



Australian Government

Department of Health

Application 1449:

Genetic testing for Alport Syndrome

PICO Confirmation

(to guide a new application to MSAC)

(Version 1.0)

This PICO Confirmation Template is to be completed to guide a new request for public funding for new or amended medical service(s) (including, but not limited to the Medicare Benefits Schedule (MBS)). It is relevant to proposals for both therapeutic and investigative medical services.

Please complete all questions that are applicable to the proposed service, providing relevant information only.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment (HTA Team) on the contact number and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Phone: +61 2 6289 7550

Email: hta@health.gov.au

Website: [MSAC Website](#)

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

Table 1 Genetic testing for the purpose of diagnosis (testing of the proband)

Component	Description
Patients	Individuals with a strong clinical suspicion of Alport syndrome (AS). AS is suspected when there is persistent glomerular haematuria. The likelihood of AS increases with a family history of AS or renal failure, and no other obvious cause; or when the characteristic clinical features (hearing loss, lenticonus, or retinopathy) are present.
Prior tests	Detailed previous medical and family history and urinalysis (including first- and second-degree relatives, if possible). May also include routine renal function investigations, ophthalmoscopy and audiometry.
Intervention	Testing for germline gene variants in one or more of the following genes: <i>COL4A5</i> , <i>COL4A3</i> or <i>COL4A4</i> .
Comparator	No genetic testing (usual care), with diagnosis reliant on previous medical history, family history and clinical criteria (e.g. urine analysis, renal function, ophthalmoscopy, audiometry), with or without renal biopsy.
Outcomes	<ul style="list-style-type: none"> • Diagnostic performance (analytical sensitivity and specificity; likelihood ratios; rate of repeat testing) • Clinical validity (clinical sensitivity and specificity; positive and negative predictive values; prognostic value) • Clinical utility (impact on clinical management; impact on reproductive choices; impact on kidney donation to a family member) • Therapeutic effectiveness (time to disease progression; time to end-stage renal disease; time to sensorineural hearing loss) • Health-related quality of life • Safety (physical harms and complications from testing; physical and psychological harms resulting from misdiagnosis; physical and psychological harms resulting from time delay to diagnosis; psychological effects to a parent of passing on a genetic disease) • Health care resource use (referrals to Clinical Genetics and Genetic Counselling services; liver biopsy and other diagnostic testing; hospitalisation; specialist visits; dialysis; kidney transplant) • Cost-effectiveness

Table 2 Cascade testing of family members

Component	Description
Patients	Family members of individuals with a confirmed diagnosis of Alport syndrome.
Prior tests	None
Intervention	Detection of a mutation in one or more of the following genes <i>COL4A5</i> , <i>COL4A3</i> or <i>COL4A4</i> , previously identified in a relative.
Comparator	No genetic testing (usual care), with diagnosis reliant on family history, previous medical history and clinical criteria (e.g. urine analysis, ophthalmoscopy, audiometry), with or without renal biopsy.
Outcomes	As for the proband

Population

Alport syndrome (AS) is a heritable kidney disease characterised by persistent haematuria, chronic renal failure, and progression to end-stage renal disease (ESRD). In addition, AS is frequently associated with sensorineural hearing loss (SNHL) and specific ocular defects, including anterior lenticonus (a cone-shaped bulging of the anterior surface of the lens), perimacular flecks (white or yellow flecks surrounding the macula), corneal endothelial vesicles, and recurrent corneal erosion.

Genetic testing for AS is proposed for two patient populations:

A. Clinically affected individuals with suspected AS, to make a genetic diagnosis and thus estimate the variation in risk for renal disease, deafness and ocular involvement;

and, when also appropriate

B. cascade testing of family members of those individuals who test positive for one or more relevant mutations, to make a genetic diagnosis of AS and thus estimate each family member's variation in future risk of renal disease, deafness and ocular involvement, and, less commonly, future risk of further disease if AS has already been diagnosed.

The most widely used estimate of the prevalence of AS is 1 in 5,000 individuals based on the findings of about 300 cases in Utah and southern Idaho in a population of 1,500,000 people.¹ The incidence of AS was found to be 1 in 53,000 in Finland² and 1 in 17,000 in southern Sweden³. According to the Applicant, the estimated number of people in Australia with AS is 2,000 to 5,000, most of whom are undiagnosed and unaware that they are affected. There are approximately 500 patients with AS on the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry.

