Australian Government

Medical Services Advisory Committee

Public Summary Document

Application 1628 – Alpha-1 Antitrypsin Genotyping

Applicant: The Royal College of Pathologists of Australasia (RCPA)

Date of MSAC consideration: MSAC 82nd Meeting, 29-30 July 2021

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 the creation of MBS items for genetic testing for the diagnosis of patients with alpha-1 antitrypsin deficiency (AATD) was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health.

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 did not support creation of new Medicare Benefits Schedule (MBS) items for genetic testing for the diagnosis of alpha-1 antitrypsin deficiency (AATD). This was based on uncertain clinical utility benefit and uncertain economic modelling, including uncertainty over the proposed fees. MSAC also advised that the isoelectric focusing (IEF) test currently used for AATD diagnosis is a functional test and its continued availability needs to be supported.

Consumer summary
This application was from the Royal College of Pathologists of Australasia for Medicare Benefits Scheme (MBS) funding of genetic testing for diagnosing alpha-1 antitrypsin deficiency (AATD). Alpha-1 antitrypsin (AAT) is a protein that is produced in the liver and helps to protect the lungs and liver from disease. People who do not make enough AAT can develop lung and/or liver disease earlier in life than most people. The two most common genetic variants in the gene for AAT, called the S and Z variants, together make up almost all of the variants found in Australians. There are many other much rarer genetic variants of the AAT genes, and some variants are worse than others. Some

Consumer summary

people have genetic variants but do not have any symptoms of disease. This makes it harder to tell, based on genetic testing for AATD, who will develop disease and who will not.

AATD is currently diagnosed using isoelectric focusing, which is a test that detects AAT protein. Isoelectric focusing (IEF) is a good test method for diagnosing AATD as it can be certain a person has 'normal' AAT (without any genetic variants). However not many laboratories conduct this test anymore because it is time-consuming and difficult to do and requires experienced technicians and scientists.

The RCPA applied for patients to be tested first with a test that looks for a set ('panel') of specific genetic variants in the AAT gene. If no variant is found the patient could then have their AAT gene sequenced, which is a test that can find any genetic variants that could change the AAT protein. MSAC did not consider genetic testing to be a good replacement for IEF, because panel testing only detects the specific variants included in the test and not all variants, so it cannot tell for certain when a person has 'normal' AAT protein.

MSAC was concerned that there was no clear benefit of this testing for patients' health, as patients with lung disease are already encouraged to stop smoking. MSAC also considered that because having a genetic variant does not always mean a person will develop AATD, the relevance of any genetic variants found is not clear. Many people would be found not to have a genetic variant by the panel test and so would go on to gene sequencing, so MSAC also considered that it was not clear that genetic testing is better value for money than IEF.

MSAC's advice to the Commonwealth Minister for Health

MSAC did not recommend funding for genetic testing for diagnosing alpha-1 antitrypsin deficiency. MSAC considered genetic testing to be less effective than the comparator, isoelectric focussing, because it cannot conclusively detect 'normal' alpha-1 antitrypsin. MSAC recommended reviewing the MBS listing for isoelectric focusing, to ensure it is appropriately supported so that isoelectric focussing remains available to diagnose alpha-1 antitrypsin deficiency.

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

MSAC noted that this application was for new MBS items for variant panel testing for at least the two most common *SERPINA1* variants, in patients with documented AATD and with no acute inflammation, followed by sequencing the *SERPINA1* protein-coding regions if the panel test is negative or inconclusive. The *SERPINA1* gene encodes the alpha-1 antitrypsin (AAT) protein; insufficient amounts of this protein can result in AATD.

MSAC noted that *SERPINA1* variants are common, detected in 1 in 9 Australians. MSAC noted the gnomAD genetic database showed most people with AAT variants are asymptomatic, at least in the first four decades of life. Having an AATD risk genotype can lead to early onset of emphysema on exposure to toxins such as cigarette smoke. However, only ~2% of children with genotype ZZ develop severe childhood liver disease. MSAC therefore considered that *SERPINA1* genetic variants have incomplete penetrance, i.e. carrying one or more *SERPINA1* variants does not necessarily result in the patient developing AATD. MSAC noted that variant panel testing cannot conclusively detect the presence of 'normal' (wildtype) *SERPINA1* sequences.

MSAC noted that 1.3% of Australians have variants in both their copies of *SERPINA1* and would be labelled as "affected" through genetic tests; however, MSAC considered that such patients would be more appropriately classified as "at risk", rather than "affected", due to incomplete penetrance. MSAC expressed concern about the social and ethical implications of over-diagnosing patients as having a condition when it is more appropriate to consider them at risk of developing that condition. MSAC noted the Department-Contracted Assessment Report (DCAR) did not address this point. MSAC noted the main safety concerns are the psychological aspects of testing and false negatives (i.e. patients denied the opportunity of preventative lifestyle choices).

MSAC noted the comparator, IEF of the AAT protein, is a functional test that has been used for decades for phenotyping. IEF has high sensitivity and specificity in trained hands, and false negatives are restricted to null alleles. MSAC noted that mass spectrometry (as used to test the AAT protein overseas) and gene sequencing are also test methods that are able to conclusively detect 'normal' AAT – but variant panel testing is not. MSAC noted the applicant's claim that IEF is being phased out because it is a time-consuming and difficult technique requiring specific expertise, and that it cannot be batch processed to the same degree as genetic tests. MSAC noted the RCPA catalogue shows AAT variant testing is only available in one Australasian laboratory, and considered it is likely not widely performed in Australia.

MSAC noted there was no direct evidence of clinical effectiveness, and agreed with the DCAR's statement that "the evidence describing the impact of testing on management decisions was of low to moderate quality". MSAC noted that patients with existing lung conditions, such as chronic obstructive pulmonary disease (COPD), would be advised to stop smoking and to adopt a healthier lifestyle regardless of their genotype status; thus, MSAC considered that genetically diagnosing patients would not meaningfully change their clinical management. MSAC noted that the main area of uncertainty was the extent to which advice to implement lifestyle change also requires genetic testing in COPD patients. MSAC noted the incremental cost-effectiveness ratio (ICER) was $35,756 per quality-adjusted life year (QALY) in the base case.

MSAC noted that the economic evaluation was a cost-utility analysis due to the claim of superior effectiveness of the 14-variant panel (and, presumably, the 2-variant panel). MSAC noted that paediatric liver disease, and cascade testing (to biological relatives, reproductive partners and fetuses) were not included in the DCAR's economic modelling. MSAC noted the key drivers of the ICER were test cost, diagnostic yield, sensitivity of IEF, and rates of FEV_1 decline and smoking (see Table 13). MSAC noted the DCAR assumed the sensitivity of IEF to be the same as that of the 2-variant panel, however it considered that IEF's sensitivity should be higher than that of a variant panel, as it is a functional test. MSAC noted that if IEF sensitivity is increased from 82% to 90%, then the ICER increases to $72,873/QALY.

MSAC noted the DCAR's claimed cost offset was fewer IEF services.

MSAC provided the following advice regarding the proposed services and fees:

- Only one Australian laboratory is currently known to offer AATD genetic testing (the 2-variant panel).
- Sanger sequencing of *SERPINA1* is estimated to require seven amplicons. The proposed fee of $260 for Sanger sequencing is based on the price for this test at a single centre and does not correspond to other Sanger sequencing test costs on the MBS.

