



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1449 – Genetic testing for Alport syndrome

Applicant: The University of Melbourne Department of Medicine

Date of MSAC consideration: MSAC 72nd Meeting, 28-29 March 2018

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of genetic testing for the diagnosis of Alport syndrome (AS) was received by the Department of Health from the Department of Medicine in the University of Melbourne.

The proposed medical service is a genetic test for heritable mutations in clinically affected individuals and, when appropriate, in family members of those individuals who test positive for one or more relevant mutations.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC supported MBS funding of genetic testing for the diagnosis of AS in clinically affected individuals and cascade testing for selected family members of these individuals who are genetically confirmed to have Alport syndrome (probands).

MSAC advised that, while the evidence base for genetic testing was limited, there was acceptable evidence of clinical safety and effectiveness, and the financial impact of funding was likely to be low in the context of this rare disease with a well-characterised phenotype and low risk of leakage. MSAC also noted that genetic testing is accepted as the reference standard for diagnosis of AS and recognised that there was a clinical need for genetic testing to reduce the need for renal biopsy, to provide prognostic information on the expected course of the disease, and to inform family planning decisions, including from cascade testing of relatives of probands.

MSAC recommended that the fee for the testing of affected individuals and the fee for cascade testing should each be consistent with those for similar genetic tests for breast and ovarian cancer (MBS items 73296 and 73297 – characterisation of germline gene mutations of the *BRCA1* and *BRCA2* genes and one or more genes). MSAC advised that all three AS-related genes would need to be sequenced at the same time by the MBS-funded test of affected individuals.

MSAC recommended a review of the MBS items in two years to assess uptake and ensure that the proposed fees continue to reflect the actual costs of providing the services.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that the genetic testing could identify mutations in one or more of the genes (*COL4A5*, *COL4A3* or *COL4A4*) that cause AS. AS is characterised by progressive kidney disease, haematuria, proteinuria, hearing loss and eye abnormalities with the severity of symptoms dependent upon gender and the mode of inheritance.

MSAC noted that there are three recognised modes of inheritance of AS:

- X-linked caused by a single mutation in *COL4A5*;
- autosomal recessive caused by two mutations in *COL4A3* or *COL4A4*; and
- autosomal dominant caused by a single mutation in either *COL4A3* or *COL4A4*.

MSAC noted that the proposed eligible populations were:

- clinically affected individuals for whom there is a strong clinical suspicion of AS based on existing signs and symptoms and
- when appropriate, selected family members of those tested individuals who are genetically confirmed to have AS (proband).

MSAC noted that the comparator was current clinical practice without genetic testing and with diagnosis relying upon clinical criteria, medical and family history, and in some cases, renal biopsy.

MSAC noted that skin biopsy had been mentioned in the ESC report as an alternative to renal biopsy. However, MSAC was satisfied with the applicant's response that skin biopsy is only used in a small number of laboratories internationally, and is not used at all in Australia because it is largely confined to a specific research setting.

MSAC noted that, while there was a lack of comparative safety data, genetic testing is performed using a blood sample. MSAC considered that this is associated with low risk of harm, particularly when compared to the risk of harm associated with renal biopsy.

MSAC noted there was no direct evidence comparing the clinical effectiveness of genetic testing compared to current practice and as such the submission relied upon a linked evidence approach.

MSAC considered the genetic test to be accurate in diagnosing people with AS. MSAC noted that analytical sensitivity and specificity were both greater than 95% (Morinière V et al 2014; Hertz JM et al 2015). MSAC noted that clinical sensitivity in individuals with clinical signs and symptoms of AS was expected to be above 80% and clinical specificity was expected to be above 95% (Hertz JM et al 2015).

MSAC noted that there was limited empiric evidence that genetic testing for AS would change clinical management. MSAC accepted that, if genetic testing provided a definitive genetic diagnosis, it may reduce renal biopsies in people in whom AS is suspected on the basis of clinical signs and symptoms alone. MSAC also accepted that, if genetic testing identified the pathogenic mutation(s), it may provide information on the expected course of the disease, may result in earlier referral for eye testing and audiology, and may lead to the commencement of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). MSAC accepted that a definitive genetic diagnosis and identification of the pathogenic mutation(s) in probands may help select relatives who do, or do not, require testing or more intensive surveillance. While MSAC accepted the rationale that earlier use of ACEIs or ARBs may delay end stage renal disease and dialysis in people with AS, the lack of

direct evidence for this meant it could only be considered hypothetical until confirmed by randomised trial evidence.

MSAC noted that the economic modelling was contingent upon earlier use of ACEIs/ARBs delaying onset of renal dialysis rather than a reduction in the use of renal biopsies. Given the lack of evidence that this delay would be realised, MSAC was not confident that the model was valid. MSAC also noted that the model did not disaggregate results for the affected individuals population and the cascade testing population. Despite all this, MSAC noted that the model suggested that genetic testing of both populations would dominate (i.e. be less costly with improved outcomes) the comparator of current practice.

