients with renal disease undergo baseline pathology tests (urine and serum biochemistry) and renal function tests (e.g. serum creatinine and eGFR). (32)

PASC queried which prior investigations should be mandated before genetic testing is considered (as opposed to potentially avoided), and what the algorithm should be. Also, it is not clear if diagnosis of the index case always requires genetic testing in all groups as a definitive clinico-pathological diagnosis may be made without; in some, it appears to be most useful for defining the specific pathogenic variant to permit cascade family testing (for reproductive planning, etc.).

POPULATION ONE – Cystic kidney disease

Prior testing primarily involves static and dynamic renal imaging (e.g. ultrasound, isotope scan and CT). (7), (11), (10), (23), (27) , (33) An oral glucose tolerance test for diabetes may be conducted (MBS item 66542) to detect diabetes caused by *HNF1B* related disease.

POPULATION TWO - Chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease)

Prior testing for chronic kidney disease in children will vary according to the suspected diagnosis of a specific renal disorder or syndrome; based on an assessment of the patient's clinical features and family history, supported by diagnostic imaging and pathology tests.

Prior testing for chronic glomerulonephritis involves routine biochemical and haematological analysis and assessment of complement proteins (34). For suspected aHUS, other causes of haemolytic uraemic syndrome should be excluded (34). Prior testing for SRNS begins with diagnosis of NS through: (i) 24 hours of urine collection, showing proteinuria >3.5g per 24 hours; (ii) blood sample, showing serum albumin <2.5g/dL; (iii) clinical evidence of peripheral oedema; and (iv) blood sample, showing hyperlipidaemia (35). Blood tests to assess renal function, liver function, blood clotting and electrolytes, and diagnostic imaging may be performed if required (35). Prior testing for renal tubular defects involves assessment of clinical features and biochemical findings (36). Typical tests include urine and serum biochemistry analyses and enzyme assays.

Prior testing for nephrolithiasis and nephrocalcinosis includes urine and serum biochemistry, kidney stone analysis, metabolic testing and diagnostic imaging. (37) Individuals presenting with clinical features of CAKUT will have received appropriate imaging (e.g. US, CT, MRI, intravenous pyelogram, DMSA, DTPA) and renal function assessment as prior tests.

The applicant confirmed that nephrocalcinosis is uncommon in children (except for cystinosis, hyperoxaluria and Bardet syndrome.

INTERVENTION

PASC noted that, once the populations are re-structured, advice will be needed from professional pathologist bodies about:

- the most suitable tests for each condition;
- what needs to be done regarding establishment of an appropriate quality assurance framework; and
- whether a technology agnostic approach would be appropriate. The applicant advised that this would be the most appropriate approach.

However, the applicant advised that pathologists (on their own) will not always be able to make a determinate diagnosis, so will need to liaise and consult with renal geneticists, particularly where complex inheritance is observed (and noting that the number of genes will be expected to increase as evidence evolves).

PASC considered that the role of a multidisciplinary team (MDT) - e.g. a multidisciplinary renal genetics clinic to oversee selection of patients and determine appropriate investigations - was not sufficiently addressed in the current application. The applicant stated that, in its Alport application, they suggested an MDT, but it had been rejected. The applicant stated they were told a nephrologist could request these tests, partly because of long waiting times to access a genetics clinic, and also because of the international trend to mainstream genetic testing.

PASC also acknowledged the already-significant issues with equity of access to funded genetic testing.

Molecular genetic testing approaches include single-gene testing, use of a multi gene panel, and next generation sequencing. Various testing platforms are listed on the Australian Register of Therapeutic Goods (ARTG) of the TGA as Class III in vitro diagnostic devices. The Application states that most laboratories use whole-exome sequencing (WES), a type of next generation sequencing.

At present, genetic testing is not widely available in Australia and very few people with suspected inherited kidney disease have had a confirmatory genetic test. There are currently 19 testing sites accredited by the National Association of Testing Authorities (NATA) to perform massively parallel sequencing (MPS), and 15 sites accredited to perform whole-exome sequencing (WES) or next generation sequencing (NGS) in Australia (38). Genetic testing for inherited kidney disease (other than Alport syndrome) is not currently funded under the MBS, but is paid for by the patient. The cost of Renal Gene Panels using MPS at a Sydney hospital ranges from $1,200 to $1,800 (39). In 2018, the cost of full exome analysis (WES) at the Victorian Clinical Genetics Services was $3,100, while the cost of analysing targeted lists of genes ranged from $1,000 for 15 exomes, to $2,400 for 400 exomes (40). The MBS fee for genetic testing for Alport syndrome is $1,200. The limited number of accredited testing facilities and the high cost of testing can therefore be considered barriers to testing and targeted treatment.

The Application Form anticipated that genetic testing will be requested by a nephrologist or a clinical geneticist. Genetic testing of index patients and their relatives is only required once in a lifetime and can be carried out using peripheral blood (5 mL) or tissue samples (41). The Application Form states that the turnaround time for genetic testing is approximately 12 weeks (4 weeks each for batching samples, testing, and interpretation at a multidisciplinary meeting). The lengthy turnaround time for

results is a barrier to testing and targeted treatment, particularly where the index case is a foetus and termination of pregnancy may need to be considered.

PASC agreed that the 12-week turnaround time for testing is an issue for decision-making following fetal testing, although fetal cascade testing for a known variant could be performed much more rapidly.

Feedback received from KidGen, following the April 2020 PASC meeting, stated that the appropriate test methodology for populations 1 and 2 is whole genome sequencing (WGS) as an add-on, rather than replacement, test to current diagnostic methods.

Genetic testing is a rapidly evolving technology. Targeted whole exome sequencing for Alport syndrome (MBS item 73298) was listed in May 2019, and MSAC recommended whole exome analysis for childhood syndromes (Application 1476) in August 2019. It is possible that in future, the number of accredited testing facilities will increase, and the cost of testing and turnaround time will decrease accordingly. However, cost of treatment and time to diagnosis are currently barriers to treatment.

Prior to testing, patients sign an informed consent form confirming that they have understood the implications, indications, and limitations of the test (42). Patients also provide specific consent regarding who has access to their results as it has implications for their relatives (42). Consultation may take place in private practice (e.g. a specialty renal clinic or consulting rooms) or in the public domain (e.g. hospital outpatient department). After the test, patients must be referred to a clinical genetics service for formal genetic counselling (e.g. discussion of the results, reproductive options, risks to relatives and their screening) (41). If the test is positive, long-term management by a nephrologist is recommended (41).

Rationale

Inherited kidney disease that causes chronic kidney disease encompasses a broad range of genetic disorders (5). The mode of inheritance determines the degree of genetic causality and genotype-phenotype correlation (16). Diseases caused by recessive genes usually manifest prenatally or during childhood, while diseases caused by dominant genes typically manifest in adulthood (16). The type of variant (missense or nonsense) provides prognostic information and may inform future treatments. Genetic testing offers a timely and accurate diagnosis that guides prognosis, intervention and monitoring.

Several genetic testing modalities are currently available, summarised in

Table 44. However, the applicant advised that most of these modalities are not used for inherited renal diseases. Rather, WES is used to examine a panel of condition, which costs $550 from AGRF (Australian Genome Research Facility) according to the applicant, and usually takes one hour of analysis.

Table 4 Genetic testing modalities

Test	Description	Indications	Example
Chromosomal microarray	Detects unbalanced chromosome abnormalities, Genome wide	Suspect genomic disorder (multi-organ anomalies)	CAKUT *The applicant advised that WES is normally used for CAKUT; not microarray.*
Single Gene Sanger	Detects SNV and small indels (<10 bp) within a DNA segment. Detects conditions associated with variants in one gene	Suspect single-gene disorder. Confirm NGS findings	Fabry disease
Targeted NGS panel	Detection of SNV and small indels (<1 kb) within specified sample of genes. Unable to re-analyse at later date	Suspect condition that affects several discrete genes	Alport syndrome
Targeted WES	'Virtual panel' which also detects SNV and small indels (<1 kb) within specified sample of genes. Able to go back and re-analyse as new genes are discovered/ of interest	Suspect condition that affects several discrete genes	Alport syndrome
WES	Detects SNV and small indels (<1 kb) within coding regions of the exome *The applicant advised that WES is generally used, but sometimes WGS is used for cystis disease). The applicant added that, in the USA, genetic test results are available within two days (at best) for urgent tests, and up to six weeks for non-urgent tests. As Australia's experience increases, the applicant believes the situation will improve (noting MDT is another source of delay.*	Suspect condition associated that affects moderate-large number of genes. Inconclusive phenotype	Nephronophthisis
WGS	Detects SNV and small indels within coding and non-coding regions of the genome	Suspect condition which involves pseudogenes. Inconclusive phenotype	ADPKD

Reproduced from Jayasinghe et al (2019) (31)

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CAKUT, congenital abnormalities of the kidney and urinary tract; NGS, next generation sequencing; WES, whole-exome sequencing; WGS, whole-genome sequencing

Due to the heterogeneous clinical presentation and large number of genes known to cause inherited kidney disease, comprehensive sequencing methods such as whole exome sequencing (WES) or WGS will likely be the approach used in clinical practice (2), (10), (11), (33).

PASC noted the uncertainty remaining on best test methodology – a "test agnostic" approach is potentially open to suboptimal testing in certain patient groups. Panel-based WES may not always be the best test, and the appropriate test may vary depending on the variation it is designed to detect (see Table 4).