- The fetal testing item's proposed fee ($100) is too low – the current cost of Sanger sequencing a single gene in a fetus at SA Pathology is $1,658. Fetal testing for unknown variants requires Sanger sequencing, so introducing item EEEE at this fee would result in significant out-of-pocket costs to patients.
- *SERPINA1* genetic testing of at-risk biological relatives is appropriate where the variant was detected using a genetic test, but not where the variant was detected using IEF.
- Reproductive partner testing should be done by sequencing to avoid the potential of having affected offspring.

MSAC noted that the estimated uptake of the variant panel testing was based on IEF test volumes, but that there is considerable variation in diagnostic yield estimates. In addition, the cascade testing (to biological relatives, reproductive partners and fetuses) was not included in the economic modelling, thus the budget impact is likely to be underestimated. If correctly modelled, MSAC estimated there would approximately 4,000 tests per year and the total cost to the MBS could be about $5.5 million over 5 years.

MSAC noted the applicant's claim that the primary benefit of AATD genetic testing is derived from the cascade testing and identifying variant-positive individuals who may avoid disease or delay its development. MSAC agreed with this claim, however it considered a genetic diagnosis to be less meaningful due to the incomplete penetrance of AAT variants.

MSAC noted that the applicant disagreed with the diagnostic yield estimates in its pre-MSAC response; the applicant claims diagnostic yield should be 11.2%. MSAC considered that this prevalence only takes into account biallelic S or Z variants and is thus underestimated.

MSAC considered *SERPINA1* variant panel testing to be inferior to IEF, because IEF is a functional test, i.e. it is able to conclusively detect the wildtype ('normal') protein. MSAC considered this functional testing to be key, making variant panel testing inferior for detecting probands. MSAC noted the declining use of IEF testing, and recommended supporting its continued availability. There were 1837 IEF tests reimbursed in the last year on the MBS. MSAC requested that the Department investigate the volume of IEF testing being undertaken outside MBS-funded services, and how it is being funded (e.g. through State/Territory funding, or patient out-of-pockets), so that it could consider actions needed (if any) to ensure the continued availability of IEF in Australia.

4. Background

This is the first time that genetic testing of the *SERPINA1* gene in patients with suspected AATD has been assessed by MSAC.

The comparator, IEF, has been listed on the MBS since 1 November 1998[1].

A related previous MSAC Application is MSAC application 1530, for blood product listing of purified human alpha-1-proteinase inhibitor (A1-PI) for the treatment of patients with AATD with significant lung disease. The public summary document (PSD) for application 1530 states that MSAC did not support A1-PI for the treatment of AATD in such patients. MSAC recognised the large unmet clinical need and the evidence of a radiologically detectable treatment effect, but was concerned with the weak evidentiary basis provided to suggest that changes in computed tomography (CT) density predict clinically meaningful health outcomes.

[1] MBS Online: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/downloads

MSAC also advised that, even with favourable assumptions regarding estimates of possible health outcomes of A1-PI treatment, the economic evaluation generated unacceptably large incremental cost-effectiveness ratios at the prices proposed by the sponsors.

5. Prerequisites to implementation of any funding advice

Genetic testing for disease should be undertaken in a National Association of Testing Authorities (NATA) accredited laboratory. The National Pathology Accreditation Advisory Council (NPAAC) advised that this testing is already provided in Australia, it is not complex testing and an EQA program is available.

6. Proposal for public funding

The proposed MBS items for the proposed affected individual testing and cascade testing of biological relatives are shown in Table 1. They were not modified in the DCAR to incorporate PASC's request that cascade testing not be restricted to first-degree relatives. Additional item descriptors are presented in Table 2 – these were developed out-of-session by the Department, at PASC's request. These were provided at a late stage in the evaluation process and consequently have not been fully addressed in the DCAR.

Table 1 Proposed MBS items

Category 6 (Pathology Services) – GROUP P7 GENETICS
Proposed item: AAAA
Genotypic testing to identify the [2 / 14]* most common pathogenic variants in the *SERPINA1* gene where the patient EITHER has abnormally low (<20 µmol/L) AAT levels, as determined by item number 66635, and any of the following: – emphysema without exposure to tobacco smoke or air pollutants – emphysema at a young age – basal emphysema – panniculitis – cirrhosis or liver function abnormalities (including neonatal hepatitis) without other risk factors – anti-proteinase 3-positive vasculitis OR – demonstrated family history of AAT deficiency, defined as a relative with an identified pathogenic or likely pathogenic variant in the *SERPINA1* gene, confirmed by a specialist or consultant physician. Maximum one test per lifetime. Fee: [$78 / $100]* Practice Note: The genotype test should have sufficient diagnostic range and sensitivity to detect at least 95% [or 99%] of pathogenic *SERPINA1* variants likely to be present in the patient. (For the 2-variant option, these should be the S (p.Glu288Val) and Z (p.Glu366Lys) variants. For the 14-variant option, these should be the 14 most common pathogenic variants.)
Proposed item: BBBB
Sequencing of the *SERPINA1* gene to identify an alpha-1 antitrypsin (AAT) pathogenic variant where the result after genotyping using item number AAAA is inconclusive; requested by a pathologist, specialist or consultant physician. Maximum one test per lifetime. Fee: $260

Proposed item: CCCC
Characterisation of a pathogenic variant in the *SERPINA1* gene in an individual who is a first-degree relative of a patient who has had a pathogenic or likely pathogenic variant identified in this gene, and has not previously received a service under items AAAA or BBBB; requested by a specialist or consultant physician. Maximum one test per lifetime. Fee: [$78 / $100]*

* Note: the square brackets indicate contingencies dependent on whether MSAC selects the 2- or 14-variant panel for item AAAA.

Source: DCAR, Table 1.

Table 2 Proposed additional MBS items

Proposed item: DDDD
Genotypic testing to identify at least [the S and Z / 14]* pathogenic variants in the *SERPINA1* gene in: (a) the reproductive partner of an individual with AAT deficiency (confirmed by AAAA or BBBB or CCCC), or (b) the reproductive partner of an individual who is a carrier of an AAT deficiency allele (confirmed by AAAA or BBBB or CCCC). Requested by a specialist or consultant physician. Maximum one test per lifetime. Fee: [$78 / $100]*
Proposed item: EEEE
Genotypic testing of pregnant patient to identify, in the fetus, the pathogenic variants in the *SERPINA1* gene present in each reproductive partner, where both reproductive partners have either AAT deficiency or carry an AAT deficiency allele (confirmed by AAAA or BBBB or CCCC or DDDD), and where no pre-implantation diagnosis is made. Requested by a specialist or consultant physician. Maximum one test per pregnancy. Fee: [$78 / $100]*

* Note: the square brackets indicate contingencies dependent on whether MSAC selects the 2- or 14-variant panel for item AAAA. The $78 fee would apply due to the lower number of variants to be identified, matching the proposed item CCCC (and proposed item AAAA) if the 2-variant panel is supported.

Source: DCAR Table 2, from Department post-PASC document providing additional item descriptors.

Several MBS listing decision options were available to MSAC (see Table 12), including the option to consider Intervention 1 (the 2-or 14-variant panel) alone, without sequencing as follow on test:

- 14-variant panel alone
- 14-variant panel with sequencing (applicant's requested listing)
- 2-variant panel alone
- 2-variant panel with sequencing (PASC's suggested alternative listing)

7. Summary of public consultation feedback/consumer issues

Targeted consultation feedback was received from three patient organisations and a professional organisation. One patient organisation also included a summary of the results of a survey of their patient community's opinion on this application (inferred ≥25 respondents). Public consultation feedback was received from an individual senior scientist who is involved in conducting AAT testing (both IEF phenotyping and variant panel testing) in a pathology laboratory, an individual specialist, three individual consumers, and an individual caregiver. All

four targeted consultation responses and all six public consultation responses were supportive of public funding for genetic testing for AATD. Feedback consistently supported the shift to a better test methodology, as laboratories replace IEF with genetic testing.