According to data from the ANZDATA registry, 296 (0.5%) patients starting renal replacement therapy had a diagnosis of Alport ESRD by their treating nephrologist.⁴ This is similar to rates from the United States Renal Data System (USRDS) registry (0.2%)⁵ and the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) registry (0.6%)⁶. However, significant variation has been reported between different countries and between adult and paediatric populations. In the US, AS accounts for up to 3% of paediatric patients with ESRD.

Rationale

AS is caused by mutation of the type IV collagen genes *COL4A3*, *COL4A4*, and *COL4A5*. Three modes of inheritance are recognised: X-linked, autosomal recessive, and autosomal dominant.

Approximately 80% to 85% of families with AS have X-linked inheritance with mutations in the

¹ Hasstedt and Atkin (1983). X-linked inheritance of Alport syndrome: Family P revisited. *Am J Hum Genet.* 35:1241–1251.

² Pajari et al (1996). Alport's syndrome in 78 patients: epidemiological and clinical study. *Acta Paediatr.* 85:1300–1306.

³ Persson et al (2005). Alport syndrome in southern Sweden. *Clin Nephrol.* 64: 85–90.

⁴ Mallett et al (2014). End-stage kidney disease due to Alport syndrome: outcomes in 296 consecutive Australia and New Zealand Dialysis and Transplant Registry cases. *Nephrol Dial Transplant.* 29:2277–86.

⁵ Kashtan CE. Alport syndrome and thin basement membrane nephropathy. In: Pagon RA, Bird TD, Dolan CR et al. (eds). *GeneReviews*. Seattle, WA: University of Washington, 1993-2016.

⁶ Gretz et al (1987). Alport's syndrome as a cause of renal failure in Europe. *Pediatr Nephrol.* 1:411–415.

COL4A5 gene.⁷ Autosomal recessive inheritance accounts for 10% to 15% of individuals with AS and arises from mutations in both alleles of either *COL4A3* or *COL4A4*. Autosomal dominant disease is less common, occurring in less than 5% of individuals with AS.

In families with X-linked inheritance, mothers heterozygous for a *COL4A5* pathogenic variant have a 50% chance of transmitting the pathogenic variant in each pregnancy.⁸ Affected males will pass the pathogenic variant to all of their daughters and none of their sons. Thus, overall, the immediate risks are greater for the offspring of an affected female than for a male with X-linked disease. In families with autosomal recessive inheritance, the parents of an affected child are obligate heterozygotes and carry one mutant allele. At conception, each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier who may or may not be symptomatic, and a 25% chance of being unaffected and not a carrier. In families with autosomal dominant inheritance, each child of an affected individual has a 50% chance of inheriting the pathogenic variant and having a collagen IV disorder (autosomal dominant AS or thin basement membrane nephropathy [TBMN]).

The mode of inheritance provides prognostic information on the onset and course of AS manifestations. In the absence of treatment, individuals with X-linked AS (XLAS) have chronic microscopic haematuria, progressive renal failure, and eventually, ESRD, often in combination with high-frequency SNHL and/or the AS-related ocular findings. The risk of progression to ESRD in males with XLAS is 50% by age 25, 90% by age 40, and nearly 100% by age 60.⁹ Diminished hearing is usually detectable by late childhood or early adolescence. By age 40 years, 80%-90% of males with XLAS have SNHL. Ocular lesions are common, occurring in 30%-40% of individuals with XLAS.⁹

Most individuals with autosomal recessive AS (ARAS) develop significant proteinuria in late childhood or early adolescence and ESRD before age 30 years. Individuals with ARAS typically exhibit juvenile onset of hearing loss. The spectrum of ocular lesions in individuals with ARAS appears to be similar to those with XLAS.

Heterozygous carriers of XLAS, or ARAS-related gene variants (i.e. the female relatives of males with XLAS or the close relatives of ARAS patients) often have asymptomatic microscopic haematuria. Female carriers of XLAS gene variants may also develop additional symptoms of AS, including renal failure and ESRD, but their phenotype is more variable and often less severe than their affected male family members. Approximately 12% of females with XLAS develop ESRD before age 40 years, increasing to 30% by age 60 years and 40% by age 80 years.¹⁰

The phenotype associated with autosomal dominant AS (ADAS) is variable and ranges from isolated microscopic haematuria to the progressive phenotype seen among patients with XLAS or ARAS. ESRD

⁷ Feingold J, Bois E, Chompret A, Broyer M, Gubler M-C, Grunfeld J-P. Genetic heterogeneity of Alport syndrome. *Kidney Int.* 1985;27:672-677.