PASC noted the potential gene list had been developed for population 2, but was unclear how such a list would be used in a practical testing situation. PASC advised that a standard WES panel is possibly inadequate for many patients with ADPKD, and they represent the largest patient subgroup; these patients require testing by WGS as described in the papers by Bullich and Jayasinghe respectively.

The use of a MDT to oversee appropriate patient and test selection, results interpretation, and counselling of the index patient and family members, may address the challenges of implementing genetic testing in clinical practice (31).

The applicant reiterated that it would be inconsistent to apply no MDT approach to Alport syndrome, but apply it to other conditions. The applicant added that, internationally, the sector is moving away from MDTs, which geneticists may be reluctant about. The applicant suggested that a better approach would be to encourage development of renal genetics.

The applicant confirmed that molecular geneticists (in RCPA) should consult renal geneticists, so they can advise together, in this highly specialised field. *PASC advised that any nephrologists requesting the testing may require support from a genetic counsellor or clinical geneticist. PASC queried how patients with complex inheritance or combination of variants would be evaluated and managed.*

PASC advised that the KidGen collaboration has offered to share data with MSAC, and that these analyses should be obtained to further inform the cost-effectiveness of testing. These data are from projects using WES developed under the auspices of the Australian Genomic Health Alliance (361 adult and paediatric patients) and Australian Genomics ("HIDDEN") in 200 patients with unexplained ESKD; in order to assess the clinical outcome/utility & health economic impacts.

COMPARATOR/S

PASC advised that the PICO needed re-structuring before the comparators could be considered. PASC also advised that clarity was needed on ancillary testing:

- how much ancillary testing should be included in the comparator;
- how much ancillary testing should be regarded as a requirement before qualifying for genetic testing; and
- how much ancillary testing could be avoided by performing the genetic testing.

The applicant advised that the recommendation at the recent renal genetics meeting in London was that genetic testing should be done before a renal biopsy (because it may avoid an unnecessary and invasive biopsy procedure). *PASC noted this advice and the consequent clinical claim of reducing the harm associated with biopsy and queried if that meant that current guidelines could be out of date.*

The Application Form proposed that the comparator is 'no genetic testing for inherited kidney disease', with diagnosis reliant on clinical criteria and (non-genetic) laboratory investigations, and previous medical and family history. *PASC advised that non-genetic laboratory investigations could include imaging.*

Although diagnosis of inherited kidney disease may be confirmed with renal biopsy and subsequent visualisation of the specific pathological changes in the tissue, renal biopsy is avoided where possible as it confers a risk to the patients (bleeding, infection and pain) and is sometimes inconclusive. (32)

A positive genetic diagnosis will obviate the need for a renal biopsy, however a renal biopsy and/or repeat renal imaging may be required where the results of genetic testing are inconclusive. Further, the time to genetic diagnosis compared to diagnosis through current non-genetic investigations (including renal biopsy) currently limits the usefulness of genetic testing in facilitating timely diagnosis and commencement of appropriate treatment.

Rationale

Literature reviewed during PICO development supports the comparator(s) proposed in Part 6c of the Application. The KDIGO Guidelines on chronic kidney disease state that kidney biopsy should only be performed when essential and the benefits justify the risks and cost. (3) Given the challenges of diagnosis, number of tests involved, and extended time to diagnosis, it is difficult to separate "prior tests" from "comparators". The comparators and treatment algorithms presented assume the decision point of "suspected diagnosis" or "disease diagnosed, cause unknown" which are dependent on specialist clinical judgement.

PASC noted that it is difficult to determine how much ancillary testing should be included in the comparator, how much should be regarded as a requirement before qualifying for genetic testing, and how much could be avoided by performing the genetic testing.

POPULATION ONE – Cystic kidney disease

Australian clinical guidelines for diagnosis and management of ADPKD (childhood/adult onset; polycystin-1 chr 16p, or polycystin-2 chr 4q) recommend ultrasound and age-related criteria for diagnosis, while kidney biopsy is not mentioned. (10) For patients less than 40 years old and a family history of ADPKD, cases with ≥ 3 cysts (unilateral or bilateral) meet the diagnostic criteria for ADPKD. Patients between 40 and 59 years and a family history of ADPKD require at least 2 cysts in each kidney to be diagnosed with ADPKD and patients aged 60 years and over require at least 4 cysts in each kidney for a diagnosis. There is limited evidence regarding diagnosis of ADPKD without family history; recommendations include ultrasound imaging of the index patient's parents, ultrasound imaging of the index patient for extra-renal cysts, and an arbitrary threshold of 10 cysts detectable on ultrasound. (10)

A global consensus report for ARPKD (fetal/neonatal onset; fibrocystin gene chr 6p) recommends ultrasound as the diagnostic modality for ARPKD, along with a family history consistent with autosomal-recessive inheritance. (11) These guidelines state that liver biopsy is not indicated for the investigation of liver disease associated with ARPKD. (11) A global consensus report for autosomal dominant tubulointerstitial kidney disease (including MCKD and *HNF1B*-related disease) concludes that a kidney biopsy (of the index patient or an affected relative) is required for a definitive diagnosis. (33) A UK review of the clinical utility of genetic testing for renal coloboma syndrome includes renal biopsy as a relevant comparator test, although notes the procedure is invasive and unable to determine the genetic cause of kidney disease. (27)

POPULATION TWO - Chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease

The comparator for chronic kidney disease in children will vary according to the suspected diagnosis and prior tests.

A 2017 global consensus statement states that a renal biopsy with immunofluorescence is required to diagnose C3 (complement 3) glomerulopathy (34). A 2016 consensus approach to the management of aHUS suggests kidney biopsy is useful to confirm thrombotic microangiopathy (TMA), however kidney biopsy is not requisite for diagnosis TMA or aHUS (43) (44). A 2012 international clinical practice guideline for the treatment of SRNS in children recommends kidney biopsy including light, immunofluorescence, and electron microscopy (45). The same guideline states that kidney biopsy is mandatory for diagnosis of glomerular nephropathy, including FSGS (45).

A kidney biopsy is necessary to diagnose FSGS (a histological subtype) but not for the associated clinical diagnosis of nephrotic syndrome

Diagnostic imaging (ultrasound, CT, MRI) and additional serum and urine tests are included the various diagnostic algorithms for renal tubular defects (46) (47) (48) (49) (50) (51). Patients with a suspected CAKUT, nephrolithiasis or nephrocalcinosis would not undergo renal biopsy. Patients with a suspected CAKUT would undergo further structural and functional diagnostic imaging and laboratory investigations (52). Similarly, patients with nephrolithiasis or nephrocalcinosis would undergo further diagnostic imaging and laboratory investigations, including measurement of serum and urine electrolytes, and serum parathyroid hormone.

OUTCOMES

PASC's First Consideration (December 2019)

PASC advised that the application needed re-structuring before it could consider the outcomes.

PASC noted there was no clear reference standard; genetic testing has previously been performed using a mixture of single gene tests, panel tests, and (more recently) targeted analysis of whole-exome sequencing (WES). The applicant advised that targeted analysis of WES had not been published.

Patient-relevant outcomes

Genetic testing assists in establishing a specific diagnosis in symptomatic individuals (index patients) and provides additional information about prognosis and clinical course, including early onset kidney failure (5), (29). Disease diagnosis reduces repeated and unnecessary tests, procedures and specialist appointments associated with the 'diagnostic odyssey', where patients spend years undergoing tests and attending appointments before a diagnosis is achieved (29).

The following outcomes were identified as being relevant to the assessment of comparative effectiveness and safety of genetic testing for inherited kidney disease.

PASC confirmed the proposed outcomes.

- Safety
  - Adverse events from inappropriate/unnecessary investigative tests & procedures
  - Adverse events from inappropriate/unnecessary treatments
  - Adverse events from inappropriate kidney donation
  - Psychological harms of time delay to diagnosis
  - Harms from passing on a genetic disease
  - Harms from genetic testing (misdiagnosis, missed diagnosis and incidental findings)
- Clinical utility
  - Change in clinical diagnosis (index patient)
  - Change in clinical management (index patient and family members)
  - Change in reproductive choices (index patient and family members)
- Clinical effectiveness
  - Incidence of continued renal impairment
  - Incidence of ESRF (including dialysis and kidney transplant)
  - Cardiovascular disease-related mortality
  - Incidence of kidney donation from a carrier relative

- Diagnostic performance (ability of testing to detect genetic variant)
    - Analytical sensitivity & specificity (versus reference standard)
    - Rate of reanalysis required
    - Time taken to achieve result
- Clinical validity (strength of genotype-phenotype relationship)
    - Diagnostic yield
    - Prognostic value
- Health related quality of life (HRQoL)

Healthcare system outcomes

The following changes to healthcare system resource utilisation as a result of listing genetic testing for inherited kidney disease on the MBS were identified.

- Genetic testing
- Specialist consultations
- Diagnosis (imaging, pathology, cystoscopy, biopsy, complications)
- Treatment
    - Medication (symptom management and preventative treatments directly related to the index disease)
    - Management of hypertension
    - Surgery
    - Screening for complications (imaging, pathology)
    - Dialysis
    - Kidney transplant (including complications)
    - Hospitalisation for kidney disease
- Genetic counselling (including reproductive counselling)
- In-Vitro Fertilisation (IVF)

Rationale

An accurate diagnosis guides the timing and intensity of intervention, allows for specific therapies to be initiated where possible (e.g. tolvaptan for ADPKD), and guides monitoring of extra-renal manifestations and potential future complications (29). In some cases, ACE inhibitor treatment delays the onset of kidney failure sufficiently long that affected individuals never need dialysis or a transplant.