Potential benefits of funding genetic testing for AATD were outlined as follows:

- Genetic testing is more robust and more accurate than IEF.
    - Sequencing is more sensitive than IEF.
    - IEF alone does not provide a firm Alpha-1 status in all cases (e.g. M/null genotype).
- Genetic testing gives more objective results – IEF is an outdated technique that requires subjective interpretation, dependent on extensive experience.
    - IEF is therefore vulnerable to loss of skill as experts retire.
    - Genetic testing is a more cost-efficient use of staff labour in pathology laboratories. Genetic testing is amenable to automation, which is not the case for IEF.
- Reducing the number of tests each patient undergoes, from 4 to 3 or potentially 2 tests.
- Additional variant classification by expert genetic pathologists.
- Genetic testing has faster turnaround times.
- Clinical opinion and recommendations support genetic testing for AATD. This testing aligns with the TSANZ February 2020 position statement, as well as recommendations from the American Thoracic Society (ATS) and the European Respiratory Society (ERS)[2].
- Helping patients to make lifestyle changes to prevent disease progression (e.g. avoiding exposure to smoking, dust, fumes, limit alcohol consumption, encourage vaccination against flu and COVID-19), and so have the best possible quality of life and life expectancy.
- Open up discussions about inheritance of AATD with potential parents or family, enabling informed reproductive decisions.
- Earlier and more timely diagnoses: one patient organisation expects it would reduce the time to diagnosis (current average 5-7 years), and reduce misdiagnosis of AATD as adult asthma, which is common. With the current delays, patients spend a lot of money on medical appointments, are forced into early retirement, have unnecessary surgeries and pharmacy costs, and can take complementary medicines hoping to relieve symptoms but not realise that some cause more damage to the liver and lungs.
- Earlier diagnosis would reduce the burden on the hospital system from reduced lung exacerbations, and reduced lung and liver transplants would be required as informed patients can take action to limit lung and liver decline.
- Consistent funding across Australia, fairness and equal access.
    - Some relatives of people who know they have a variant not detectable using IEF, have not been tested due to access, including financial difficulties.
- Provide important data on utilisation of testing and the prevalence of AATD in Australia.
- Support policy development.
- Providing knowledge to the general public about the ramifications of this deficiency.
- There would not be a delay to availability as this testing is already done in Australia.
- Potential downsides of funding genetic testing for AATD were outlined as follows:

[2] American Thoracic Society/European Respiratory Society Statement Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency: https://doi.org/10.1164/rccm.168.7.818

- Rare variants may be missed in patients where sequencing is not clinically indicated.
- Risk of psychological consequences if no support is available whilst waiting for the results or after the result.
- Over-testing, at increased cost to patients.
- Implications of a genetic diagnosis on increased insurance premiums.
- No readily available treatment options.

Two individuals and a patient organisation stated that counselling or genetic counselling should delivered alongside this intervention, as well as referral to support services and patient organisations. Appropriate consumer information and education would need to be given to health professionals (including training for medical students) as well as consistent information and guidelines for all pathology providers to follow. Consumer resources such as those from the NHMRC[3] could be useful for general practitioners (GPs) and consumers.

Two consumers and a patient organisation stated that only allowing specialist or consultant physicians to access both tests would impair access to testing. GPs can currently request AATD phenotyping, genetic variant panel testing and sequencing, and this access to request should remain.

Key technical comments from the consultation feedback were:

- Genetic testing requires whole blood, whereas IEF requires serum.
- A laboratory scientist stated the proposed serum AAT threshold of 20 µMol/L was adequate, as it is slightly higher than the 11 µMol/L considered to be the clinically significant threshold concentration, according to Brode et al., 2012[4]. They suggested the inclusion of patients who have respiratory symptoms but have a serum AAT concentration above the 20 µMol/L threshold, to allow the detection of non-functional AAT variants.
- A patient organisation suggested reviewing and broadening the population after 12 months, as proposed access depends on serum AAT testing, which is not highly sensitive.
- A laboratory scientist commented that the fee for the 14-variant panel could be lowered from $100 to $80, and the fee for gene sequencing increased to $360, as the gene panel test does not require expensive reagents and will have greater economies of scale than sequencing. Sequencing is labour intensive but also does not require expensive reagents. Some laboratories charge up to $400 for sequencing. A patient organisation supported the proposed $100 and $260 fees.
- Progenika Biopharma's panel may not be suitable for the 14-variant panel as the cost would most likely be more than full *SERPINA1* sequencing. Registration of the Progenika panel in Australia would also need to be considered. Most likely, laboratories would not use an international commercial product.
- Some countries have testing kits where patients send samples directly to the lab.
- Two consumers provided further information related to null alleles:
    - IEF cannot detect null alleles, and for M/null individuals would provide a false MM result. A two-variant panel would also not detect null variants – sequencing is required to detect null variants.

[3] Understanding Direct-to-Consumer Genetic DNA Testing – An Information Resource for Consumers. NHMRC, 2014. Available online: https://www.nhmrc.gov.au/sites/default/files/documents/reports/direct-consumer-genetic-testing.pdf

[4] Brode SK, Ling SC, Chapman KR. Alpha-1 antitrypsin deficiency: a commonly overlooked cause of lung disease. CMAJ. 2012 Sep 4;184(12):1365-71.

    - Compound heterozygotes (e.g. Z/null) have just as high risk as null/null individuals of developing lung and liver disease.
    - Null/null homozygotes have more severe lung disease than ZZ or SZ individuals[5].
    - M/null individuals have increased lung symptomatology and obstructive lung disease. M/null individuals have about 50% of the normal AAT concentration, whereas ZM individuals have about 60%[6].
- A consumer stated that the application title is confusing, as it in fact includes not only genotyping but also sequencing. It could be renamed "Alpha-1 antitrypsin genetic testing".

8. Proposed intervention's place in clinical management

Description of proposed intervention
There are two proposed medical services in this application: i) panel testing of the 2 or 14 most common *SERPINA1* variants, and ii) sequencing of the *SERPINA1* protein-coding exons. These interventions are diagnostic laboratory tests for diagnosing AATD that are not currently publicly funded.

Sequencing of the *SERPINA1* protein coding exons is proposed to only be conducted if the result of the 2- or 14-variant panel test is negative or inconclusive, which occurs in individuals with variants not included on the panel and in individuals without a variant. It is proposed by the applicant that a 14-variant panel test containing the 14 most prevalent pathogenic variants in Australia might be more informative than isoelectric focusing (IEF), the current publicly funded test used to diagnose AATD, and may reduce the number of patients requiring gene sequencing for negative or inconclusive results. The PICO Advisory Sub-Committee (PASC) additionally proposed the 2-variant panel be considered for the panel intervention, as it may be more cost-effective than the originally requested 14-variant panel.

Description of medical condition
AAT is a protein that is mainly produced in the liver and released into the bloodstream. Its function in the body is to regulate the action of the enzyme elastase. Elastase is produced by neutrophils (a type of white blood cell) to protect the lungs by removing inhaled material, such as smoke and other pollutants. People with AATD either produce a dysfunctional form of AAT, or have low serum concentrations of functional AAT. Inadequate concentration of serum AAT means that elastase is not neutralised after removing inhaled pollutants and it begins to break down lung tissue as well, which can lead to lung disease. Dysfunctional AAT tends to accumulate in the liver and can lead to liver disease[7,8]. Paediatric patients with AATD predominantly present with liver manifestations, whereas patients with later onset AATD more often show symptoms in the lungs.