⁸ Kashtan CE. Alport syndrome and thin basement membrane nephropathy. In: Pagon RA, Bird TD, Dolan CR et al. (eds). *GeneReviews*. Seattle, WA: University of Washington, 1993-2016.

⁹ Jais et al (2000). X-linked Alport syndrome: natural history in 195 families and genotype-phenotype correlations in males. *J Am Soc Nephrol.* 11:649-57.

¹⁰ Jais et al (2003). X-linked Alport syndrome: natural history and genotype-phenotype correlations in girls and women belonging to 195 families: a "European Community Alport Syndrome Concerted Action" study. *J Am Soc Nephrol.* 14:2603-10.

is frequently delayed until later adulthood in individuals with ADAS. SNHL is also relatively late in onset and ocular involvement is rare.

The nature of the pathogenic variant also provides prognostic information on the course of disease. Large rearrangements of *COL4A5* and pathogenic nonsense and frameshift variants confer a 90% probability of ESRD before age 30 years, with 50% reaching ESRD by age 20 years.⁹ In affected individuals with splice-site variants, the probability of ESRD before age 30 years is 70%, with 50% reaching ESRD by age 25 years. The risk for deafness in individuals with large rearrangements of *COL4A5* or nonsense, frameshift, or splice site variants is 50% at age ten years. In individuals with missense variants, the risk for deafness does not reach 50% until age 20 years.

All three types of AS are associated with specific changes in the glomerular basement membrane (GBM) – most often thickening, thinning, splitting, and lamellation – which is detectable on ultrastructural examination of renal biopsy specimens. In addition, affected patients may have altered expression of the collagen type IV alpha chains in the GBM, which is detectable by immunohistochemistry or immunofluorescence.

In most cases, molecular genetic testing can confirm a diagnosis of AS and help to distinguish between subtypes. Genetic testing is necessary to exclude heterozygosity in a female who does not have haematuria but with a family history of XLAS. Genetic testing may also be useful when results of a skin or kidney biopsy are not conclusive.

Additionally, genetic testing may be useful to exclude XLAS in cases where TBMN is suspected. TBMN is an autosomal dominant condition resulting from variants in either *COL4A3* or *COL4A4*. It is estimated to affect 1% of the population. Individuals with TBMN share some of the clinical features of AS, most notably persistent microscopic haematuria often first observed in childhood. However, unlike AS, TBMN is a relatively benign condition; progressive renal disease is relatively unusual and extra-renal abnormalities are rare. As such, distinction between AS and TBMN is critical to the affected individual and their family members.

Currently, there is no specific treatment for AS. The goal is to treat the symptoms and help slow the progression of kidney disease. Evidence from retrospective analysis of registry data, animal models and other forms of renal failure suggest that angiotensin-converting enzyme (ACE) inhibition delays ESRD and improves life expectancy in AS patients in a time-dependent manner.¹¹ Prospective randomised controlled clinical trials are difficult to undertake because of the small numbers of patients at individual treatment centres and their different stages of disease at presentation. However, a multicentre, double blind, randomised, placebo-controlled, phase III trial (NCT01485978) is currently underway to examine the safety and efficacy of the ACE inhibitor ramipril in paediatric patients aged 24 months to 18 years with early stages of AS (isolated haematuria or microalbuminuria). The EARLY PRO-TECT Alport trial has an estimated enrolment of 120 children (80 patients randomised 1:1 to ramipril or placebo, and another 40 patients receiving open-label ramipril contributing to the safety database). The trial started in March 2012 and the expected study

¹¹ Gross et al (2015). Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. *Kidney Int.* 291:494-501.

completion date is August 2019. Primary endpoints are 'time to progression to next disease level' and 'incidence of adverse drug events before disease progression'.

Early and accurate diagnosis at birth or in children with AS with isolated haematuria may open a window of opportunity for early intervention. ACE inhibitors are widely available and relatively inexpensive. Although not registered specifically for the treatment of AS in children, ramipril has Therapeutic Goods Administration (TGA) approval for the treatment of hypertension and the prevention of progressive renal failure in patients with persistent proteinuria in excess of 1 g/day. Ramipril and other ACE inhibitors have an unrestricted listing on the Pharmaceutical Benefits Schedule (PBS).