MSAC considered that the financial impact of funding genetic testing would be low. MSAC noted that the number of services was expected to be higher in year 1 due to the prevalent pool of patients to be tested. MSAC noted that the financial estimates had been based upon approximately 2000 services in the first year at a cost to the MBS of ~\$2.3 million. This fell to approximately 1000 services per year in years 2–5 at a cost to the MBS of ~\$1.2 million.

MSAC noted that, while the calculation of the number of services used an AS incidence of 1:53,000 live births (based upon Finnish data), an AS prevalence of 1:5000 individuals (based upon US data) is also widely quoted (Hertz JM et al 2015). However, MSAC considered that using the higher prevalence to calculate MBS costs would increase costs in year 1, and more intensive cascade testing might increase the incidence rate and thus MBS costs in years 2–5.

MSAC suggested that the number of services used for the financial estimates may also have been slightly underestimated because it was assumed that the test result was never negative (which meant that the number of tests is exactly the same as the prevalence or incidence of the disease). On the other hand, MSAC was also aware that not all tests of the prevalent population would necessarily be billed to Medicare.

MSAC noted that, as microscopic haematuria was a common presentation caused by a variety of conditions, it was important that there be a high probability that the patient has AS before the test is requested. MSAC suggested that any risk of leakage to patients with a lower pre-test probability would be mitigated if the ability to request genetic testing for AS was limited to specialists. MSAC recommended that the item descriptor specify that the requesting specialist should be a nephrologist or clinical geneticist, and advised that this would be expected to result in better identification of affected individuals suitable for genetic testing than if the item descriptor listed signs and symptoms suggestive of AS.

MSAC noted that the fee proposed by the applicant for genetic testing included costs for genetic counselling. MSAC noted that genetic counselling cannot be funded through the MBS. MSAC considered that genetic counselling is part of the requesting specialist's standard of care. MSAC noted that genetic and family counselling would also be able to be provided by general practitioners.

MSAC noted that submissions for genetic tests were becoming increasingly common and that a standardised approach to address genetic counselling issues was required. MSAC referred these issues to the MSAC Executive for further examination.

MSAC noted there are three different genes that may carry mutations responsible for AS. MSAC considered that while gene testing for other conditions may be best undertaken sequentially, all three AS-related genes would need to be sequenced at the same time by the MBS-funded test. This is because of the different inheritance pathways for AS, and because a person may carry multiple mutations on different genes.

MSAC noted that different methods could be used for genetic testing of affected individuals (multi-gene panels, whole exome sequencing and next-generation sequencing). MSAC advised that, given the strong test performance in terms of genetic diagnostic accuracy overall, and in the absence of detailed data comparing the analytical performance across the alternative techniques, and ongoing improvements in gene sequencing methodologies, MBS listing need not be restricted to particular sequencing methods, but the proposed fee would need to be benchmarked against similar MBS items.

MSAC advised that a fee of \$1200 for the proband and a fee of \$400 for cascade testing of related family members were appropriate. MSAC noted that these fees were consistent with those for similar genetic tests on the MBS for breast and ovarian cancer (MBS item 73296 – characterisation of germline gene mutations of the *BRCA1* and *BRCA2* genes and one or more genes [\$1200] and MBS item 73297 – characterisation of germline gene mutations of the *BRCA1* and *BRCA2* genes and one or more genes in a patient who is a biological relative of a patient with an identified pathogenic mutation [\$400]). MSAC noted that probands may uncommonly have multiple mutations on different genes, which may result in more complex cascade testing, but considered that although this variation should be permitted in the relevant item descriptor, the associated variation in costs could be absorbed within the proposed fee.

With reference to these benchmark MBS items, MSAC suggested the following item descriptors:

- for affected individuals (Item XXXXX): Characterisation of germline gene variants, requested by a nephrologist or clinical geneticist, in the following genes COL4A5, COL4A3 and COL4A4, in a patient for whom clinical and family history criteria, as assessed by the nephrologist or clinical geneticist, have been determined to be strongly suggestive of Alport syndrome.
- for cascade testing (Item XXXXY): Characterisation of germline gene variants, requested by a nephrologist or clinical geneticist, in one or more of the following genes COL4A5, COL4A3 and COL4A4, in a patient who is a biological relative of a patient who has had one or more pathogenic variants identified in one or more of the genes specified above, and has not previously received a service under item XXXXX.

MSAC suggested that, if there is an existing Australian registry, it would be helpful if information on all people with a confirmed genetic diagnosis of AS be included on the registry so that the impact of genetic testing for AS and its repercussions on cascade testing of relatives can be better understood. It would also be informative if the registry also included patients with a high clinical suspicion of AS, but do not get a confirmed genetic diagnosis.

MSAC suggested a review of the MBS items in two years to assess uptake and provide information on who is requesting the tests. MSAC also noted that the cost of gene sequencing will fall as the technology improves and the two-year review would be an opportunity to ensure that the MBS fees reflect the actual costs of providing the service.

4. Background

MSAC has not previously considered this application.

5. Prerequisites to implementation of any funding advice

Various testing platforms are listed on the Australian Register of Therapeutic Goods (ARTG) of the TGA as Class III in vitro diagnostic devices.