The draft gene panel list for Population 2 indicates the genes that have diagnostic, predictive and prognostic utility. Diagnostic utility includes making a definitive diagnosis (indicating mode of inheritance) and identifying the underlying variant type (e.g. nonsense or missense variants).

Predictive utility includes whether the diagnosis will guide monitoring or treatment. Prognostic utility includes whether the diagnosis and treatment will change the disease trajectory and increase life expectancy. For instance, in a patient with SRNS, the diagnosis of a *COQ2* gene variant would guide treatment with daily COQ10. Treatment with daily COQ10 can be considered curative for these patients. Diagnosis of SRNS through genetic testing also avoids inappropriate treatment with steroids and immunosuppressants. In FSGS patients (with a known monogenic cause), deteriorating kidney function following transplant is likely due to rejection, which can be treated immediately with antirejection therapy, avoiding an otherwise customary investigative biopsy.

Identifying a genetic cause to chronic kidney disease also enables genetic counselling for family planning (29). In cases where a parent has a known genetic variant, prenatal diagnosis or pre-implantation genetic diagnosis (PGD) may be options (41). Cascade testing enables the diagnosis of currently asymptomatic relatives and carriers unsuitable for donating a kidney.

Patients who are misdiagnosed (false positive test result) may be labelled as having a chronic, rapidly progressive disease when none exists, creating anxiety for them and their families (41). Patients may also be 'misdiagnosed' through a positive test result for a gene with low penetrance, which weakens the genotype-phenotype correlation (5). Misdiagnosed patients may then go on to receive inappropriate therapy (potentially lifelong), exposing them needlessly to possible side effects (albeit usually minor), health care resource use and costs, while the true underlying pathology remains undiagnosed and untreated (41).

The consequence of a missed diagnosis (false negative test result) includes further diagnostic testing, delayed treatment onset and faster progression to ESRF in the index patient and other family members, and a risk of inadvertently passing on the genetic abnormality to their offspring (41).

PASC again noted the lack of a clear reference standard. Genetic testing has previously been performed using a mixture of single gene tests, panel tests and (more recently) targeted analysis of WES; very few patients have had full WES/WGS. In most patients, a presumptive diagnosis has been made without the inclusion of genetic testing.

A number of issues remain to be resolved:

- *What is the prevalence of each condition?*
- *Which conditions in the list can be presumptively diagnosed with high confidence by clinical assessment and family history alone?*
- *What proportion of patients will have changed diagnosis or management from genetic testing in each subpopulation? Please provide details about the specific change in diagnosis or management.*
- *Which genes are the exemplar genes in each condition (linked to OMIM number)?*
- *For the set of exemplar genes, what proportion of tests are expected to require additional orthogonal testing for validation because of the gene or variant type expected?*
- *What is the penetrance of the exemplar genes? How will low penetrance genes be managed?*

CURRENT AND PROPOSED CLINICAL MANAGEMENT ALGORITHMS FOR IDENTIFIED POPULATION

PASC's First Consideration (December 2019)

PASC recommended the application needed re-structuring before it could consider the clinical management algorithms.

PASC also acknowledged that the application had genetic testing as an additive to no genetic testing (usual care).

The applicant advised that patients are often not given an accurate diagnosis, but rather, are described by clinical features (e.g. cystic kidney disease), which all have different modes of inheritance, as well as prognostic implications.

Current management pathway

The Application Form stated that, in the absence of genetic testing, the diagnosis of an inherited kidney disease (and its differentiation from other conditions) relies on:

- History and clinical examination
- Diagnostic tests (imaging, pathology, urine analysis, diabetes testing)
- Detailed family history and urine analysis on first- and second-degree relatives
- Renal biopsy (including light microscopy, immunohistochemistry and electron microscopy of tissue)

Using these tools, a diagnosis of inheritable kidney disease can sometimes often be made, but without a formal genetic diagnosis. However, diagnostic accuracy is dependent on disease type and extra-renal clinical features and time to diagnosis is between three and five years. (32)

Renal biopsy can be performed in an inpatient or outpatient setting. General anaesthesia may be used during the procedure. Tissue samples are assessed in accredited pathology laboratories. As discussed above, renal biopsy is avoided where possible as it is an invasive procedure with associated risks and is sometimes inconclusive. Avoiding kidney biopsy may result in repeated and unnecessary alternative diagnostic tests and delayed or inappropriate treatments.

Management of inherited kidney disease is specific to the disease type, with specific treatments available for some diseases (e.g. tolvaptan ADPKD) and specific extra-renal monitoring appropriate for others (e.g. adult-onset diabetes for *HNF1B* related disease).

Information provided in the Application indicated that individuals with a diagnosis of inherited kidney disease are managed by a nephrologist. The nephrologist will provide information about inheritance or refer the patient to a genetic counsellor for advice. Depending on the diagnosis and the patient's disease status, the consultant will arrange further follow-up and review for monitoring kidney function and deterioration. Multidisciplinary care healthcare professionals (including GPs, other specialists, and allied health practitioners) may be involved in patient management. Dietary assessment and advice may be sought from an Accredited Practicing Dietician with experience in kidney disease.

Hypertension is a common consequence of chronic kidney disease and a major risk factor of cardiovascular disease. (53) Appropriate blood pressure management through blood pressure lowering medication (e.g. ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, thiazide diuretics) and lifestyle modification (e.g. physical activity, dietary modification, smoking cessation, alcohol moderation) is fundamental to the care of patients with chronic kidney disease of any stage. (53)

Once patients progress to end-stage kidney failure they require treatment with dialysis and/or a kidney transplant. Renal failure has a high morbidity with a risk of myocardial infarction, pulmonary oedema, extreme lethargy, peripheral neuropathy, bone fractures, stunted growth, and serious infections. Risks associated with dialysis include myocardial ischemia, arrhythmias due to fluid shifts, and profound hypertension. Dialysis also impacts a patient's ability to work and travel. Chronic kidney disease is associated with lower physical quality of life, with declines in quality of life with each progressive stage of CKD. (54)

Patients are dialysed for an average of 3 years and then undergo renal transplantation. (55) Renal transplantation is associated with increased mortality around the time of surgery, and then an increased risk of losing the transplant through immunological rejection or surgical complications in the first year. Over the next 10 years, the patient is at risk of infections due to immunosuppression and cancer. The average life expectancy of a kidney graft is about 12 years. Patients may have up to three transplants in their lifetime, interrupted with periods of dialysis while waiting for a new immunologically-matched kidney.

Patients with renal failure experience multiple hospital admissions associated with end-stage disease.

Proposed management pathway

Genetic testing is intended to be used as an adjunct diagnostic tool to clinical examination, family history and renal imaging. If inherited kidney disease is suspected, the index patient would be referred for genetic testing. The Application proposes that the availability of genetic testing on the MBS would reduce the need for renal biopsy and repeat imaging and pathology tests to confirm a diagnosis of inherited kidney disease.

Once a definitive diagnosis is made for the index patient through genetic testing, their family members may also be screened for the disease (cascade testing). This enables earlier monitoring and treatment of currently asymptomatic individuals and ensures that disease carriers do not act as kidney donors for the index patient. Targeted genetic and reproductive counselling can be provided, including prenatal diagnosis, IVF and pre-implantation genetic diagnosis.

The addition of genetic testing in the clinical management algorithm for index patients is relatively simple and may reduce the time taken to reach a definitive diagnosis and commence optimal medical therapy. Cascade testing of asymptomatic family members brings forward the diagnosis and management of currently asymptomatic individuals. This may increase health care resource utilisation in the short term but may delay the onset of renal failure and the costs associated with end stage kidney disease.

PASC's Second Consideration (April 2020)

PASC noted that the algorithm to determine the appropriate investigative pathway prior to genetic testing still needs to be clarified.

PASC noted that the clinical claim of improved safety due to fewer renal biopsies was unclear, because the algorithms that included introduction of genetic testing did not remove the necessity for renal biopsy.

Following the April 2020 PASC meeting, the clinical algorithms below were updated to reflect advice provided by the applicant and KidGen.

POPULATION ONE – Cystic kidney disease

Figure 2 outlines the **current** clinical management algorithm for patients with cystic kidney disease.