Prior tests

Genetic testing should be reserved for individuals with a strong clinical suspicion of AS after clinical examination and a detailed medical and family history. Prior testing primarily involves urinalysis (also on first- and second-degree relatives, if possible). Routine investigations for renal disease may also be undertaken (e.g. measurement of serum creatinine concentration or other estimates of glomerular filtration rate such as creatinine clearance or serum cystatin C levels) together with measurement of blood pressure. Ophthalmoscopy and audiometry may also be undertaken.

AS is suspected when there is persistent glomerular haematuria. The likelihood of AS increases with a family history of AS or renal failure, and no other obvious cause; or when the characteristic clinical features (hearing loss, lenticonus, or retinopathy) are present.

The availability on the MBS of genetic testing for AS will obviate the need for renal biopsy and subsequent immunohistochemical and ultrastructural examination of the GBM to confirm a diagnosis of AS.

Intervention

At present, genetic testing is not widely available in Australia and very few people with AS or suspected AS have had a confirmatory genetic test. The test is usually requested by a nephrologist who specialises in AS or a clinical geneticist, and is currently funded by the pathology budgets of individual nephrology and genetics services. Genetic testing of index patients (probands) and their relatives is only required once in a lifetime and can be carried out using peripheral blood (5 mL) or tissue samples. The current barriers to testing are cost, access to a Clinical Genetics service, and the lengthy turnaround time for results.

Prior to testing, patients need to sign an informed consent form to ensure they have understood the implications, indications, and limitations of the test. They also need to consent to who has access to their results as it has implications for their relatives. 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). If the test is positive, long-term management by a nephrologist is recommended.

Genetic testing for AS is currently undertaken by Approved Pathologists in only a few accredited pathology testing laboratories across Australia. The molecular genetic testing approaches for AS can include single-gene testing, use of a multi-gene panel, and more comprehensive genomic testing (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.

In single-gene testing, sequence analysis is performed first followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found. The choice of which of the three genes to test first is based on family history, clinical findings and histopathology. In individuals with an X-linked family history, *COL4A5* is tested first. In individuals with a family history of either autosomal dominant or autosomal recessive inheritance, *COL4A3* is tested first, followed by *COL4A4*. In some individuals with a negative family history, only a single variant may be found in either *COL4A3* or *COL4A4*. In such cases it may be difficult to determine if the patient has a *de novo* dominant variant or a single autosomal recessive variant (with the other variant perhaps not detectable).

A multi-gene panel is the preferred methodology in some centres worldwide and includes *COL4A5*, *COL4A3*, *COL4A4*, plus other genes of interest (depending on the differential diagnosis). A wider panel of genes is used for the proband (affected individual), while only the identified mutation may be tested in biological family members.

Whole exome sequencing (WES), whole mitochondrial sequencing (WMitoSeq) and whole genome sequencing (WGS) may be considered if serial single-gene testing and/or use of a multi-gene panel fails to confirm a diagnosis in an individual with features of AS. In some centres, the use of next generation sequencing is preferred, particularly given the very large size of the *COL4A5*, *COL4A3* and *COL4A4* genes (48–53 exons and a coding sequence of more than 5000 base pairs). More than 1168 unique variants are known for *COL4A5*, more than 268 for *COL4A4*, and more than 266 for *COL4A3*.¹²

Targeted next generation sequencing offers several advantages over other molecular testing methods, including the identification of some large *COL4A3* and *COL4A4* rearrangements that are not detected by Sanger sequencing, and the possibility of a diagnosis not previously considered (e.g. mutation of a different gene that results in a similar clinical presentation). Best practice guidelines for genetic testing for AS are expected to be published later this year and will recommend the use of WES, with the expectation that this will ultimately lower costs and turn-around time.¹³

Rationale

Genetic testing for AS can serve several purposes:

- Assists in establishing a diagnosis of AS in asymptomatic individuals or confirming a diagnosis of AS in symptomatic or oligosymptomatic individuals.
- Provides additional information about prognosis and the risk of onset and progression of renal disease and SNHL, thereby guiding the timing and intensity of intervention.
- Identifies at risk family members and carriers.