Each person has two copies of the *SERPINA1* gene, which encodes the AAT protein—one inherited from each parent—with each copy being responsible for producing half of the body's

[5] Miravitlles, M. et al. 2017. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in α1-antitrypsin deficiency. European Respiratory Journal 50(5): 1700610.
[6] Cortes-Lopez, R. & Barjaktarevic, I. 2020. Alpha-1 Antitrypsin Deficiency: a Rare Disease? Curr Allergy Asthma Rep 20, 51.
[7] Alpha-1 Association of Australia. 2017. *A guide to alpha-1 antitrypsin deficiency* [Online]. Available: https://www.alpha1.org.au/doc/AAAbooklet.pdf [Accessed March 10 2021].
[8] Lab Tests Online. 2021. *Alpha-1-antitrypsin* [Online]. Available: https://www.labtestsonline.org.au/learning/test-index/alpha1-antitrypsin [Accessed March 10 2021].

AAT. If there is a variant in one or both copies of the gene, the result can be an inadequate concentration of serum AAT or an AAT protein that does not work properly[1,2], though not all people with pathogenic or likely pathogenic variants develop AATD.

Current and proposed testing pathways for the management of patients suspected of AATD are depicted in Figures 1 and 2, respectively. Intervention 1 (2- or 14-variant panel testing) is proposed to replace IEF, and intervention 2 (sequencing) is proposed to be an addition to the algorithm.

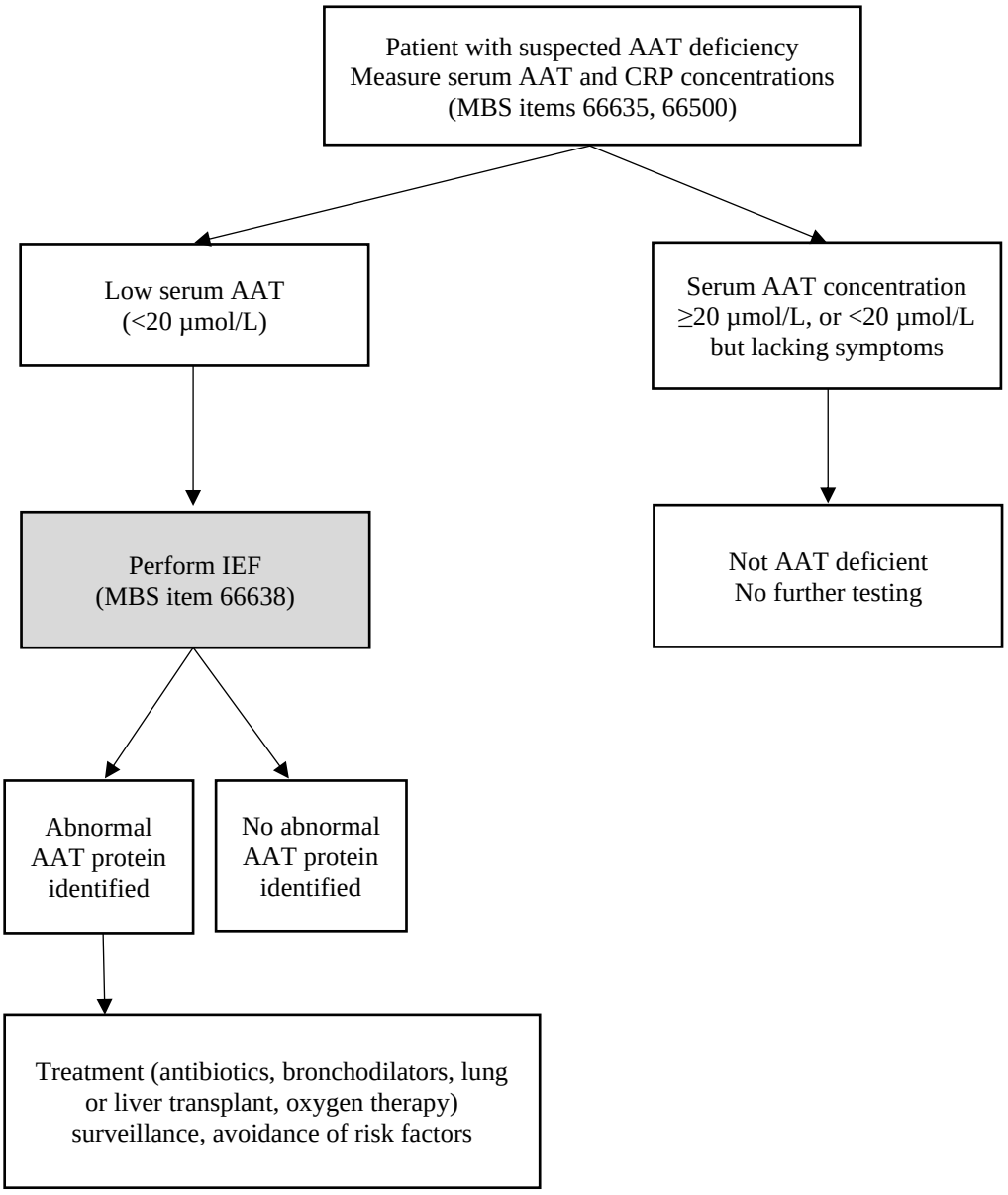

Figure 1 Current clinical management pathway for patients with suspected AATD

AAT = alpha-1 antitrypsin, CRP = C-reactive protein, IEF = isoelectric focusing, MBS = Medicare benefits schedule.
Source: Based on DCAR, Figure 1.