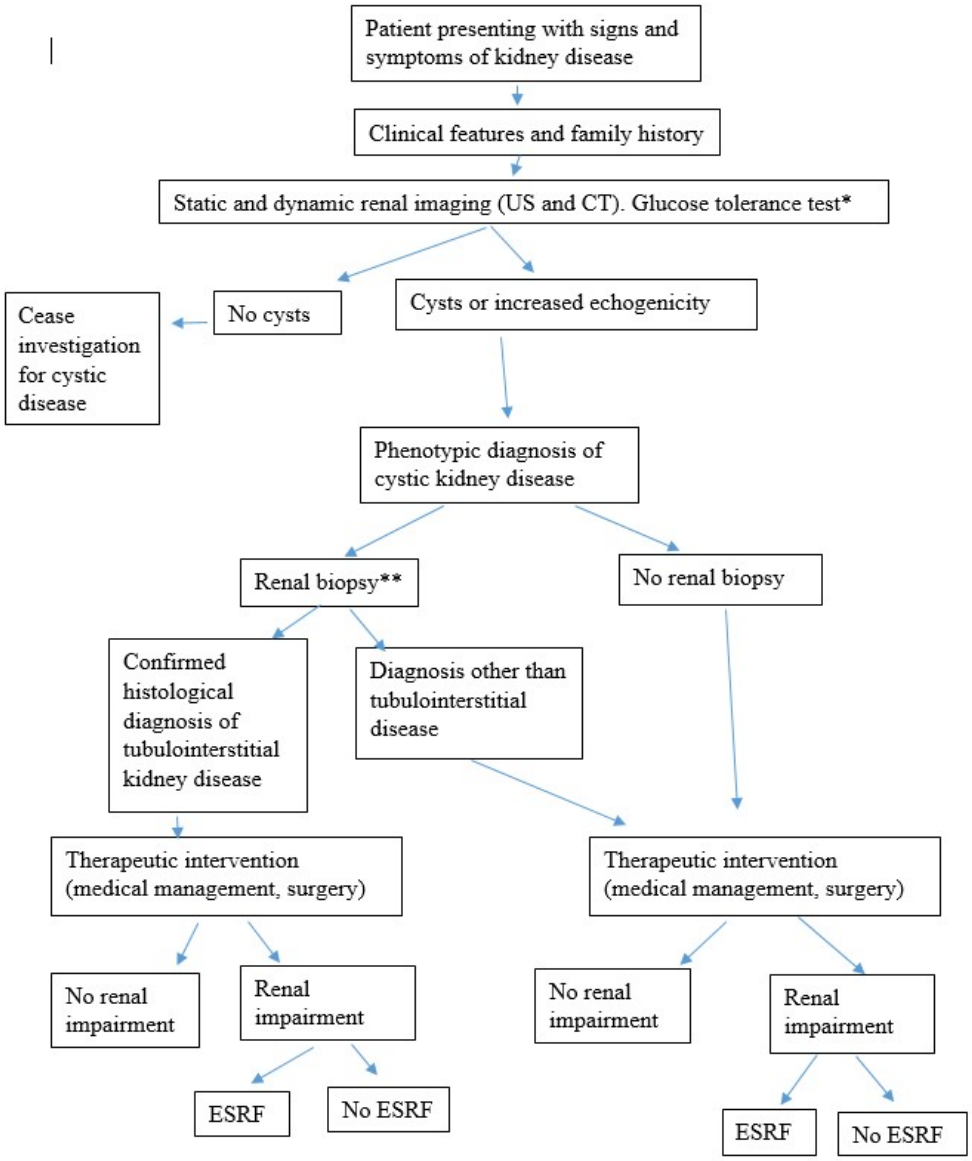

Figure 2 Current clinical management algorithm for cystic kidney disease

Algorithm compiled based on literature reviewed during the assessment.

Abbreviations: CT, computed tomography; ESRF, End Stage Renal Failure; US, ultrasound

Notes: * an oral glucose tolerance test for diabetes may be conducted to detect diabetes caused by *HNF1B* related disease; ** Renal biopsy is only required for definitive diagnosis of autosomal dominant tubulointerstitial kidney disease (including MCKD and *HNF1B*-related disease)

Figure 3 outlines the **proposed** clinical management algorithm for patients with cystic kidney disease.

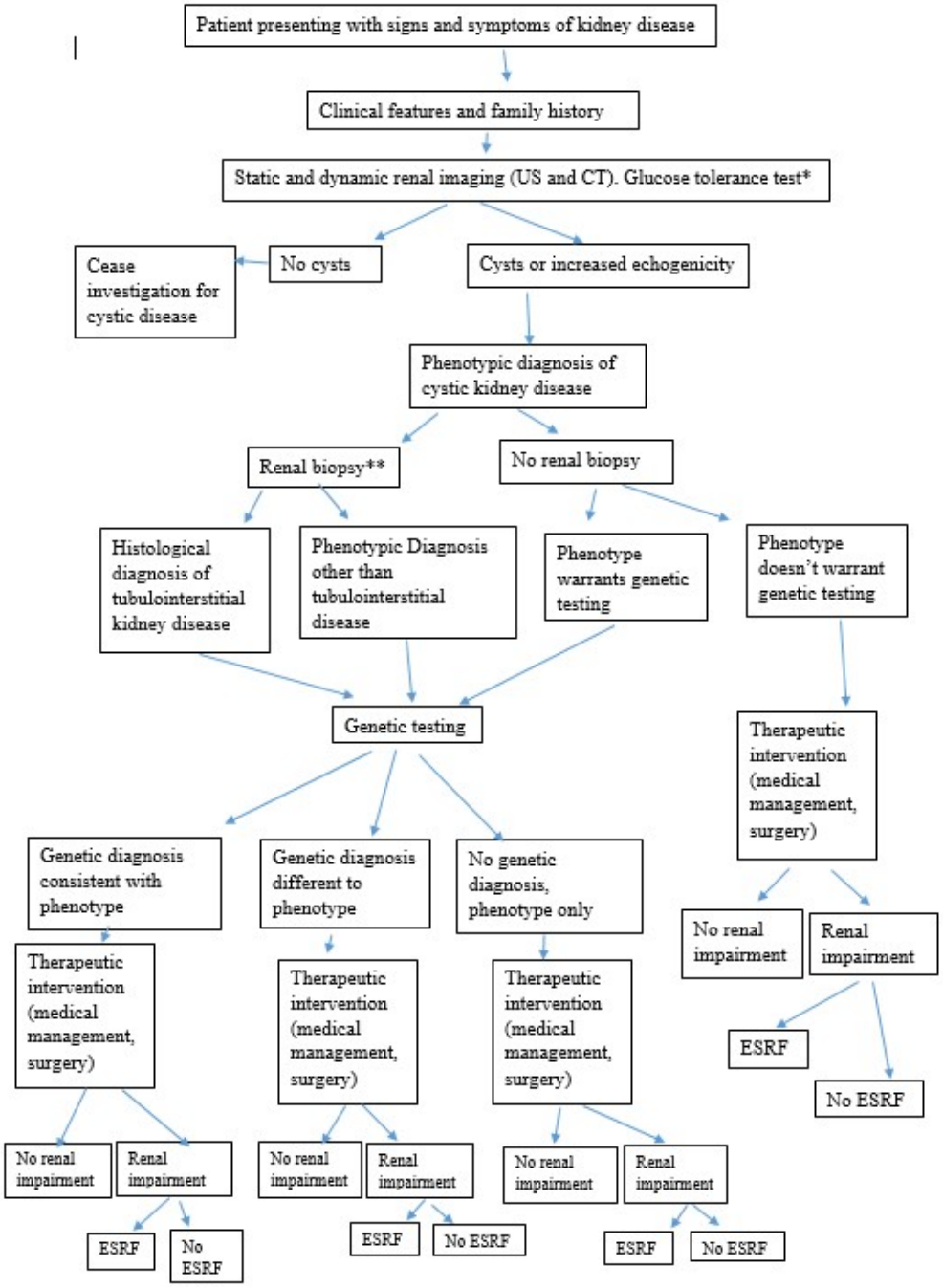

Figure 3 Proposed clinical management algorithm for cystic kidney disease

Algorithm compiled based on literature reviewed during the assessment.

Abbreviations: CT, computed tomography; ESRF, End Stage Renal Failure; US, ultrasound

Notes: * an oral glucose tolerance test for diabetes may be conducted to detect diabetes caused by *HNF1B* related disease; ** Renal biopsy is only required for definitive diagnosis of autosomal dominant tubulointerstitial kidney disease (including MCKD and *HNF1B*-related disease)

POPULATION TWO - Chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease)

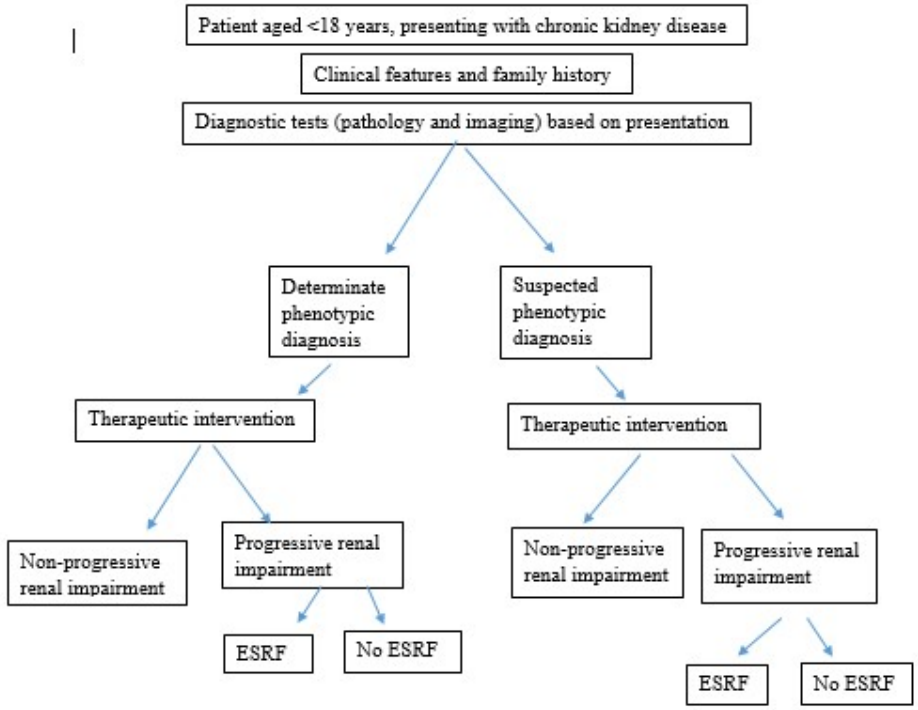

Figure 4 outlines the **current** clinical management algorithm for children aged under 18 years with chronic kidney (renal disease), excluding Alport syndrome and cystic disease.