Genetic testing for AS is undertaken by Approved Pathologists in only a few accredited pathology testing laboratories across Australia.

6. Proposal for public funding

The proposed MBS item descriptors are summarised in Table 1 and Table 2.

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

Category 6 – Pathology services
Item XXXXX Characterisation of germline gene variants in one or more of the following genes [COL4A5, COL4A3 or COL4A4], 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. 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.
Fee: \$1800

Table 2 Proposed descriptor: Genetic testing for the purpose of diagnosis (testing of the family member)

Category 6 – Pathology services
Item XXXXY Request by a clinical geneticist or a nephrologist for the detection of a mutation previously identified in a gene listed in Item XXX 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: \$ (no fee provided in the PICO confirmation)

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.

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. Indicative prices range between \$200 and \$600 for cascade testing compared to \$1500 for testing of the proband.¹

7. Summary of Public Consultation Feedback/Consumer Issues

The Department received responses to the consultation survey from peak bodies and one “other”. All responses were positive and believed there were significant benefits to the affected individual, their family and the community.

¹ *Australian Renal Gene Panels by Massively Parallel Sequencing*. 2015. Department of Molecular Genetics, The Children’s Hospital Westmead.

The key issues raised were:

- the need for pre-test assessment by a nephrologist to identify patients with clinical suspicion of Alport;
- the test should only be ordered by specialist and be accompanied by pre/post-test counselling from a geneticist or genetic counsellor;
- the need to review the diagnosis for test-negative individuals; and
- follow up from renal specialists, including a renal dietician, may be required post-test.

8. Proposed intervention's place in clinical management

AS is a heritable kidney disease characterised by persistent haematuria, chronic renal failure, and progression to end-stage renal disease (ESRD). AS is also 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.

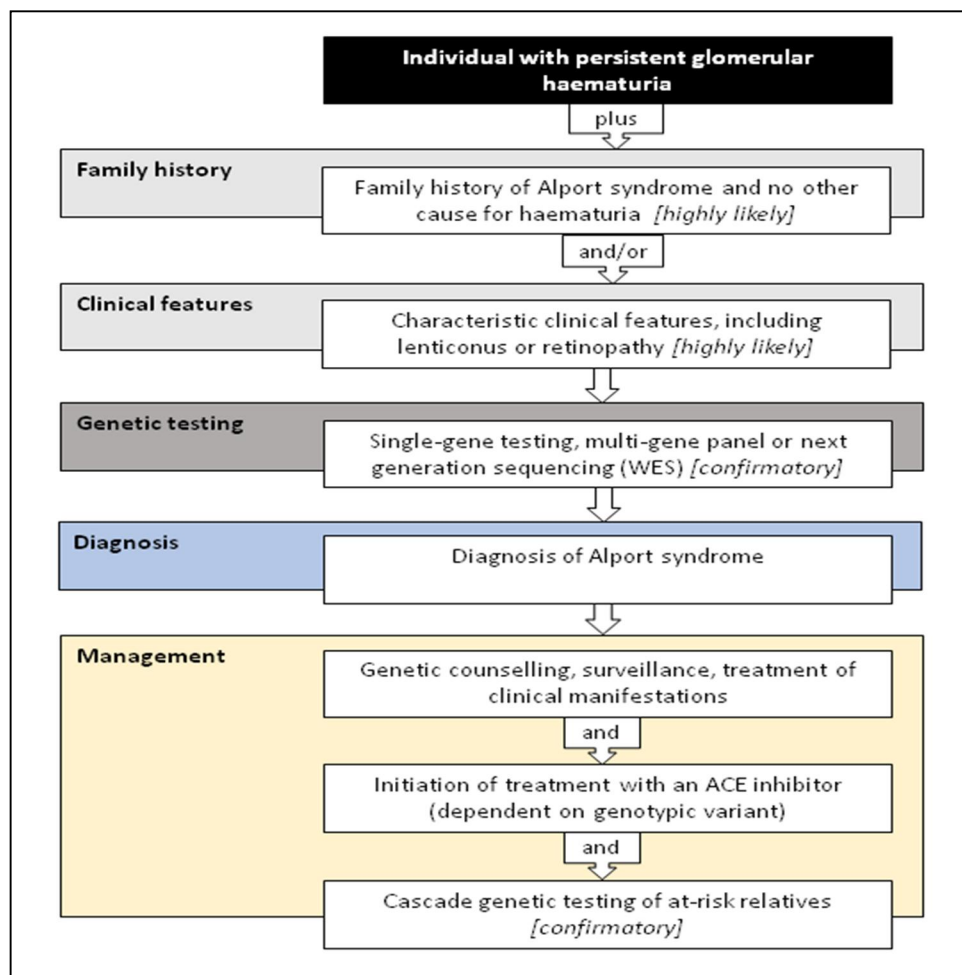
The proposed service would include DNA extraction (if required), target enrichment and library preparation, sequencing, bioinformatics analysis and variant interpretation. The genetic testing is to identify one mutation in the *COL4A5* gene to confirm diagnosis of X-linked AS (XLAS), or two mutations in the *COL4A3* or *COL4A4* genes to confirm diagnosis of autosomal recessive AS (ARAS).