¹² Leiden Open Variation Database, available at https://grenada.lumc.nl/LOVD2/COL4A/home.php?action=switch_db

¹³ Personal communication with the Applicant.

- Clarifies family members who are unsuitable for donating a kidney within the family as they are at risk of developing the disease.
- Provides reproductive information for those affected and for family members at risk of having a child with the disease. In cases where a parent has a known genetic mutation, prenatal diagnosis (through chorionic villi sampling or amniocentesis) or pre-implantation genetic diagnosis (PGD) may be options.

Comparator

The main comparator is no genetic testing for AS, with diagnosis reliant on clinical criteria (e.g. urine analysis, renal function, ophthalmoscopy, audiometry) and previous medical and family history, with or without renal biopsy. Although diagnosis of AS can often be confirmed with renal biopsy and subsequent visualisation of the specific pathological changes in the GBM, renal biopsy is avoided, where possible, as it confers a risk to the patient (bleeding, infection and pain) and is insensitive for children and for women with XLAS, and in ESRD where extensive scarring masks the distinctive features of AS.

Although genetic testing will obviate the need for a renal biopsy in the majority of cases, biopsy may be helpful when interpreting 'grey area' results in genetic tests (e.g. variants of unknown significance).

The known strong genotype-phenotype correlation provides a rationale for using genotype data to guide the timing and intensity of intervention. In the absence of *COL4A5* genotype data, timing of ESRD is predicted for a young affected male on the basis of ESRD timing in older affected male relatives, as age at ESRD is fairly similar among affected males in most families with XLAS. In XLAS females, where no such relationship exists, the timing and intensity of intervention is guided by risk factors for progression to ESRD, such as proteinuria, gross haematuria and hearing loss. In individuals with ADAS, disease tends to progress relatively slowly and there is less urgency to consider initiation of intervention in childhood.

Outcomes

From a clinical perspective, an accurate genotypic diagnosis of AS is important because of its prognostic and therapeutic implications for the patient.

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. 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.

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

The following outcomes are considered relevant to the assessment of the comparative effectiveness and safety of genetic testing for AS.

Diagnostic performance

- Analytical sensitivity
- Analytical specificity
- Likelihood ratios
- Rate of repeat testing required
- Time taken to achieve confirmed result

Clinical validity

- Clinical sensitivity
- Clinical specificity
- Positive and negative predictive values
- Prognostic value

Clinical utility

- Impact on clinical management of proband (other diagnostic testing, referrals, onset and intensity of therapy)
- Impact on clinical management of family members (genetic testing, other diagnostic testing, referrals, onset and intensity of therapy)
- Impact on reproductive choices of proband (prenatal diagnosis and PGD)
- Impact on reproductive choices of family members (prenatal diagnosis and PGD)
- Impact on kidney donation to a family member
- Therapeutic effectiveness
 - Time to disease progression
 - Time to ESRD
 - Time to SNHL
- Health-related quality of life (HRQoL)

Safety

- Physical harms and complications from testing
- Physical and psychological harms resulting from misdiagnosis
- Physical and psychological harms of time delay to diagnosis
- Psychological effects to a parent of passing on a genetic disease
- Physical and psychological effects to a child of being born with a genetic disease

Health care system

The availability of genetic testing for AS will have implications for the Australian health care system. Genetic testing of probands and their families will require access to Clinical Genetic services and Genetic Counselling services. Depending on the genetic variant identified, probands may be initiated on treatment earlier, which has implications for the PBS and other health care resource use due to more frequent follow-up. However, earlier diagnosis and initiation of treatment has the potential to result in cost and health care resource use offsets due to delayed ESRD, dialysis and kidney transplant.