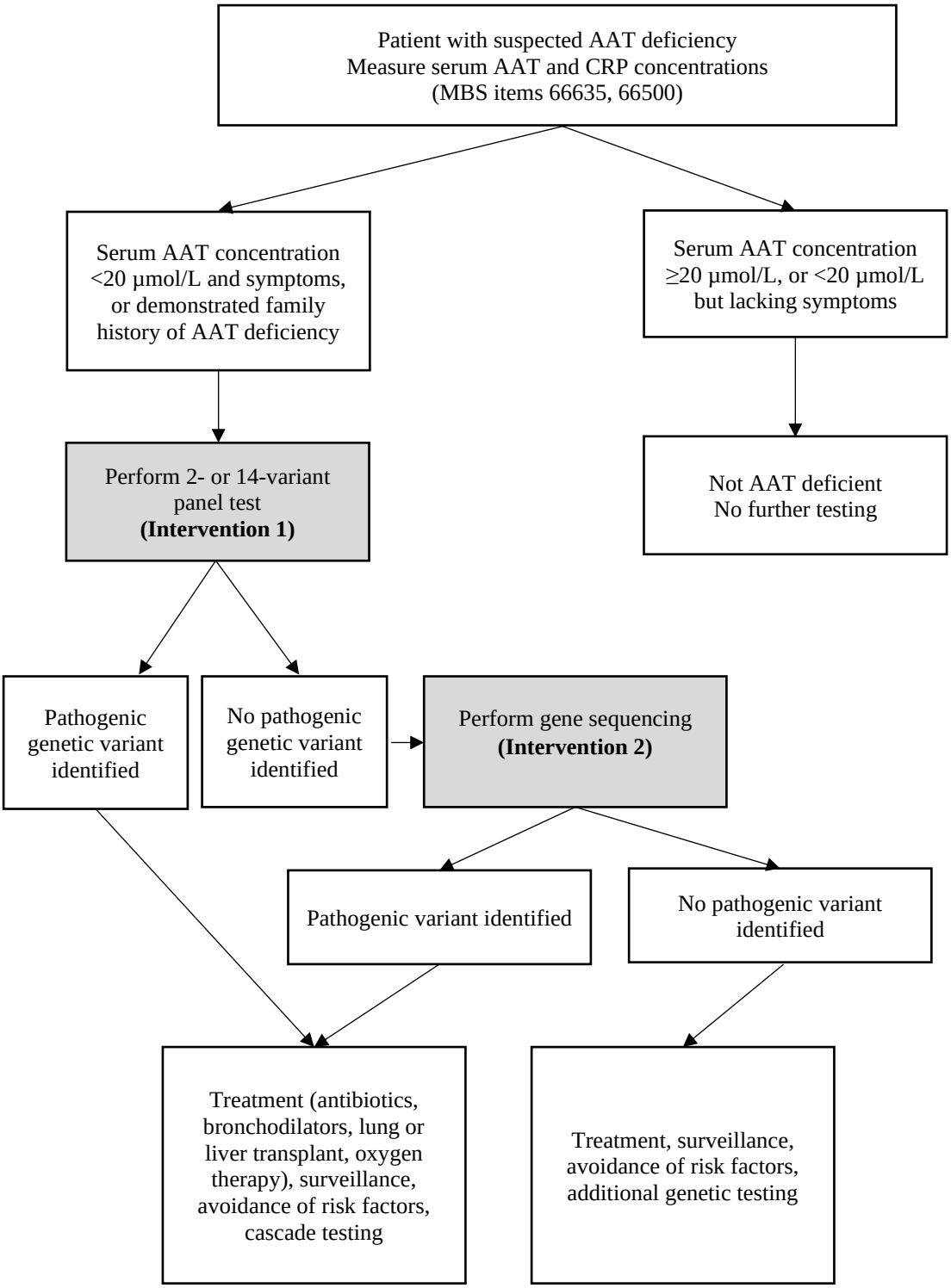

Figure 2 Proposed clinical management pathway for patients with suspected AATD

AAT = alpha-1 antitrypsin, CRP = C-reactive protein, MBS = Medicare benefits schedule.
Source: Based on DCAR, Figure 2.

The DCAR stated that a genetic diagnosis provides management opportunities in family planning, cascade testing and subsequent preventative management. Individuals who test positive for a variant are recommended to make lifestyle changes, particularly to avoid smoking, pursue a healthy lifestyle and maintain a healthy weight.

In the applicant's proposed algorithm, a genetic variant panel would replace the current IEF test. The expanded 14-variant panel (targeting the 14 most prevalent pathogenic variants) would be expected to make more genetic diagnoses than the 2-variant panel. The second intervention, *SERPINA1* exon sequencing, would be expected to have even greater analytical sensitivity than either variant panel testing or IEF because it can detect all genetic variants in the sequenced region. It was proposed as a subsequent test for affected individuals who have inconclusive or negative results from the 2- or 14-variant panel. ESC noted that neither panel can conclusively identify a wildtype M allele, whereas both IEF and sequencing tests can do so.

9. Comparator

The DCAR stated that the comparator for variant panel testing (intervention 1) is phenotyping by IEF. Phenotyping of the AAT protein by IEF is conducted under MBS item 66638 (Table 3) and is central to the current clinical management algorithm.

Table 3 Relevant MBS item descriptor for IEF, the comparator for intervention 1 (gene panel test)

Category 6 – PATHOLOGY SERVICES
MBS Item 66638 (isoelectric focusing or similar methods for determination of alpha-1 antitrypsin phenotype in serum). 1 or more tests.
Fee: $49.05

Source: DCAR, Table 14.

The DCAR stated that the IEF test is currently used to infer a genetic cause of a low serum AAT concentration. The test is used to identify all variants with an isoelectric point different from the fully functional PI*M allele, the most prevalent variants being PI*Z and PI*S. The DCAR further stated that Australian laboratories appear to be phasing out IEF techniques. IEF can be technically challenging and requires expertise for the interpretation of results.

The DCAR stated that gene sequencing (intervention 2) is considered the gold standard test for detecting *SERPINA1* variants. There is no direct comparator for this test.

10. Comparative safety

The comparative harms of genetic testing versus IEF or sequencing are identical, in terms of sample collection. Testing requires a blood draw or saliva swab, which are very safe and commonly performed procedures.

False negatives resulting from variant panel testing or sequencing are rare. The primary harm of false negatives would be to biological relatives who may miss the opportunity for familial testing and consequent early detection and pre-emptive education. For example, individuals identified with AATD at birth are less likely to begin smoking[9]. The likelihood of a false positive result from genetic testing is negligible. However, in the case of a false positive, patients would be recommended to adopt healthy lifestyle choices, which has no attendant risk of physical harm.

A genetic diagnosis may be psychologically challenging for some individuals and family members who undergo cascade testing. Providing access to genetic counselling is crucial for managing any misinformation and increased anxiety that may be associated with genetic

[9] Thelin, T., et al. 1996. Primary prevention in a high-risk group: smoking habits in adolescents with homozygous alpha-1-antitrypsin deficiency (ATD). *Acta Paediatrica*, 85**,** 1207-1212.

testing. The inability to predict symptoms of a genetic disease may increase anxiety, fear and worry[10]. In addition, knowledge of genetic predisposition to disease may impact the reproductive and marital decisions of affected individuals or their partners[11].

A study of 172 parents of young children diagnosed with AATD at age 3–6 months found that most (92%) did not feel that their child's diagnosis negatively affected their own sense of self[12]. Upon receiving the AATD diagnosis, 80% of parents reacted indifferently and/or did not fully understand the diagnosis (44%). Shock or depression was experienced by the remaining 20% of parents—12% were depressed and 6% felt guilt. Most individuals (92%) claimed the diagnosis did not affect their self-image and 50% of parents felt positive about early detection of the condition.

11. Comparative effectiveness

Clinical claim
On the basis of the benefits and harms reported in the evidence base, the DCAR suggested that, relative to IEF, genetic testing for AATD has non-inferior safety and superior effectiveness.

The DCAR stated that it identified no direct evidence for effectiveness, but found evidence pertaining to effectiveness obtained through the linked evidence approach (Table 4).

[10] Worthington, A. K., et al. 2018. Spirituality, illness unpredictability, and math anxiety effects on negative affect and affect-management coping for individuals diagnosed with alpha-1 antitrypsin deficiency. *Health communication,* 33**,** 363-371.
[11] Klitzman, R. L. 2010. Misunderstandings concerning genetics among patients confronting genetic disease. *Journal of genetic counseling,* 19**,** 430-446.
[12] Sveger, T. & Thelin, T. 1981. Four-year-old children with alpha 1-antitrypsin deficiency. Clinical follow-up and parental attitudes towards neonatal screening. *Acta Paediatrica Scandinavica,* 70**,** 171-177.