The proposed medical service would be reserved for individuals with a strong clinical suspicion of AS after clinical examination and a detailed medical and family history. Genetic testing for AS is proposed for two patient populations:

- clinically affected individuals with strong clinical suspicion of AS, to make a genetic diagnosis and thus estimate the variation in risk for renal disease, deafness and ocular involvement; and, when also appropriate,
- 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.

A proposed clinical management algorithm for diagnosis and management of AS assuming MBS listing for genetic testing of AS is provided in Figure 1.

Figure 1 Proposed clinical management algorithm for genetic testing for Alport Syndrome



9. Comparator

The main comparator as specified in the PICO Confirmation 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.

In the absence of genetic testing, diagnosis of AS is reliant on patients (who typically present with persistent haematuria) meeting at least three of four clinical criteria that are characteristic of the disease (Flinter et al., 1988). These include:

- positive family history of macroscopic/microscopic haematuria or chronic renal failure;
- electron microscopic evidence of AS on renal biopsy (irregular thickening and splitting of the GBM);
- characteristic ophthalmic signs (anterior lenticonus and macular flecks); and
- high-tone sensorineural deafness.

Although clinically accepted, it is widely recognised that Flinter's criteria provide an imperfect diagnostic standard, making definitive diagnosis of AS difficult on the basis of clinical information alone (i.e., without genetic confirmation). Genetic heterogeneity of the disease requires family history of at least three generations, ophthalmic changes are hard to detect, and may be absent in younger patients, especially females (Hanson et al., 2011). SNHL may be present in other diseases associated with chronic renal failure and the characteristic thickening and splitting of the GBM observed in AS may not be present in females or in early childhood.

10. Comparative safety

Genetic testing usually involves blood sampling, which is assumed to have a low risk of harms. Using peripheral blood as the DNA source for genetic analysis would be associated with much less trauma for the patient (especially children) compared to the kidney biopsy, which carries a level of risk of severe complications.

11. Comparative effectiveness

There was no direct evidence found comparing the safety and clinical effectiveness of genetic testing compared to current practice in patients with AS, therefore a linked evidence approach was provided to show evidence of linkage between diagnosis, change in management and treatment effectiveness in individuals with suspected AS and their family members.

A summary of the characteristics of included studies is shown in Table 3.

Table 3 Key features of the included evidence comparing genetic testing for variants in COL4A3, COL4A4, or COL4A5 with clinical diagnosis of AS against Sanger sequencing

Trial/Study	N	Level of evidence	Risk of bias	Patient population	Key outcome(s)	Result used in meta-analysis
Next generation sequencing						
Morinière 2014	101	III-3	High	Individuals with suspected AS (n=90), BFH (n=10) or unclear (n=1)	Analytical Sensitivity/Specificity Clinical Sensitivity/Specificity	Not used
Fallerini 2014	271	III-3	High	Individuals with suspected AS (n=171) and their family members (n=100)	Clinical Sensitivity/Specificity	Not used
Kovacs 2016	62	III-3	High	Unrelated individuals with suspected AS or BFH (n=17) and their family members (n=45)	Clinical Sensitivity/Specificity	Not used
Sanger sequencing						
Nabais 2015 (a&b)	65	III-3	High	Unrelated individuals with suspected AS or TBMN	Clinical Sensitivity/Specificity	Not used
Hanson 2011	206	III-3	High	Individuals with suspected XLAS	Clinical Sensitivity/Specificity	Not used
Slajpah 2007	141	III-3	High	Individuals with suspected AS or BFH	Clinical Sensitivity/Specificity	Not used
Zhang 2012	17	III-3	High	Individuals with suspected ARAS	Clinical Sensitivity/Specificity	Not used

AS=Alport syndrome; BFH=benign familial haematuria; TBMN=thin basement membrane neuropathy
 III-2=a comparison with reference standard that does not meet the criteria for level II and III-1 evidence
 III-3=diagnostic case-control study

A summary of the trial characteristics of studies providing evidence relating to the health impact from the change in management is provided in Table 4.

Table 4 Key features of the included evidence assessing impact of change in patient management

Trial/Study	N	Design <i>Duration</i>	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Gross 2012	283	Retrospective Cohort ?2006-2010	Unclear risk	Males with XLAS or individuals with genetically proven homozygous ARAS	Age at onset of RRT Life expectancy Side effects of therapy	Yes
Temme 2012	234	Retrospective Cohort ?-2010	Unclear risk	Individuals heterozygous for XLAS or ARAS	Age at onset of RRT Age at death	Not used
Stock 2017	63	Prospective Cohort	High risk	Individuals heterozygous for XLAS or ARAS	Age at onset of RRT	Not used

ARAS=autosomal recessive Alport syndrome; RRT=renal replacement therapy; XLAS=X-linked Alport syndrome

Analytical sensitivity/specificity

One study was identified (Morinière 2014) that suggested targeted next generation sequencing of all three genes has a sensitivity of 99% and a specificity of 99.99%.