Current clinical management algorithm for identified population

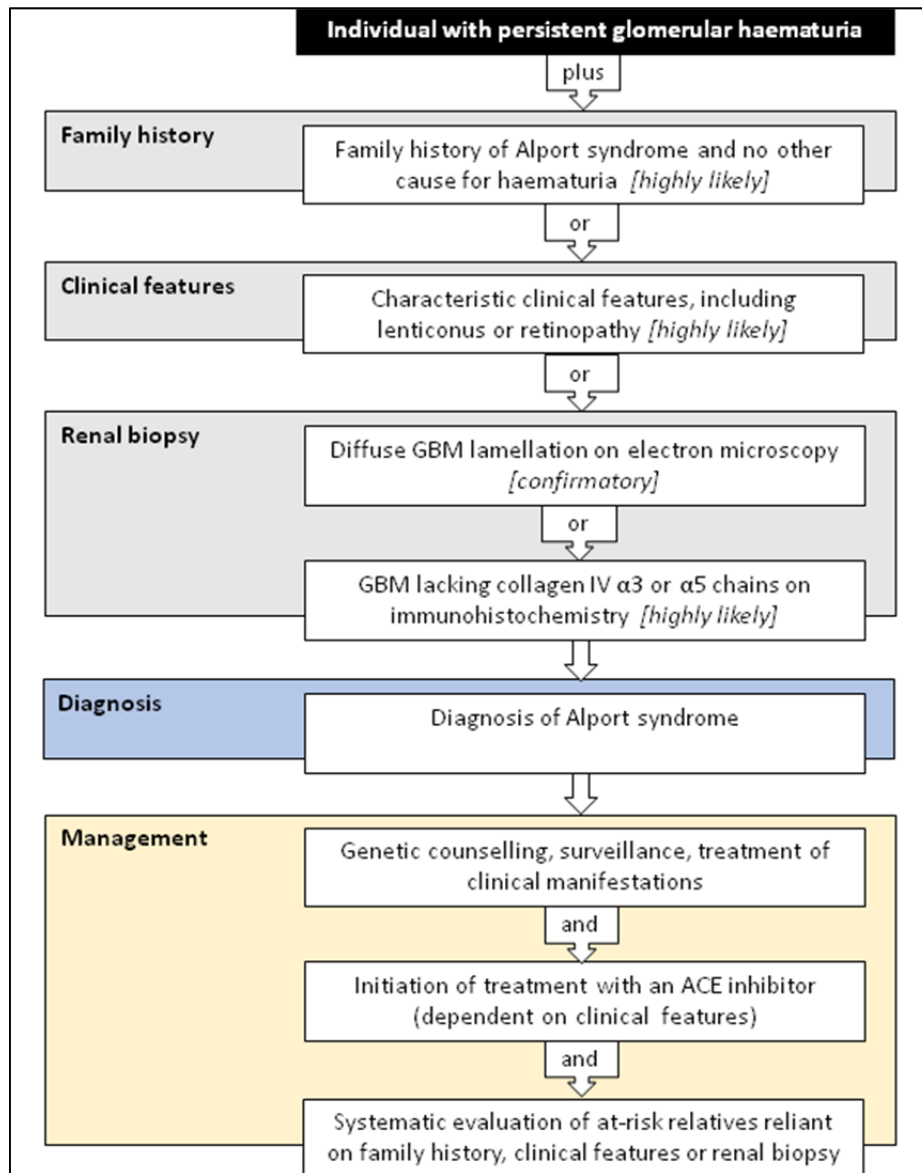


Figure 1 Current clinical management algorithm for identified population

In the absence of genetic testing, the diagnosis of AS, and its differentiation from other conditions (including TBMN), relies on:

- history and clinical examination, which may include urine analysis, renal function study, ophthalmoscopy and audiometry;
- detailed family history and possibly urinalyses on first- and second-degree relatives;
- immunohistochemical/immunofluorescence analysis of basement membrane type IV collagen expression, using skin and/or renal biopsy specimens; and
- examination of renal biopsy specimens by electron microscopy for characteristic ultrastructural changes (GBM lamellation).

Using these tools, particularly electron microscopy of the GBM, the diagnosis can be confirmed in most cases. Renal biopsy (MBS item 36561) can be performed in an inpatient or outpatient setting. General anaesthesia may be required during biopsy, particularly in children.

As mentioned above, renal biopsy is avoided, where possible, as it carries risks and is insensitive in some patient subgroups (equivocal or false negative test result). Treatment may therefore be withheld from, or initiated in, a patient without a confirmed diagnosis of AS.

Management of AS relies on surveillance, systematic evaluation of at-risk relatives, treatment of clinical manifestations and prevention of secondary complications. Clinical practice guidelines for the treatment of individuals with AS have been published,^{14,15} with recommendations relying largely on the experience and opinions of the authors, as well as retrospective studies in humans, animal experiments, and analysis of the Alport registries. These recommendations encourage early detection of microalbuminuria and proteinuria through regular surveillance and early intervention aimed at suppressing proteinuria using an ACE inhibitor with or without angiotensin receptor blockade (ARB).