Table 4 Clinical trial data (linked evidence approach)

Type of evidence	Description	Number	Risk of bias
Diagnostic performance	Diagnostic studies were used to assess diagnostic accuracy[a]. Observational studies were used to address diagnostic yield[b] and analytical concordance[b]	**Diagnostic accuracy:** (k = 2) 14-variant panel: k = 2, n = 3,224 **Diagnostic yield:** (k = 9) IEF: k = 1, n = 512 2-variant panel: k = 5, n = 1,690 14-variant panel: k = 2, n = 3,530 Sequencing: k = 4, n = 668 **Concordance** (k = 4) IEF and 2-variant test: k = 3, n = 4,453 14-variant panel and sequencing: k = 1, n = 112 14-variant panel and traditional algorithm: k = 1, n = 512	**Diagnostic accuracy** Low, with uncertain risk of bias and applicability for patient selection **Diagnostic yield** Low to moderate. Issues pertaining to blinding, statistical analysis, analysis of confounding factors, and study power **Concordance** Low to moderate. Issues pertaining to patient characteristics, confounding factors, statistical analysis, blinding, and power
Clinical validity	Prevalence of AATD genetic variants and their association with lung and liver disease	k = 2 n = 11,769	Not applicable
Therapeutic efficacy	Observational cohort studies show that test results guide behavioural and lifestyle changes	k = 4 n = 3,984	Moderate to high
Therapeutic effectiveness	1 review and 4 observational studies on the effect of knowledge of AATD status on health outcomes such as survival and lung function	Review: k = 18, n = 14,750 Observational: k = 4, n = 26,401	Moderate to high

Source: DCAR, Table 3.

Diagnostic performance

Diagnostic accuracy

No diagnostic accuracy study was identified that closely reflects the population in the PICO criteria. The populations of the included studies reporting on diagnostic accuracy are less enriched than that in the proposed PICO. It is unclear how this may affect the test accuracy. No study reported on diagnostic accuracy of IEF, the 2-variant panel or sequencing. Furthermore, only one study used the gold standard (sequencing) as a reference standard. There were two studies with low risk of bias that reported on the diagnostic accuracy of the 14-variant panel test compared to sequencing or a 'traditional algorithm' (incorporating both phenotyping and the 2-variant panel). The sensitivity and specificity of the 14-variant panel test were reported as 98.2–100% and 100%, respectively.

Diagnostic yield

No studies on the diagnostic yield in children with liver disease were identified. No studies on diagnostic yield cascade testing or testing of first-degree relatives of probands were identified.

The populations and serum AAT thresholds varied among the included nine diagnostic yield studies (Table 4). The studies had a low to moderate risk of bias. No study was closely aligned to the PICO population. Due to the scant evidence available, the inclusion criteria were broadened in the interests of providing data indicative of a lower bound for the diagnostic yield of IEF, the 2- and 14-variant panels, and sequencing. Thus, the studies presented were performed in broader populations than that proposed in the PICO. It is expected that the population in the proposed PICO would be more enriched, yielding a greater proportion of patients with a pathogenic variant than reported in the included studies. Therefore, results may

be an underestimate of the diagnostic yield from the PICO population. ESC noted that the 2- and 14-variant panels are not able to conclusively identify wildtype M alleles, therefore patients testing negative to a panel test could be either M or undetected non-panel variant alleles. The DCAR stated that for clarity, these have been described as non-S, non-Z or non-14-variant.

No studies performed in the Australian context were identified. Due to the generally lower prevalences of PI*S and PI*Z alleles in the countries of the included studies (compared with Australia), it is possible that the diagnostic yields presented in this report may underestimate the yields of these alleles in the Australian population. This does not account for the prevalence of non-S/Z variants, which is unknown for the Australian population. In addition, most of the diagnostic yield estimates were derived from studies with populations that were less enriched than that proposed in the item descriptor. Generally, these were samples from patients with low AATD but no other clinical symptoms or adult patients with COPD (not restricted to <40 years).

One study reported on the diagnostic yield of IEF, five studies reported on the 2-variant panel, two on the 14-variant panel and four on sequencing (Table 5). For all tests (excluding IEF), there was significant variation among the studies in terms of the clinical characteristics of the populations and serum AAT thresholds used to define AATD, which did not allow for any meaningful aggregation of results. Of the nine included studies, five were selected as being the most informative with respect to the proposed population and algorithm, in particular the studies by Snyder et al. 2006[13] (reporting on IEF) and Ottaviani et al. 2020[14] (reporting on the 14-variant panel and sequencing, with results inferred for 2-variant panel) (Figure 3).

[13] Snyder, M. R., et al. 2006. Diagnosis of alpha-1-antitrypsin deficiency: An algorithm of quantification, genotyping, and phenotyping. *Clin Chem,* 52**,** 2236-42.
[14] Ottaviani, S., et al. 2020. Molecular diagnosis of alpha1-antitrypsin deficiency: A new method based on Luminex technology. *Journal of Clinical Laboratory Analysis,* 34.

Table 5 Summary results of diagnostic yield of IEF, 2- and 14-variant panel testing and sequencing among 9 included studies

Test method	Serum AAT threshold	Author, year (n)	Population (country)	Diagnostic yield
IEF	<18.4 µmol/L	Snyder 2006 (n = 512)	Patients referred for AAT phenotypic analysis. Samples of whole blood and serum (USA)	Non-MM: **14.6%**
2-variant panel	<14.7 µmol/L	Menga 2020 [A] (n = 519)	Patients >30 years of age with a COPD diagnosis (Argentina)	≥1 S or Z: **25.8%**
	<18.4 µmol/L	Snyder 2006 (n = 512)	Patients referred for AAT phenotypic analysis. Samples of whole blood and serum (USA)	≥1 S or Z: **13.7%**
		Sorroche 2015 [A] (n = 217)	Adult patients diagnosed with COPD (Argentina)	≥1 S or Z: **33.6%**
	<20.8 µmol/L	Ottaviani 2020 (n = 418)	DBS samples submitted to the Italian reference laboratory from January 2016 to April 2016 for AATD testing (Italy)	≥1 S or Z: **20.1%**
		Russo 2016 [15] (n = 24)	Patients 40 years of age or older having been diagnosed with COPD (Brazil)	≥1 S or Z: **95.8%**
14-variant panel	<19.1 µmol/L (internal quantification) or <16.6 µmol/L (external quantification)	Veith 2019 [16] (n = 3,112)	Routine diagnosis of AATD (Germany)	Variant (14-variant panel or other): **61.2%**
	<20.8 µmol/L	Ottaviani 2020 (n = 418)	DBS samples submitted to the Italian reference laboratory from January 2016 to April 2016 for AATD testing (Italy)	≥1 Progenika allele: **24.2%**
Sequencing	<18.4 µmol/L	Graham 2015 (n = 42)	Samples sent to clinical laboratory (USA)	Variant: **38.0%**
	<20.8 µmol/L	Ottaviani 2020 (n = 418)	DBS samples submitted to the Italian reference laboratory from January 2016 to April 2016 for AATD testing (Italy)	Variant: **5.3%**
	<22.1 µmol/L	Rodriguez-Frias 2012 (n = 108)	Retrospective analysis of samples in previous AAT studies within the laboratory (Spain)	Variant: **78.7%**
		Duk 2016 (n = 100)	Patients with chronic respiratory disorders (Poland)	Variant: **11.0%**

AAT = alpha-1 antitrypsin, AATD = alpha-1 antitrypsin deficiency, COPD = chronic obstructive pulmonary disease, DBS = dried blood spot, IEF = isoelectric focusing.

[A] = likely cross over with patients included in Sorroche et al. (2015)[17]

Source: based on DCAR Table 18, with the serum AAT threshold for Ottaviani 2020 corrected as per the rejoinder

[15] Russo, R., et al. 2016. Prevalence of alpha-1 antitrypsin deficiency and allele frequency in patients with COPD in Brazil. *Jornal Brasileiro de Pneumologia: publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia,* 42**,** 311-316.