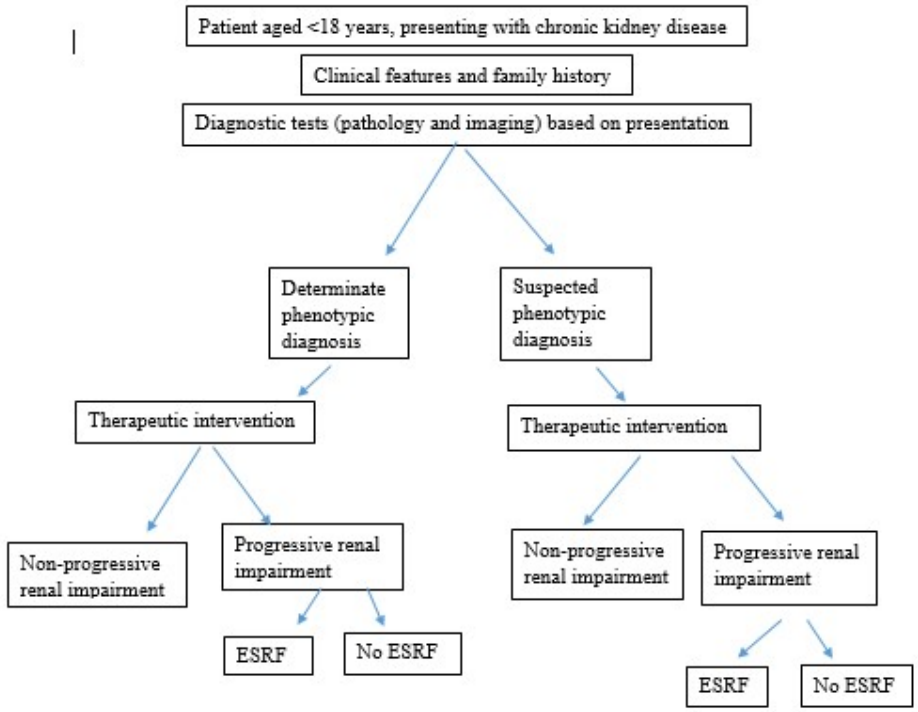

Figure 4 Current clinical management algorithm for chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease)

Algorithm compiled based on literature reviewed during the assessment.

Abbreviations: ESRF, End Stage Renal Failure

Figure outlines the **proposed** clinical management algorithm for children aged under 18 years with chronic kidney (renal disease), excluding Alport syndrome and cystic disease.

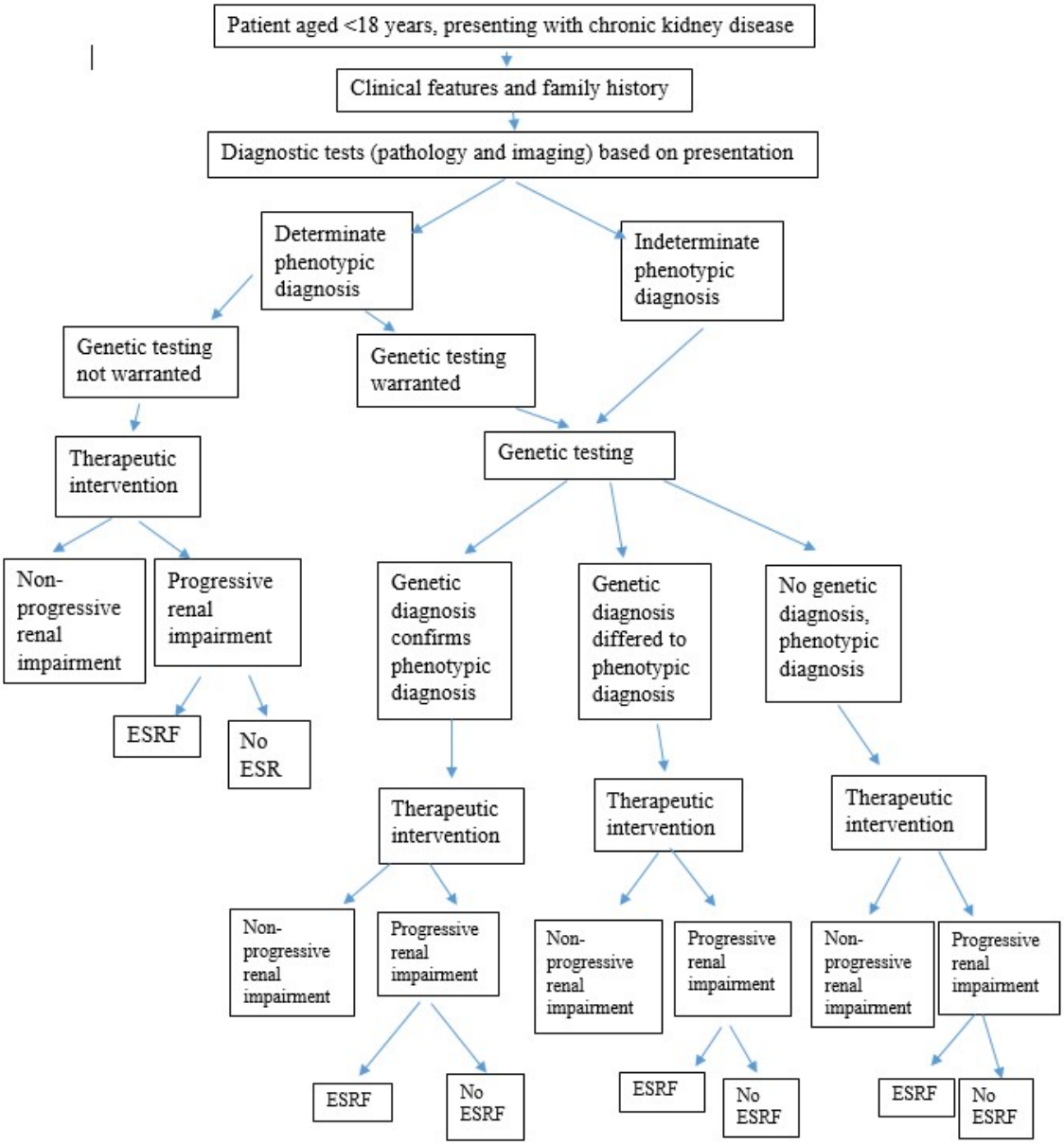

Figure 5 Proposed clinical management algorithm for chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease)

Algorithm compiled based on literature reviewed during the assessment.

Abbreviations: ESRF, End Stage Renal Failure

PROPOSED ECONOMIC EVALUATION

PASC's First Consideration (December 2019)

PASC advised that the application needed re-structuring before it could consider the economic evaluation.

PASC advised that this application fit a CUC approach. While PASC discussed whether ADPKD would be the exemplar condition among adult onset conditions, it was acknowledged that the main impact of this application will be in the paediatric (<18 years of age) population.

The applicant advised that the main implication of ADPKD is in the adult population, when most people are diagnosed.

It may therefore be inappropriate if "adult-onset" disease was used as an exemplar. PASC also noted that most of the conditions being considered will NOT be autosomal dominant (although ADPKD will probably be the single most common disease). PASC suggested that this raises the question of reproductive partner testing for recessive conditions.

The applicant advised this was not considered in earlier Application 1449 (for autosomal-recessive Alport syndrome), and many forms of CAKUT (and most adult-onset inherited renal disease) is autosomal dominantly inherited. Most (but not all) paediatric-onset disease is autosomal recessive, with the exception of CAKUT and some forms of nephrotic syndrome and atypical haemolytic uraemic syndrome.

PASC noted that, in the CUC model, the exemplar disease pairings may justify facilitation of other gene/disease pairings, with the proviso that: (a) unit cost of the test does not increase; and (b) downstream consequences are expected (on balance) to result in net improvement to health outcomes and cost.

The clinical claim is that genetic testing for inherited kidney disease is superior in terms of safety and clinical effectiveness to usual care, defined as diagnosis based on patient history, clinical examination, diagnostic imaging and family history. The following efficacy and safety outcomes are relevant to the evaluation:

- Genetic testing is more accurate than usual care in identifying individuals with inherited kidney disease who are at risk of renal failure and extra-renal morbidities.
- Genetic testing is safer than usual care
    - reducing the number of renal biopsies
    - avoids complications associated with inappropriate tests, procedures and treatments
- Genetic testing is more effective than usual care
    - delays disease progression
    - reduces cardiovascular disease-related mortality
    - enables appropriate reproductive counselling and IVF
- Genetic testing improves HRQoL

As renal biopsy to determine a histological diagnosis is not indicated for some patient populations, particularly those with ADPKD, (and not always used in the remaining populations), the superiority of genetic testing over other tests is uncertain. Time to diagnosis, misdiagnosis, missed diagnosis, incidental findings, and associated harms should be compared for each patient population.

The appropriate economic evaluation is a cost-utility analysis, capturing the benefits of more accurate diagnosis and improved HRQoL due to early intervention and delayed onset and progression of renal failure in the index patient and biological family members.