Individuals with a diagnosis of AS should be followed by a nephrologist in addition to a primary care physician. All women with a diagnosis of AS need to be monitored regularly for the development of proteinuria and hypertension. Once overt proteinuria has developed in an individual with AS, renal function should be assessed periodically by serum creatinine concentration or other estimates of glomerular filtration rate (e.g. creatinine clearance or serum cystatin C levels), and blood pressure should be monitored. Children with AS should have audiologic evaluation every one to two years beginning at age six to seven years. Periodic cardiac evaluation for aortic dilation for males with XLAS is appropriate.

Relatives found to have proteinuria and hypertension should be referred to a nephrologist for further evaluation. In the absence of proteinuria or hypertension, relatives at risk should, at a minimum, have an annual urinalysis and measurement of blood pressure if molecular genetic testing is not available.

Exposure to loud noise should be minimised in individuals with AS and hearing aids should be prescribed when appropriate. The ocular manifestations of AS rarely require specific ophthalmologic intervention, although some individuals develop cataracts that interfere with vision and these should be extracted when necessary. Individuals who suffer recurrent corneal erosions may need to take measures to protect their corneas from minor trauma.

Routine treatment of hypertension may be necessary as disease progresses. In patients with ESRD, renal transplantation is an option. Transplant recipients should be monitored for development of anti-glomerular basement membrane antibody-mediated glomerulonephritis. Potential living related donors must be evaluated carefully to avoid nephrectomy in an affected individual.

¹⁴ Savige et al (2013). Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. *J Am Soc Nephrol.* 24:364-75.

¹⁵ Kashtan et al (2013). Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport Syndrome Research Collaborative. *Pediatr Nephrol.* 28:5-11.