The European clinical utility gene card for AS (Hertz et al., 2015) reports the analytical sensitivity and specificity for Sanger sequencing of genomic DNA and MLPA for the individual genes: *COL4A3*, *COL4A4*, and *COL4A5* to be above or probably above 99%.

Clinical sensitivity / specificity

Five studies of variable quality were identified that assessed genetic testing for variants in all three Collagen IV genes (*COL4A3*, *COL4A4* or *COL4A5*) in individuals with strong clinical suspicion of AS and their family members compared with usual care (Morinière 2014, Kovacs 2016, Fallerini 2014, Nabais 2015, Slajpah 2007). One study assessed genetic testing for variations in the *COL4A5* gene in individuals with clinical suspicion of XLAS (Hanson 2011) and one study assessed genetic testing for variations in the *COL4A3* and *COL4A4* genes in individuals with clinical suspicion of ARAS (Zhang 2012). The studies used either next generation sequencing or Sanger sequencing coupled with multiplex ligation-dependent probe amplification, reverse transcriptase polymerase chain reaction, or single-stranded conformational polymorphism.

All included studies were assessed to have an overall high risk of bias. Patient selection likely resulted in the exclusion of difficult to diagnose patients (or inclusion) and assessment of the index test results were interpreted with knowledge of the results of the reference standard (Sanger sequencing and Flinter's clinical criteria). Pathogenic variants were detected using different methodologies; either using online databases to confirm variants of known significance, or based on the type of mutation observed (e.g., nonsense or frameshift mutations); some studies also included comparisons with polymorphisms identified in healthy controls.

All studies showed high sensitivity (0.98 to 1.00) and specificity (1.00) of the genetic test compared with usual care (clinical suspicion based on Flinter's criteria). With an assumed pre-test prevalence of 100%, the positive predictive value of genetic testing was estimated to provide an 18% to 45% improvement over diagnosis based on usual care (meeting 1–4 Flinter's criteria). Data were conflicting regarding the probability of detecting at least one pathogenic mutation in any of the *COL4A* genes according to the number of Flinter's clinical criteria met.

Overall, the evidence suggests that genetic testing for variants in one or more of the following genes *COL4A5*, *COL4A3* or *COL4A4* is more accurate than no genetic testing (usual care) in confirming a diagnosis AS in individuals with strong clinical suspicion of AS or their family members.

Therapeutic efficacy (change in management)

Genetic testing for variations in *COL4A3*, *COL4A4*, or *COL4A5* provides additional information about prognosis of the disease, thereby guiding the timing and intensity of intervention. At a top level, confirmation of genotype provides useful information regarding the mode of inheritance of the disease and is likely to be highly valuable to the patient and their extended family. Given the prognosis for males with XLAS and those homozygous for autosomal AS is worse than patients who are heterozygous for AS, knowledge of the genotype would also afford better patient management in patients and their family members (as opposed to watchful waiting).

No studies were identified that provided definitive information regarding the effect of genetic testing for variants in *COL4A3*, *COL4A4*, or *COL4A5* genes on treatment decisions (other diagnostic tests, referrals, onset and intensity of therapy) in individuals with strong clinical suspicion of AS or their family members.

Three studies were identified that provided poor quality evidence that genetic testing for variants in the *COL4A3*, *COL4A4*, or *COL4A5* genes resulted in a change in diagnosis in individuals with strong clinical suspicion of AS or their family members. The studies suggested that genetic testing provided 25% to 30% of patients with improved genetic counselling, identification of at-risk family member, and possible change in therapeutic management, but specific details on the treatment decisions were not provided.

For probands who receive a true *COL4A3*, *COL4A4*, or *COL4A5* positive result, treatment could be provided in a timely manner, and appropriate surveillance in their family members could be carried out on kidney function, hearing and vision problems. If required, access to genetic counselling and assisted reproductive technologies could also be provided. Patients and their family members would also be able to make more informed decisions about kidney donations and appropriate lifestyle choices to minimise kidney damage (e.g., avoiding certain drugs, maintaining normal blood pressure).

For probands who receive a true negative result, probands (and family members) who are experiencing renal symptoms can investigate other causes of their pathology. For asymptomatic family members, the absence of a pathogenic variant could prevent unnecessary patient worry and would avoid regular surveillance by clinicians. Probands and their family members can make informed decisions about kidney donations as in the case of true positives.

Probands who receive false negative test results may miss out on early treatment, and may undergo additional unnecessary diagnostics tests that further investigate their symptoms, whereas probands and their family members who receive a false positive result may receive unnecessary treatment and surveillance. Patients experiencing renal symptoms may fail to have their true renal pathology uncovered.

Therapeutic effectiveness (health benefit from change in management)

Overall, very low quality evidence was identified that suggested in individuals with strong clinical suspicion of AS or their family members, early nephroprotective therapy compared with usual care may delay onset of RRT and improve life expectancy.