PASC's Second Consideration (April 2020)

PASC confirmed that the most appropriate analysis is a cost-utility analysis, using an approach based on diagnostic yield.

PASC advised that input or data from services actually providing testing (i.e. 'real world data') would be very helpful for the financial modelling.

PROPOSED MBS ITEM DESCRIPTORS AND MBS FEES

The item descriptors for the index populations are consistent with the Application Form and MSAC Clinical Utility Card template. Given the number of genes associated with each index patient population, it may not be feasible to list the relevant genes in the item descriptor, as per MBS Item 73298 for Alport Syndrome.

The item descriptor for Population Three - Cascade testing was modified from that proposed in the Application Form. The updated text removed reference to lists of genes in the index population item descriptors.

The MBS fees proposed by the applicant for testing of the index patient and cascade testing are consistent with MBS Items 73298 (genetic testing of a patient with clinical and family history are strongly suggestive of Alport Syndrome) and 73299 (genetic testing of a first degree relative of a patient with Alport syndrome) respectively. These fees are intended to incorporate the cost of venesection and transport of the specimen to the testing laboratory; the cost of the genetic test (testing, laboratory equipment, analysis, and reporting); and cost of consultations and counselling (before and after testing).

The applicant sought clarification on whether autosomal recessive Alport syndrome is included in 'causative variant' (because it was not included in the descriptor for earlier Application 1476).

PASC's First Consideration (December 2019)

PASC advised that the application needed re-structuring before it could consider MBS item descriptors and fees.

PASC queried if the revised application should consider the need for an MBS item for data re-interrogation (as new genes are identified).

PASC's Second Consideration (April 2020)

PASC agreed with the additional wording suggested by the Department (in green) for items AAAA1, AAAA2 and CCCC below.

PASC recommended the changes suggested in red for item BBBB. It also suggested that the wording for this item could be tightened.

PASC noted the following issues:

- *Descriptors AAAA/BBBB refer to use of a quantitative algorithm to determine likelihood of a genetic cause, but the availability of such algorithms has not been addressed.*
- *It is assumed (but not made explicit) that the clinician has pursued other modes of non-genetic testing as part of the algorithm.*
- *The number of genes that need to be explored in different clinical scenarios varies widely, but the rebate does not.*
- *The test methodology is unspecified, and it is unclear how it would be ensured that adequate and/or appropriate testing is performed*
- *If the item is used ("once per lifetime") on inadequate/suboptimal testing, it will not be available for more comprehensive testing.*
- *The necessity for family history is inappropriate, since AR conditions generally have no family history (and many paediatric renal diseases are AR).*
- *Item BBBB does not exclude cystic kidney disease or Alport syndrome, which means two MBS items could be used for the same test.*

PASC advised that the wording 'clinically actionable' should be removed from the descriptors as it is not appropriate.

POPULATION ONE – Cystic kidney disease

Table 5 Genetic testing for the purpose of diagnosis (testing of the index patient)

Category 6 – PATHOLOGY SERVICES
Group P7 - GENETICS Item AAAA1 Characterisation of germline gene variants **requested by a specialist or consultant physician** in one or more of the genes implicated in inherited cystic kidney disease in a patient with a renal abnormality, for whom clinical and family history criteria, as assessed by a treating specialist using a quantitative algorithm, place the patient at > 10% risk of having a clinically actionable pathogenic variant identified. Fee: $1,200.00 Benefit: 75% = $900.00 85% = $1,115.30

POPULATION TWO - Chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease)

Table 6 Genetic testing for the purpose of diagnosis (testing of the index patient)

Category 6 – PATHOLOGY SERVICES
Group P7 - GENETICS Item AAAA2 Characterisation of germline gene variants **requested by a specialist or consultant physician** in one or more of the genes implicated in inherited kidney disease in a patient aged under 18 years with chronic kidney disease, for whom clinical and family history criteria, as assessed by a treating specialist using a quantitative algorithm, place the patient at > 10% risk of having a clinically actionable pathogenic variant identified. Fee: $1,200.00 Benefit: 75% = $900.00 85% = $1,115.30

An additional MBS item has been proposed for data re-interrogation, based on MSAC Application 1476 – Genetic testing for childhood syndromes.

Table 7 Data re-interrogation

Category 6 – PATHOLOGY SERVICES
Group P7 - GENETICS Item BBBB Re-analysis of genetic data obtained under item AAAA1 or AAAA2, for characterisation of previously unreported germline gene variants related to the clinical phenotype, as requested by a consultant physician practising as a clinical geneticist or a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist, for a patient with ~~a strong~~ **clinical** suspicion of a monogenic condition. Performed no more than twice per patient. Performed at an interval of not less than 18 months following AAAA1 or AAAA2. If repeated, must be at an interval of not less than 18 months from previous BBBB Fee: $285.71 [based on earlier application 1476, where the MBS fee for WES re-analysis was 24% of the initial analysis fee] Benefit: 75% = $214.28 85% = $242.86

POPULATION THREE - Cascade testing

Table 8 Cascade testing of family members

Category 6 – PATHOLOGY SERVICES
Group P7 - GENETICS Item CCCC Request by a clinical geneticist, or **requested by a specialist or consultant physician** ~~medical specialist~~ providing professional genetic counselling services, *for detection of a single gene variant in a first degree relative of a patient with a known monogenic cause of kidney disease where previous genetic testing under item AAAA1, AAAA2, or BBBB has identified the causative variant.* Fee: $400.00 Benefit: 75% = $300.00 85% = $340.00

CONSULTATION FEEDBACK

PASC's First Consideration (December 2019)

PASC advised that the PICO needed to be re-structured before it could consider any consultation feedback.

PASC's Second Consideration (April 2020)

PASC noted the consultation feedback from professional societies and consumers. PASC agreed with the professional societies' concerns about the implications of genetic screening without adequate genetic counselling.

NEXT STEPS

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as a DCAR (Department-contracted assessment report).

References

(Please note: Where publication titles include 'mutation' or 'mutations', these have been retained, noting the current correct terms are 'variant' or 'variants')

1. *Whole-Exome Sequencing in Adults With Chronic Kidney Disease A Pilot Study.* Lata, Sneh, et al. 2, 2018, Ann Intern Med, Vol. 168, pp. 100-109.

2. *Massively parallel sequencing and targeted exomes in familial kidney disease can diagnose underlying genetic disorders.* Mallett, Andrew J, et al. 2017, Kidney International, Vol. 92, pp. 1493-1506.

3. *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.* Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. 2013, Kidney Inter Suppl, Vol. 3, pp. 1-150.

4. Australian Institute of Health and Welfare. *Chronic Kidney Disease.* Canberra : Australian Government, 2019.

5. *Personalized medicine in chronic kidney disease by detection of monogenic mutations.* Connaughton, Dervla M and Hildebrandt, Friedhelm. 2019, Nephrol Dial Transplant, pp. 1-8.

6. *A kidney-disease gene panel allows a comprehensive genetic diagnosis of cystic and glomerular inherited kidney diseases.* Bullich, Gemma, et al. 2018, Kidney International, Vol. 94, pp. 363-371.

7. *Ciliopathies.* Braun, Daniela A and Hildebrandt, Friedhelm. 2017, Cold Spring Harbor Perspectives in Biology, p. 9:a028191.

8. *The prevalence and epidemiology of genetic renal disease amongst adults with chronic kidney disease in Australia.* Mallett, Andrew, et al. 98, 2014, Orphanet Journal of Rare Diseases, Vol. 9, pp. 1-9.

9. Australian Institute of Health and Welfare. National Hospital Morbidity Database, Principal data cube under ICD-10-AM Edition 10. [Online] 2017-18. [Cited: 16 Oct 2019.] https://www.aihw.gov.au/reports/hospitals/principal-diagnosis-data-cubes/contents/data-cubes.

10. *KHA-CARI guideline recommendations for the diagnosis and management of autosomal dominant polycystic kidney disease.* Rangan, Gopala K, et al. 2016, Nephrology, Vol. 21, pp. 705-716.

11. *Consensus Expert Recommendations for the Diagnosis and Management of Autosomal Recessive Polycystic Kidney Disease: Report of an International Conference.* Guay-Woodford, Lisa M, et al. 3, 2014, The Journal of Pediatrics, Vol. 165, pp. 611-617.

12. *A mechanistic approach to inherited polycystic kidney disease.* Bissler, John J and Dixon, Bradley P. 2005, Pediatr Nephrol, Vol. 20, pp. 558-566.

13. *Clinical utility gene card for: Tuberous sclerosis complex (TSC1, TSC2).* Mayer, Karin, et al. 2014, European Journal of Human Genetics, Vol. 22, p. doi:10.1038/ejhg.2013.129.

14. Orphanet Report Series. Prevalence of rare diseases: Bibliographic Data. [Online] January 2019 - Number 1. [Cited: 11 Oct 2019.] http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf.

15. *Adult patients with sporadic polycystic kidney disease: the importance of screening for mutations in teh PKD1 and PKD2 genes.* Neumann, Hartmut P H, et al. 2012, Int Urol Nephrol, Vol. 44, pp. 1753-1762.

16. *Renal Medicine 1: Genetic Kidney Diseases.* Hildebrandt, Friedhelm. 2010, Lancet, Vol. 375, pp. 1287-95.

17. *Neonatal Polycystic Kidney Disease.* Verghese, Priya and Miyashita, Yosuke. 2014, Clin Perinatol, Vol. 41, pp. 543-560.