Proposed clinical management algorithm for identified population

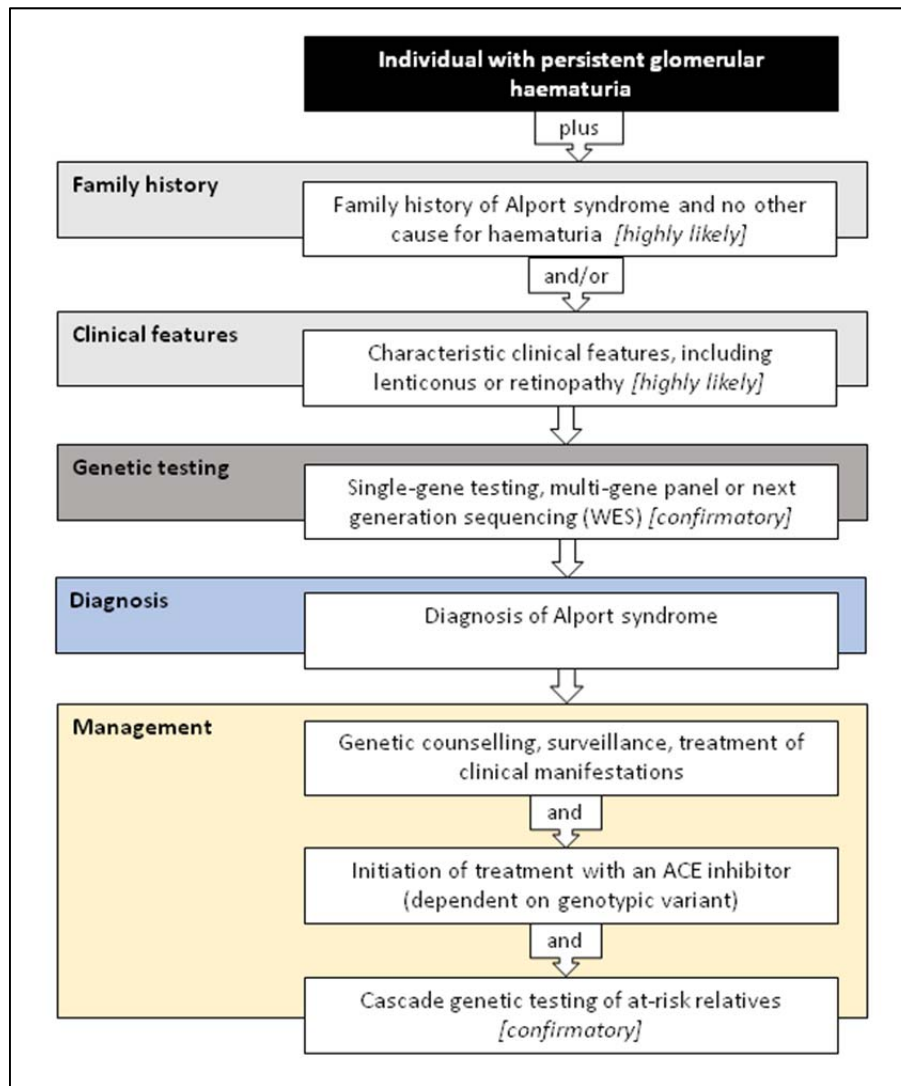


Figure 2 Proposed clinical management algorithm for identified population

The availability on the MBS of genetic testing for AS will obviate the need for renal biopsy to confirm a diagnosis of AS. If a pathogenic variant is identified in the proband, genetic counselling and testing for the familial variant could be offered to symptomatic or presymptomatic relatives, who are at risk of developing renal failure or passing the genetic abnormality to their offspring. Couples with a known sequence variant may elect to have prenatal diagnosis or PGD if they wish to avoid having an affected child. If a relative of the proband tests negative, then none of their offspring are at risk and they will not need to be tested.

There are key differences in the post-test consequences across the two populations proposed for genetic testing. For diagnostic genetic testing of an affected individual (proband), the consequences of a mutation being identified are relatively simple and can be readily incorporated into the care plans of their pre-existing specialist. On the other hand, unaffected family members who are shown by genetic testing to carry the mutation have more care pathways potentially available because they

have yet to manifest the disease. The care pathways for these individuals will likely involve new consultations with a nephrologist and a clinical geneticist or genetic counsellor. For relatives that undergo cascade testing, liver biopsy is avoided.

Proposed economic evaluation

The clinical claim is that genetic testing for AS is superior in terms of clinical effectiveness and safety to no genetic testing (usual care, defined as diagnosis on the basis of history, clinical examination and family history, with or without renal biopsy).

- Genetic testing is more accurate in identifying individuals with AS who are at risk of early onset renal failure, SNHL, and ocular defects.
- Genetic testing provides prognostic information that could be used to guide treatment initiation and intensity. Earlier initiation of treatment (before the development of overt proteinuria) may delay the onset of renal failure, thereby improving HRQoL.
- Genetic testing enables appropriate reproductive counselling for those at risk of passing the genetic abnormality to their offspring.

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 proband and biological family members.

Proposed item descriptor

Table 3 Genetic testing for the purpose of diagnosis (testing of the proband)

Category 6 – PATHOLOGY SERVICES	
Group P7 – GENETICS	
Item XXXX	
<p>Characterisation of germline gene variants in one or more of the following genes [<i>COL4A5</i>, <i>COL4A3</i> or <i>COL4A4</i>], in a patient for whom clinical and family history criteria have been determined by a nephrologist to be strongly suggestive of Alport syndrome. Alport syndrome is suspected when there is persistent glomerular haematuria. The likelihood of Alport syndrome increases with a positive family history or renal failure, and no other obvious cause; or when the characteristic clinical features (hearing loss, lenticonus, or retinopathy) are present.</p> <p>Prior to ordering this test, the ordering practitioner should ensure the patient (or an appropriate proxy) has given informed consent. Testing can only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results in order to explain the diagnostic risks, implications to other family members, and limitations for the particular test.</p> <p>Fee: \$1800</p>	

The fee proposed by the Applicant is 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 the cost of consultation and counselling before and after testing.

Table 4 Cascade testing of family members

Category 6 – PATHOLOGY SERVICES	
Group P7 – GENETICS	
Item XXXX	
Request by a clinical geneticist or a nephrologist for the detection of a mutation previously identified in a gene listed in Item XXXX in a relative.	
Prior to ordering this test, the ordering practitioner should ensure the patient (or an appropriate proxy) has given informed consent. Testing can only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by a specialist practitioner, a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results in order to explain the diagnostic risks, implications to other family members, and limitations for the particular test.	
Fee: \$	

The Applicant has not proposed a fee for cascade testing of biological family members of the proband. The fee for the genetic testing component could be expected to be lower for family members than for the proband, given that the mutation is already known.