Three observational studies with high risk of bias were identified that reported early nephroprotective therapy with ACE inhibitors in individuals with AS delays renal failure in a time-dependent manner. The studies had high risk for selection bias, with individuals less affected by the disease likely to be underestimated. Baseline characteristic of treatment groups were not clearly presented thus it is difficult to assess if any potential confounders exist. The data suggested a significant delay in onset of RRT, with subgroup analysis in 15 sibling pairs suggesting a delayed onset of RRT by 13 years (median). This study also reported that early nephroprotective therapy in males with XLAS and individuals with homozygous autosomal AS may improve life expectancy (log-rank test; $p=0.0369$).

In individuals with strong clinical suspicion of AS or their family members, the effectiveness of early nephroprotective therapy compared with no treatment on time to SNHL or HRQoL is unknown (no studies identified).

In individuals with strong clinical suspicion of AS or their family members, the effectiveness of genetic counselling or diagnostic surveillance compared with no genetic counselling or diagnostic surveillance is unknown (no studies identified).

In individuals with strong clinical suspicion of AS or their family members, the effectiveness of genetic counselling or diagnostic surveillance compared with no genetic counselling or diagnostic surveillance is unknown (no studies identified).

Clinical claim

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 clinical history, clinical examination and family history, with or without renal biopsy). The benefits of more accurate diagnosis are improved health outcomes in the proband and biological family members due to earlier intervention and delayed onset and progression of renal disease.

12. Economic evaluation

A summary of the economic evaluation is presented in Table 5.

Table 5 Summary of the economic evaluation

Population	Patients with strongly suggestive symptoms of AS, siblings and children
Perspective	Australian government
Comparator	Usual care
Type of economic evaluation	Cost utility analysis
Primary sources of evidence	Gross et al. (2012); Jais et al. (2003); Temme et al. (2012)
Time horizon	Life time
Outcomes	Quality Adjusted Life Years (QALYs)
Methods used to generate results	Markov cohort model
Health states	Normal, treat early, treat late, dialysis, death
Cycle length	1 year
Discount rate	5%
Software packages used	TreeAge Pro® 2017 R2.0

The overall costs and outcomes, and incremental costs and outcomes as calculated for the test and comparator in the model are shown in Table 6.

Table 6 Cost effectiveness from base case analysis of genetic testing of probands, siblings and children

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
With genetic testing	\$97,748.27	-\$65,039.82	17.00	0.54	Dominant
Without genetic testing	\$162,788.09		16.46		

ICER = incremental cost effectiveness ratio

Three individual analyses were run to determine the cost effectiveness of genetic testing in proband patients, siblings and children. The drivers of the model are the estimated benefit of delay to renal replacement therapy and the cost of dialysis.

Sensitivity analyses

The sensitivity analyses found genetic testing to be dominant when compared with standard care, with an incremental QALY gain of 0.28 (16.74-16.46) and cost savings of \$26,375.75 (\$162,788.09-\$136,412.35). In all scenarios tested, genetic testing was found to be dominant.

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of genetic testing for AS. As no data is available on the potential number affected family members, these were extrapolated based on the expected number of detected individuals and on the inheritance patterns of the disease. In addition, statistics on the fertility rate and on the main characteristics of families in Australia were retrieved from the Australian Bureau of Statistics, to estimate the number of children, partners and siblings to be tested.

The net financial implications to the MBS resulting from the proposed listing of genetic testing for AS are summarised in Table 7.

Table 7 Total net costs to the MBS associated with genetic testing for AS, 2018-2022

	2018	2019	2020	2021	2022
MBS cost associated with proposed listing					
Total cost	\$2,761,137	\$1,402,973	\$1,425,300	\$1,447,463	\$1,469,719
MBS rebate (85%)	\$2,346,967	\$1,192,527	\$1,211,505	\$1,230,344	\$1,249,262
Patient contributions	\$414,171	\$210,446	\$213,795	\$217,119	\$220,458
Savings in fees for substituted MBS services					
Savings in total costs	-\$438,871	-\$223,030	-\$226,613	-\$230,172	-\$233,737
Savings in MBS rebate	-\$372,712	-\$189,409	-\$192,452	-\$195,474	-\$198,501
Savings in patient contributions	-\$66,159	-\$33,621	-\$34,162	-\$34,698	-\$35,236
Net change					
Net change in MBS costs	\$2,322,267	\$1,179,943	\$1,198,687	\$1,217,291	\$1,235,983
Net change in MBS benefits	\$1,974,255	\$1,003,119	\$1,019,053	\$1,034,870	\$1,050,760
Net change in patient contributions	\$348,012	\$176,825	\$179,633	\$182,421	\$185,222

Financial implications for other medical services

The net financial implications to the PBS for the provision of ACE inhibitors to family members diagnosed through the genetic testing, and therefore resulting from the proposed listing of genetic testing for AS are summarised in Table 8.