18. *A case of sporadic medullary cystic kidney disease type 1 (MCKD1) with kidney enlargement complicated by IgA nephropathy.* Suzuki, Taihei, et al. 2015, Pathology International, Vol. 65, pp. 379-382.

19. *New insights: nephronophthisis-medullary cystic kidney disease.* Hildebrandt, F and Omram, H. 2001, Pediatr Nephrol, Vol. 16, pp. 168-176.

20. *Autosomal Dominant Tubulointerstitial Kidney Disease DUe to MUC1 Mutation.* Yu, Samuel Mon-Wei, et al. 4, 2017, Am J Kidney Dis, Vol. 71, pp. 495-500.

21. *Diagnosis, management, and prognosis of HNF1B nephropathy in adulthood.* Faguer, Stanislas, et al. 2011, Kidney International, Vol. 80, pp. 768-776.

22. *ARPKD and early manifestations of ADPKD: the original polycystic kidney disease and phenocopies.* Bergmann, Carsten. 2015, Pediatr Nephrol, Vol. 30, pp. 15-30.

23. *Cystic Kidney Disease: A Primer.* Cramer, Monica T and Guay-Woodford, Lisa M. 4, 2015, Advances in Chronic Kidney Disease, Vol. 22, pp. 297-305.

24. *Neonatal renal cystic diseases.* Khare, Anishka, et al. 2018, The Journal of Maternal-Fetal & Neonatal Medicine, Vol. 31, pp. 2923-2929.

25. *Intrafamilial Phenotypic Variability in Tuberous Sclerosis Complex.* Lyczkowski, David A, et al. 12, 2007, Journal of Child Neurology, Vol. 22, pp. 1348-1355.

26. *Update of PAX2 Mutations in Renal Coloboma Syndrome and Establishment of a Locus-Specific Database.* Bower, Matthew, et al. 3, 2012, Human Mutation, Vol. 33, pp. 457-466.

27. *Clinical utility gene card for: renal coloboma (papillorenal) syndrome.* Bower, Matthew, et al. 2011, European Journal of Human Genetics, Vol. 19, p. doi:10.1038/ejhg.2011.16.

28. Otsuka Australia Pharmaceutical Pty Ltd. Australian Product Information: Jinarc (Tolvaptan) Tablets. [Online] 13 May 2019. [Cited: 24 Oct 2019.] https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2017-PI-01500-1&d=201910241016933.

29. *Exploring the genetic basis of early-onset chronic kidney disease.* Vivante, Asaf and Hildebrandt, Friedhelm. 3, 2016, Nature Reviews Nephrology, Vol. 12, pp. 133-146.

30. *Prevalence of genetic renal disease in children.* Fletcher, Jeffrey and McDonald, Stephen. Sydney : s.n., 2013, Pediatric Nephrology, Vol. 28, pp. 251-256.

31. *Renal Genetics in Australia: Kidney medicine in the genomic age.* Jayasinghe, Kushani, et al. Brisbane : s.n., 2019, Nephrology, Vol. 24, pp. 279-286.

32. Personal communication with the applicant.

33. *Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management - A KDIGO consensus report.* Eckardt, Kai-Uwe, et al. 4, 2015, Kidney International, Vol. 88, pp. 676-683.

34. *Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference.* Goodship, Timothy H J, et al. 2017, Kidney International, Vol. 91, pp. 539-551.

35. *Diagnosis and Management of Nephrotic Syndrome in Adults.* Kodner, Charles. 6, 2016, Am Fam Physician, Vol. 93, pp. 479-485.

36. *Renal tubular disorders.* Broodbank, David and Christian, Martin T. 2018, Paediatrics and Child Health, pp. 308-317.

37. *Medical Management of Kidney Stones: AUA Guideline.* Pearle, Margaret S, et al. 2014, The Journal of Urology, Vol. 192, pp. 316-324.

38. National Association of Testing Authorities, Australia. Keyword search of NATA Accredited Facilities. [Online] [Cited: 18 Oct 2019.] https://www.nata.com.au/accredited-facility.

39. Department of Molecular Genetics, The Children's Hospital at Westmead. Australian Renal Gene Panels by Massively Parallel Sequencing. [Online] 2015. [Cited: 18 Oct 2019.] https://www.kidney-research.org/ARGP/MPS_Renal_panels_info_sheet_v1_1.pdf.

40. Victorian Clinical Genetics Services. NEW! Tiered Clinical Exome Sequencing test options. [Online] [Cited: 18 Oct 2019.] https://www.vcgs.org.au/news/new-tiered-clinical-exome-sequencing-test-options.

41. MSAC PICO Confirmation. Application 1449: Genetic testing for Alport syndrome. [Online] [Cited: 17 Oct 2019.] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1449-Public.

42. Department of Molecular Genetics, The Children's Hospital at Westmead. Consent Form for Massively Parallel Sequencing Testing. [Online] [Cited: 21 Oct 2019.] https://www.kidney-research.org/ARGP/MPS_testing_consent_form_v1_1.pdf.

43. *An international consensus approach to the management of atypical hemolytic uremic syndrome in children.* Loirat, Chantal, et al. 2016, Pediatr Nephrol, Vol. 31, pp. 15-39.

44. *Thrombotic Microangiopathy and the Kidney.* Brocklebank, Vicky, Wood, Katrina M and Kavanagh, David. 2018, Clin J Am Soc Nephrol, Vol. 13, pp. 300-317.

45. *KDIGO Clinical Practice Guideline for Glomerulonephritis.* Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. 2012, Kidney Inter Suppl, Vol. 2, pp. 139-274.

46. *Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference.* Blanchard, Anne, et al. 2017, Kidney International, Vol. 91, pp. 24-33.

47. *EAST/SeSAME syndrome: Review of the literature and introduction of four new Latvian patients.* Celmina, M, et al. 2019, Clinical Genetics, Vol. 95, pp. 63-78.

48. *Treatment and long-term outcome in primary distal renal tubular acidosis.* Lopez-Garcia, Sergio Camillo, et al. 2019, Nephrol Dial Transplant, Vol. 34, pp. 981-991.

49. Knoers, Nine. Nephrogenic Diabetes Insipidus. [Online] 14 Jun 2012. [Cited: 30 Oct 2019.] https://www.ncbi.nlm.nih.gov/books/NBK1177/pdf/Bookshelf_NBK1177.pdf.

50. *Congenital nephrogenic diabetes insipidus with end-stage renal disease.* Ryu, Hyun Ho, et al. 2015, Korean J Intern Med, Vol. 30, pp. 259-261.

51. *Molecular characterization of a recurrent 10.9kb CYP24A1 deletion in Idiopathic Infantile Hypercalcemia.* Molin, Arnaud, et al. 2019, European Journal of Medical Genetics, Vol. 62, p. 103577.

52. Rosenblum, Norman D. Evaluation of congenital anomalies of the kidney and urinary tract (CAKUT). [Online] UpToDate, Sep 2019. [Cited: 02 Nov 2019.] https://www.uptodate.com/contents/evaluation-of-congenital-anomalies-of-the-kidney-and-urinary-tract-cakut.

53. National Heart Foundation of Australia. *Guideline for the diagnosis and management of hypertension in adults.* Melbourne : National Heart Foundation of Australia, 2016.

54. *The impact of progressive kidney disease on health-related quality-of-life: a 12 year community cohort study.* Wyld, Melanie L R, et al. s.l. : Quality of Life Research, 2019, Vol. 28, pp. 2081-2090.

55. Kidney Health Australia. Kidney transplant. [Online] 2019. [Cited: 23 Oct 2019.] https://kidney.org.au/your-kidneys/support/kidney-transplant.

56. National Organization for Rare Disorders. Rare Disease Database - Atypical hemolytic uremic syndrome. [Online] [Cited: 16 Oct 2019.] https://rarediseases.org/rare-diseases/atypical-hemolytic-uremic-syndrome/.

57. *Complement and the atypical hemolytic uremic syndrome in children.* Loirat, Chantal, Noris, Marina and Fremeaux-Bacchi, Veronique. 2008, Pediatr Nephrol, Vol. 23, pp. 1957-1972.

58. Martin, B and Smith, R J H. C3 Glomerulopathy. [Online] 5 Apr 2018. [Cited: 16 Oct 2019.] http://www.ncbi.nlm.nih.gov/books/NBK1425/.

59. *Updated on C3 glomerulopathy.* Barbour, Thomas D, Ruseva, Marieta M and Pickering, Matthew C. 2016, Nephrol Dial Transplant, Vol. 31, pp. 717-725.

60. *High-Throughput Genetic Testing for Thrombotic Microangiopathies and C3 Glomerulopathies.* Bu, Fengxiao, et al. 2016, J Am Soc Nephrol, Vol. 27, pp. 1245-1253.

61. *Genetics and Outcome of Atypical Hemolytic Uremic Syndrome: A Nationwide French Series Comparing Children and Adults.* Fremeaux-Bacchi, Veronique, et al. 2013, Clin J Am Soc Nephrol, Vol. 8, pp. 554-562.

62. *Kidney disease 2: Rare inherited kidney diseases: challenges, opportunities, and perspectives.* Devuyst, Olivier, et al. 2014, Lancet, Vol. 383, pp. 1844-1859.

63. Alexion Pharmaceuticals Australasia Pty Ltd. Australian Product Information - Soliris (Eculizumab RMC) Concentrated Solution for Intravenous Infusion. [Online] 09 Jul 2019. [Cited: 24 Oct 2019.] https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02947-3.