[16] Veith, M., et al. 2019. Diagnosing Alpha-1-Antitrypsin Deficiency Using a PCR/Luminescence-Based Technology. *Int J Chron Obstruct Pulmon Dis,* 14**,** 2535-2542.

[17] Sorroche, P. B., et al. 2015. Alpha-1 Antitrypsin Deficiency in COPD Patients: A Cross-Sectional Study. [Spanish]. Archivos de Bronconeumologia, 51, 539-543.

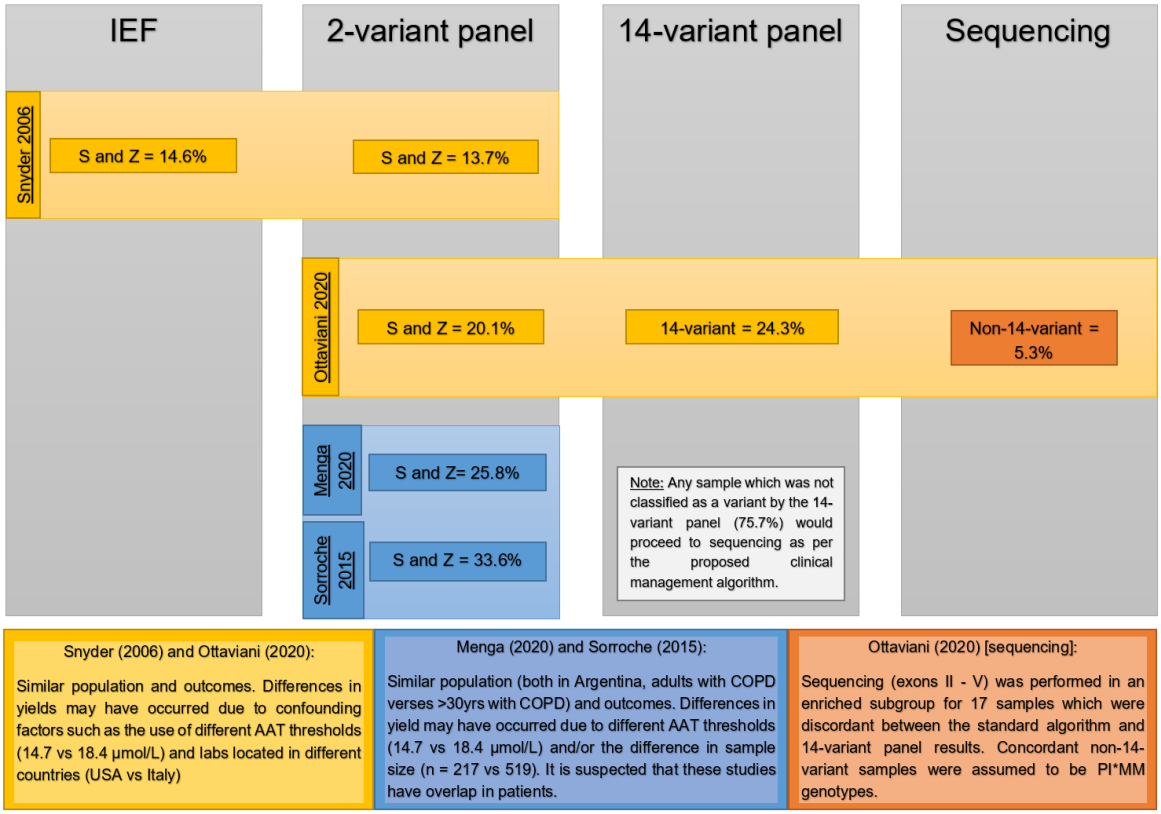

Figure 3 Diagnostic yield of AAT or *SERPINA1* variants as determined by IEF, 2- and 14-variant panel testing and exon sequencing among key studies

Source: DCAR Figure 5, though note that the rejoinder corrected the AAT threshold for Ottaviani 2020 to 20.8 µmol/L.

Studies by Menga et al. 2020[18] and Sorroche et al. 2015[19] reporting on the 2-variant panel, were also considered informative because of the population of COPD patients, but due to population differences they could not be compared with the studies by Snyder and Ottaviani. Additionally, it is suspected that there may be overlap in participants between these papers, so caution was exercised when drawing conclusions from these findings.

The phenotypic diagnostic yield of IEF used in the DCAR's analysis was 14.6%, as reported by a single study, Snyder et al. 2006. The yield for the 2-variant panel was estimated to be 13.7% to 20.1%. Within a single population, the diagnostic yield of IEF was higher than that of the 2-variant panel, 14.6% and 13.7%, respectively. In patients with COPD (k = 2), the 2-variant panel gave a diagnostic yield of 25.8% and 33.6%. The 14-variant panel (Progenika) gave a diagnostic yield of 24.2%, which is slightly higher than the estimated diagnostic yield for the 2-variant panel (20.1%). This higher comparative diagnostic yield (additional 4.1%) is likely to have occurred because the Progenika panel captures 12 further *SERPINA1* variants in addition to the PI*S and PI*Z variants targeted by the 2-variant panel.

The DCAR noted that the diagnostic yield of sequencing was calculated from highly enriched populations. The diagnostic yield in samples that had a negative result on the 14-variant panel was 12.3%. In a highly enriched population, the yield for sequencing ranged from 38% to 79%.

[18] Menga, G., et al. 2020. Prevalence of Alpha-1 Antitrypsin Deficiency in COPD Patients in Argentina. The DAAT.AR Study. *Archivos de Bronconeumologia*, 56**,** 571-577.
[19] Sorroche, P. B., et al. 2015. Alpha-1 Antitrypsin Deficiency in COPD Patients: A Cross-Sectional Study. [Spanish]. *Archivos de Bronconeumologia*, 51**,** 539-543.

The diagnostic yield of sequencing after performing the 14-variant panel test was 5.3% in a comparatively less enriched (and consequently more applicable) population.

The effect of the varied serum thresholds used for inclusion in the studies on the diagnostic yields is uncertain. A lower AAT concentration typically (but not exclusively) indicates more severe disease and is a result of pathogenic alleles such as PI*Z or null alleles. Consequently, studies implementing comparatively lower AAT thresholds than the proposed PICO (<20 µmol/L) may be biased towards the inclusion of participants with pathogenic variants causing more severe AATD. Studies with a lower threshold than this may overestimate the number of pathogenic variants in a sample population. However, diagnostic yields were calculated based on the presence of ≥1 variant irrespective of pathogenicity. Given that most of the study populations (by inclusion criteria) were less enriched than the PICO population, and consequently underestimate the diagnostic yield, the applicability of the diagnostic yields to the Australian setting is highly uncertain.

Concordance

Four of the studies that reported on diagnostic accuracy and diagnostic yield also reported on concordance or discrepancies between tests. A report by the US Food and Drug Administration[20] found 100% agreement between the 14-variant panel and sequencing. However, there was substantial risk of bias in this study because the samples were selected based on the presence of the variants targeted by the panel test being investigated. Discordance between the 14-variant panel and a traditional algorithm (IEF and 2-variant panel) was 4%. In the same population, 33% of samples tested with IEF and the 2-variant panel were discordant. An additional two studies (Ottaviani et al. 2020, Graham et al. 2015[21]) reported rates of discordance between IEF and the 2-variant panel at 1.2% and 2% of samples. The higher rate of discordant results in the study by Ottaviani et al. may be attributable to the greater proportion of patients with non-panel variants in the sample population, compared with those in the studies by Graham or Snyder. Snyder et al. also reported on discordance between IEF and the 2-variant panel, reporting a rate of 15%. These discrepant results were mainly explained by the presence of null alleles (3 of 8 cases) or variants not captured by the 2-variant panel test (3 of 8 cases). The remaining discrepancies were detected in one patient with a PI*Z allele, where AAT was either not produced or not secreted into the bloodstream, resulting in the identification of the PI*MM phenotype only; and one patient who was receiving augmentation therapy unbeknownst to the investigators.