Table 8 Total net healthcare costs associated with genetic testing for AS, 2018-2022

	2018	2019	2020	2021	2022
Net change in MBS cost associated with proposed listing					
Net change in MBS benefits	\$1,974,255	\$1,003,119	\$1,019,053	\$1,034,870	\$1,050,760
Net change in patient contributions	\$348,012	\$176,825	\$179,633	\$182,421	\$185,222
Net change in MBS costs	\$2,322,267	\$1,179,943	\$1,198,687	\$1,217,291	\$1,235,983
Net change in PBS cost associated with proposed listing					
Net change in PBS/RPBS benefits	\$80,374	\$81,198	\$82,495	\$83,783	\$85,076
Net change in patient contributions	\$46,309	\$46,784	\$47,531	\$48,273	\$49,018
Net change in PBS costs	\$126,682	\$127,982	\$130,025	\$132,056	\$134,094
Net change in healthcare sector cost associated with proposed listing					
Net change in healthcare benefits	\$2,054,629	\$1,084,317	\$1,101,548	\$1,118,653	\$1,135,836
Net change in patient contributions	\$394,320	\$223,608	\$227,164	\$230,694	\$234,240
Net change in healthcare costs	\$2,448,949	\$1,307,926	\$1,328,712	\$1,349,347	\$1,370,077

14. Key issues from ESC for MSAC

The submission requests new Medicare Benefits Schedule (MBS) items for genetic testing for mutations in one or more of the following genes (*COL4A5*, *COL4A3* or *COL4A4*) that cause Alport Syndrome (AS). The eligible population are symptomatic individuals in whom there is a strong clinical suspicion of AS and, when appropriate, selected family members of those symptomatic individuals who test positive for AS.

ESC noted that there are three recognised modes of inheritance:

- X-linked caused by a single mutation in *COL4A5*;
- autosomal recessive caused by two mutations in *COL4A3* or *COL4A4*; and
- autosomal dominant caused by a single mutation in either *COL4A3* or *COL4A4*.

Alport Syndrome is characterised by progressive kidney disease, haematuria, proteinuria, hearing loss and eye abnormalities. The severity of symptoms is dependent upon gender and the mode of inheritance. The goal of treatment is to slow the progression of kidney disease, typically using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), to delay end stage renal disease.

ESC noted that there are a number of different methods that could be used for genetic testing of affected individuals, including single gene testing sequenced based on family history if available, multi-gene panels, whole exome sequencing and next-generation sequencing. ESC noted that none of the studies provided in the application to support genetic testing for AS used whole exome sequencing and considered this technology was yet to be proven.

ESC noted that the extent of testing that would need to be undertaken in family members of an identified proband would depend on the gender of the family member and the mode of inheritance of each genetic subtype.

ESC noted that the comparator was no genetic testing with diagnosis relying upon clinical criteria, medical and family history, and in some cases, renal biopsy. ESC noted that while the contracted assessment referred to the Flinter clinical criteria, the applicant had stated that these were outdated and that a lamellated glomerular basement membrane, lenticonus or a

fleck retinopathy by itself was diagnostic for AS. ESC also noted that the applicant had advised that new consensus guidelines for AS have been submitted for publication.

ESC noted that skin biopsy is less invasive than renal biopsy, is mentioned in the [2013 consensus guidelines](#) (Savige J et al 2013) and in the European Clinical Utility Card (2015), and could be considered to be a cheaper and safer alternative to renal biopsy in the context of the X-linked version of Alport syndrome (the most common manifestation of Alport syndrome). ESC noted that this form of testing was associated with 80% sensitivity in males and 60% sensitivity in females, and suggested that the relative place of skin biopsy and genetic testing should be further discussed by the applicant or any other appropriate source of expertise. ESC also suggested that information on if, and how many, skin biopsies are being done for AS may be available from the Royal College of Pathologists of Australasia (RCPA).

ESC noted that the clinical claim was that the requested genetic testing would:

- establish the diagnosis of AS in symptomatic and asymptomatic patients avoiding the need for renal biopsy;
- identify the mode of inheritance and provide information about prognosis;
- enable earlier initiation of treatment to reduce the rate of progression to end-stage renal disease and sensorineural hearing loss; and
- inform appropriate reproductive counselling for individuals at risk of passing the genetic mutation on to their offspring.

ESC noted that no comparative safety evidence had been provided. ESC considered that as genetic testing is performed on a blood sample it is assumed to have a low risk of harm and will be safer than renal biopsy. ESC noted that no comparative evidence was provided on the harms of any change in management resulting from testing (i.e. initiation of ACEIs/ARBs) nor on the outcomes of false test results.

ESC noted that there was no direct comparative effectiveness data and that a linked evidence approach had therefore been taken.

ESC noted that there was a lack of studies providing sufficient information on the analytical sensitivity and specificity of single gene testing. A single study (Morinière V et al 2014) suggested targeted next generation sequencing of all three genes has a sensitivity of 99% and a specificity of 99.99% and the [European Clinical Utility Card](#) for AS (Hertz JM et al 2015) reports the analytical sensitivity and specificity for Sanger sequencing of genomic DNA and multiplex ligation-dependent probe amplification (MLPA) for *COL4A3*, *COL4A4* and *COL4A5* to be above or probably above 99%.