64. *C3 glomerulopathy: consensus report.* Pickering, Matthew C, et al. 2013, Kidney International, Vol. 84, pp. 1079-1089.

65. *Clinical Utility of Genetic Testing in Children and Adults with Steroid-Resistant Nephrotic Syndrome.* Santin, Shiela, et al. 2011, Clin J Am Soc Nephrol, Vol. 6, pp. 1139-1148.

66. *Whole Exome Sequencing of Patients with Steroid-Resistant Nephrotic Syndrome.* Warejko, Jillian K, et al. 2018, Clin J Am Soc Nephrol, Vol. 13, pp. 53-62.

67. *Simultaneous sequencing of 37 genes identified causative mutations in the majority of children with renal tubulopathies.* Ashton, Emma J, et al. 2018, Kidney International, Vol. 93, pp. 961-967.

68. Orphanet. Orphanet Rare Diseases. [Online] 2019. [Cited: 27 Oct 2019.] https://www.orpha.net/consor/cgi-bin/Disease.php?lng=EN.

69. *Bartter syndrome: causes, diagnosis, and treatment.* da Silva Cunha, Tamara and Pfeferman Heilberg, Ita. 2018, International Journal of Nephrology and Renovascular Disease , Vol. 11, pp. 291-301.

70. *Hyperkalemic Forms of Renal Tubular Acidosis: Clinical and Pathophysiological Aspects.* Batlle, Daniel and Arruda, Jose. 4, 2018, Adv Chronic Kidney Dis, Vol. 25, pp. 321-333.

71. *Clinical Approach to Proximal Tubular Acidosis in Children.* Finer, Gal and Landau, Daniel. 4, 2018, Adv Chronic Kidney Dis, Vol. 25, pp. 351-357.

72. Waldman, Steven D. 72 - Nephrolithiasis. *Atlas of Common Pain Syndromes (Fourth Edition).* Missouria : Elsevier, 2019, pp. 278-281.

73. Kidney Health Australia. Fact sheet: Kidney Stones. [Online] September 2017. [Cited: 1 Nov 2019.] https://kidney.org.au/cms_uploads/docs/kidney-stones-fact-sheet-%E2%80%93-kidney-health-australia.pdf.

74. *Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis.* Daga, Ankana, et al. 2018, Kidney International, Vol. 93, pp. 204-213.

75. *Prevalence of Monogenic Causes in Pediatric Patients with Nephrolithiasis or Nephrocalcinosis.* Braun, Daniela A, et al. 2016, Clin J Am Soc Nephrol, Vol. 11, pp. 664-672.

76. *Nephrocalcinosis and urolithiasis in children.* Habbig, Sandra, Beck, Bodo B and Hoppe, Bernd. 2011, Kidney International, Vol. 80, pp. 1278-1291.

77. *Genetic, pathophysiological, and clinical aspects of nephrocalcinosis.* Oliveira, Ben, et al. 2016, Am J Physiol Renal Physiol, Vol. 311, pp. F1243-1252.

78. *Fourteen monogenic genes account for 15% of Nephrolithiasis/Nephrocalcinosis.* Halbritter, Jan, et al. 2015, J Am Soc Nephrol, Vol. 26, pp. 543-551.

79. *Primary hyperoxaliuria Type 1: indications for screening and guidance for diagnosis and treatment.* Cochat, Pierre, et al. 2012, Nephrol Dial Transplant, Vol. 27, pp. 1729-1736.

80. *Clinical and Genetic Analysis of Patients with Cystinuria in the United Kingdom.* Rhodes, Hannah L, et al. 2015, Clin J Am Soc Nephrol, Vol. 10, pp. 1235-1245.

81. *A molecular and genetic view of human renal and urinary tract malformations.* Woolf, Adrian S. 2000, Kidney International, Vol. 58, pp. 500-512.

82. Rosenblum, Norman D. Overview of congenital anomalies of the kidney and urinary tract (CAKUT). [Online] UpToDate, Sep 2019. [Cited: 02 Nov 2019.] https://www.uptodate.com/contents/overview-of-congenital-anomalies-of-the-kidney-and-urinary-tract-cakut?search=treatment%20of%20congenital%20anomalies%20of%20the%20kidney%20and%20urinary%20tract%20(CAKUT)&source=search_result&selectedTitle=2~103&usage_ty.

83. *Targeted gene sequencing and whole-exome sequencing in autopsied fetuses with prenatally diagnosed kidney anomalies.* Rasmussen, M, et al. 2018, Clinical Genetics, Vol. 93, pp. 860-869.

84. *Whole-Exome Sequencing Identifies Causative Mutations in Families with Congenital Abnormalities of the Kidney and Urinary Tract.* van der Ven, Amelie T, et al. 2018, J Am Soc Nephrol, Vol. 29, pp. 2348-2361.

85. *Monogenic causes of chronic kidney disease in adults.* Connaughton, Dervla M, et al. 2019, Kidney International, Vol. 95, pp. 914-928.

86. *Clinical utility gene card for: Fabry diseases - update 2016.* Gal, Andreas, et al. 2017, European Journal of Human Genetics, Vol. 25, p. doi:10.1038/ejhg.2017.17.

87. *Screening, diagnosis, and management of patients with Fabry disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Contorversies Conference.* Schiffmann, Raphael, et al. 2017, Kidney International, Vol. 91, pp. 284-293.

88. *Fabry disease: Baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry.* Eng, C M, et al. 2007, J Inherit Metab Dis, Vol. 30, pp. 184-192.

89. Australian Government Department of Health. Public Summary Document: Updated literature review of agalsidase alfa (Replagal) and agalsidase beta (Fabrazyme) for the treatment of Fabry disease. [Online] Nov 2009. [Cited: 5 Nov 2019.] http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2009-11/Agalsidase_Fabry_Review_PSD_2009-11_FINAL.pdf.

90. Public Summary Document: Migalastat: Capsule containing migalastat hydrochloride 150 mg; Galafold. [Online] Nov 2017. [Cited: 5 Nov 2019.] http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2017-11/files/migalastat-psd-november-2017.pdf.

91. *von Hippel–Lindau disease: A clinical and scientific review.* Maher, Eamonn R, Neumann, Hartmut P H and Richard, Stephane. 2011, European Journal of Human Genetics, Vol. 19, pp. 617-623.

92. *Clinical utility gene card for: von Hippel–Lindau (VHL).* Decker, Jochen, et al. 2014, European Journal of Human Genetics, Vol. 22, p. doi:10.1038/ejhg.2013.180.

93. *Life expectancy and cause of death in males and females with Fabry disease: Findings from the Fabry Registry.* Waldek, Stephen, et al. 11, 2009, Genetics in Medicine, Vol. 11, pp. 790-796.

94. *Fabry disease revisited: Management and treatment recommendations for adult patients.* Ortiz, Alberto, et al. 2018, Molecular Genetics and Metabolism, Vol. 123, pp. 416-427.

95. *Survival and causes of death in patients with von Hippel-Lindau disease.* Binderup, Marie Louise Molgaard, et al. 2017, J Med Genet, Vol. 54, pp. 11-18.

96. *Current Management of Pheochromocytoma/Paraganglioma: A Guide for the Practicing Clinican in the Era of Precision Medicine.* Nolting, Svenja, et al. 2019, Cancers, Vol. 11, p. doi:10.3390/cancers11101505.

97. *Carnitine Palmitoyltransferase II Deficiency: A Clinical, Biochemical, and Molecular Review.* Sigauke, Ellen, et al. 11, 2003, Laboratory Investigation, Vol. 83, pp. 1543-1554.

98. *A novel mutation in BCS1L associated with deafness, tubulopathy, growth retardation and microcephaly.* Jackson, C B, et al. 2016, Eur J Pediart, Vol. 175, pp. 517-525.

99. *Adams Oliver Syndrome: A Family With Extreme Variability in Clinical Expression.* Bamforth, J S, et al. 1994, American Journal of Medical Genetics, Vol. 49, pp. 393-369.

100. *Expanding the phenotype in Adams–Oliver syndrome correlating with the genotype.* Dudoignon, Benjamin, et al. 2019, Americal Journal of Medical Genetics, pp. 1-9.

101. *Risk Factors for Severe Renal Disease in Bardet-Biedl Syndrome.* Forsythe, Elizabeth, et al. 2017, J Am Soc Nephrol, Vol. 28, pp. 963-970.

102. *Clinical utility gene card for: Bardet-Biedl syndrome.* Slavotinek, Anne and Beales, Philip. 2011, European Journeal of Human Genetics, Vol. 19, p. doi:10.1038/ejhg.2010.199.

103. *Controversies and research agenda in nephropathic cystinosis: conclusions from a "Kindey Disease: Improving Global Outcomes" (KDIGO) Controversies Conference.* Langman, Craig B, et al. 2016, Kidney International, Vol. 89, pp. 1192-1203.

104. *C3 Glomerulopathy: Clinicopathologic Features and Predictors of Outcome.* Medjeral-Thomas, Nicholas R, et al. 1, 2014, Clin J Am Soc Nephrol, Vol. 9, pp. 46-53.

105. *Steroid-resistant nephrotic syndrome: past and current perspectives.* Nourbakhsh, Noureddin and Mak, Robert H. s.l. : Pediatric Health, Medicine and Therapeutics, 2017, Vol. 8, pp. 29-37.