ESC noted that seven studies at high risk of bias and with varying patient selection and methodologies indicated that the clinical sensitivity and specificity of genetic testing compared with usual care was high at 98% or more (Morinière V et al 2014; Kovacs G et al 2016; Fallerini C et al 2014; Nabais S et al 2015; Slajpah M et al 2007; Hanson H et al 2011; Zhang Y et al 2012). ESC noted that three cohort studies, all at high risk of bias, reported genetic testing resulted in a change in diagnosis in 25% to 30% of patients suspected of having AS prior to testing (Mallett A et al 2016; Morinière V et al 2014; Fallerini C et al 2014), but little detail on any subsequent decisions to change clinical management.

ESC noted that the evidence that early treatment with ACEIs or ARBs improve outcomes was of poor quality. ESC noted that three retrospective observational studies at high risk of bias suggested early treatment was associated with a delay to the onset of renal replacement therapy (kidney transplant or dialysis; Gross O et al 2012; Temme J et al 2012; Stock J et al

2017). ESC noted that a randomised clinical trial of the ACEI, ramipril, compared with placebo in children with AS is scheduled for completion in mid-2019 ([NCT01485978](#)).

ESC considered that the proposed fee of \$1800 for proband testing had not been justified and noted that no fee for cascade testing of family members had been proposed. ESC noted that the lack of detail provided in response to section 5 of the Clinical Utility Card (CUC) proforma on the resources required to perform the test made it difficult to determine if such a fee was reasonable. ESC suggested that the RCPA may be able to provide some of this information. ESC advised that unless the resourcing information justified such a high fee, the fee should be aligned with MBS items 73296 (\$1200) and 73297 (\$400) which are for germline mutation testing of *BRCA1* and *BRCA2* genes and one or more other genes in affected individuals and for a known mutation in the relatives of identified probands, respectively. ESC noted that the fee for cascade testing should be lower because testing would be focussed on a known mutation.

ESC noted that the economic modelling suggested genetic testing dominated no genetic testing in both the proband group and for siblings in the base case and considered that the economic model was driven by cost offsets from avoiding renal dialysis. However, ESC noted that there were several issues with the model including the assumption that the sensitivity in the no testing group was 0% and the assumption that the test is always positive (i.e. there are never any negative results). ESC considered that these assumptions biased the model towards the genetic testing arm. ESC suggested that sensitivity analyses varying these assumptions would be useful for decision making. ESC also noted that many of the assumptions in the model were based upon expert advice but the sources and reasoning behind this advice were not made transparent. ESC suggested that, beyond the univariate sensitivity analyses presented, multi-way sensitivity analyses, including a probabilistic sensitivity analysis, should also be carried out.

ESC noted that it had not been provided with the pre-test probability and post-test prevalence of AS. ESC suggested that the applicant may be able to provide these estimates as requested in section 1 of the CUC proforma.

ESC also considered that the assumption that the test would never be negative also impacted upon the financial estimates because these assumed that the number of people who get the test is exactly the same as the prevalence of the disease. ESC also noted that, while information on costs and utilisation of dialysis had been included in the model, it had not been included in the financial estimates, which implied that all dialysis was managed within the public hospital system.

ESC advised that the provision of genetic counselling was best practice, but should be specified in the explanatory notes rather than in the item descriptor. ESC suggested the item descriptor limit testing to once per lifetime. ESC questioned whether it would be helpful for the item descriptor to define the types and severities of symptoms that would be sufficient to raise the pre-test clinical suspicion of Alport Syndrome, such as those provided by the Flinter clinical criteria, noting that any such definition would change over time. ESC considered that while the extent of family testing was dependent upon the mode of inheritance, the term 'relative' in the item descriptor could be better defined.

ESC Key ISSUES	ESC ADVICE
Fee	Unless input based, align with current MBS items 73296 and 73297.
Genetic counselling	Best practice; suggest include in explanatory notes rather than item descriptor.
WES performance – emerging	Emerging technology e.g. Alport syndrome cold cases: missing mutations identified by exome sequencing and functional analysis http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0178630 This would affect incremental costs, is this justifiable?
Comparator	Is it appropriate, given the lack of clinical evidence? Approach to assessing specificity and sensitivity needs clarification – could affect sensitivity analyses of the economic evaluation.
Costs to MBS may be underestimated	For example include dialysis cost into budget projections where relevant to the MBS budget.
Use of expert advice in assumptions	Further clarification is required as to experts providing advice.
Use of simulation modelling	Noted also by critique: use modelling and PSA for sensitivity analyses. Model is a simplistic decision tree in the CA.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

The applicant noted that a higher fee of \$1500 is currently charged for gene testing for Alport syndrome by Westmead hospital which does not include venesection, DNA extraction, transport or the consultation fee. The COL4A5, COL4A3 and COL4A4 genes are all very large and it takes 1 – 2 hours of a scientist's time to decide whether a variant is pathogenic or not.

The applicant advised that it is currently very difficult to get an appointment to see a geneticist (more than 6 months in most places) and agreed that this should not be a requirement for testing.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)