Clinical validity

When penetrance is low, clinical validity is significantly reduced. Evidence on the prevalence of AATD genetic variants and the association between these variants and lung and liver disease was used to establish which specific variants cause disease and the number of Australians affected/degree of penetrance of known variants of the *SERPINA1* gene.

The prevalence of variants can depend on the ethnicity of the population. Two studies reported on the prevalence of AATD in the Australian population (Table 6). In a recent study of eight AAT cohort studies in Australia[22], the reported prevalence of the PI*ZZ genotype (severe AATD) is 1 in 5,572—equating to a total of 4,126 affected individuals (95% CI; 2,894–5,695)

[20] United States Food and Drug Administration 2017. 510(k) Substantial equivalence determination decision summary K171868. *In:* Administration, US FDA (ed.).

[21] Graham, R. P., et al. 2015. *SERPINA1* Full-Gene Sequencing Identifies Rare Mutations Not Detected in Targeted Mutation Analysis. *Journal of Molecular Diagnostics,* 17**,** 689-694.

[22] Blanco, I., et al. 2017. Alpha-1 antitrypsin Pi*SZ genotype: Estimated prevalence and number of SZ subjects worldwide. *International Journal of COPD,* 12**,** 1683-1694.

of 22,992,654 individuals (the population of Australia when the study was conducted). The study by de Serres et al.[23] reported on mean frequency of AATD protein variants among the Indigenous and non-Indigenous populations; however, this does not represent the complete demographic profile of the Australian population. A significant limitation was the lack of studies representing the west and southwest regions of Australia. The most common *SERPINA1* variants specific to the different ethnicities within the Australian population should be determined by Australian laboratories to ensure the adequate clinical validity of targeted genotyping.

Table 6 Prevalence of two most common AAT protein variants in Australia

Author, Year Study Design	Population and Sample Size	Results
Blanco et al., 2017 Cross-sectional study	n = 5,536 from 8 cohorts in Australia	PI*ZZ frequency 13 per 1,000 (11–16) PI*ZZ prevalence 1:5,572
de Serres et al., 2003 Cohort study	n = 6,233 from 12 cohorts in Australia (4 Aboriginal, 8 Caucasian)	PI*Z mean frequency Overall: 13.4 per 1,000 (11.4–15.7) Aboriginal: 0.8 per 1,000 (0.04–5.4) Caucasian: 13.4 per 1,000 (11.4–15.7) PI*S mean frequency Overall: 44.4 per 1,000 (40.7–48.5) Aboriginal: 26.0 per 1,000 (18–37) Caucasian: 44.5 per 1,000 (40.8–48.5) Estimates of PI genotype prevalence Overall (5 phenotypic classes): 1 in 8.9 individuals PI*MS: 1 in 12 individuals PI*MZ: 1 in 40 individuals PI*SS: 1 in 507 individuals PI*SZ: 1 in 841 individuals PI*ZZ: 1 in 5,584 individuals

PI = protease inhibitor.
Source: DCAR, Table 23

On the association between gene variants and disease, the DCAR stated that AATD severity depends on the patient's genotype and the resultant serum AAT concentration. Table 7 shows the serum AAT concentrations and level of risk of developing lung or liver disease associated with various *SERPINA1* genotypes.

[23] de Serres, F. J.,et al. 2003. Genetic epidemiology of alpha-1 antitrypsin deficiency in North America and Australia/New Zealand: Australia, Canada, New Zealand and the United States of America. *Clinical Genetics,* 64**,** 382-397.

Table 7 Genotype, serum concentration and risk of disease associated with AATD deficiency

Genotype	Median serum AAT concentration in µmol/L (5th–95th percentile)	Risk of lung disease	Risk of liver disease	Explanatory information
PI*MM	27 (19–47) Normal	No increased risk	No increased risk	The PI*M allele encodes normal AAT
PI*MS	23 (16–40)	No increased risk	No increased risk	
PI*MZ	17 (11–28) Low to normal	Risk only increased in smokers or those with environmental exposure	Slight increased risk	Some studies found an increased risk of developing COPD due to exposure to cigarette smoke in individuals with the PI*MZ allele; other studies found no association
PI*SS	18 (8–28) Borderline normal to low	No increased risk	No increased risk	No conclusive evidence linking homozygous PI*SS to increased risk for lung or liver disease; however, the PI*S allele is associated with increased degradation of AAT in hepatocytes
PI*SZ	11 (6–20) Low	20–50%	Slight increased risk	The PI*SZ allele has been associated with increased risk of COPD
PI*ZZ	5 (≤5–10) Very low	High risk 80–100%	High risk	The PI*Z allele leads to polymerisation in hepatocytes and less frequent binding to neutrophil elastase in the lungs
PI*null/null	Absent	High risk 100%	No increased risk	Null alleles are characterised by absent circulating AAT due to transcriptional or translational errors

AAT = alpha-1 antitrypsin, COPD = chronic obstructive pulmonary disease; PI = protease inhibitor.
Source: DCAR Table 25, which was adapted from the application form

The DCAR stated that there are 211 *SERPINA1* variants listed in the ClinVar database that are associated with AATD[24].

Table 8 shows the variants included on the 14-variant panel developed by Progenika and their frequency among individuals with AATD. However, many of the non-S/Z variants are specific to European populations[25], so Australian laboratories will need to determine the 14 most common variants in the Australian population.

[24] Landrum, M. J., et al. 2018. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic acids research,* 46**,** D1062-D1067.
[25] Silva, D., et al. 2016. Alpha-1-antitrypsin (*SERPINA1*) mutation spectrum: Three novel variants and haplotype characterization of rare deficiency alleles identified in Portugal. *Respiratory Medicine,* 116**,** 8-18.

Table 8 The allelic variants and associated alleles included in the Progenika gene panel test

Allelic variant	Most common associated allele	AAT protein activity	Frequency among individuals with AATD
c.187C>T	PI*I	Impaired secretion and mild plasma deficiency	<0.001% (heterozygous)
c.194T>C	PI*M procida	Impaired secretion (degradation) and severe plasma deficiency	<0.001% (heterozygous)
c.226_228delTTC	PI*M malton	Impaired secretion (polymerisation) and severe plasma deficiency	<0.0001% (PI*M malton carriers)
	PI*M palermo		
	PI*M nichinan		
c.230C>T	PI*S iiyama	Impaired secretion (polymerisation) and severe plasma deficiency	Unknown
c.552delC	PI*Q0 granite falls	None (no protein)	<0.001% (carriers)
c.1096G>A	PI*Z	Impaired secretion (polymerisation) and severe plasma deficiency	1–3% (carriers)
c.1130dupT	PI*Q0 mattawa	Truncated protein/intracellular degradation	<0.001% (PI*Q0 mattawa carriers)
	PI*Q ourem		
c.646+1G>T	PI*Q0 west	Truncated protein/intracellular degradation	Unknown
c.721A>T	PI*Q0 bellingham	None (no protein)	<0.001% (heterozygous)
c.1158dupC	PI*Q0 clayton	Truncated protein/intracellular degradation	<0.001% (PI*Q0 clayton heterozygous)
	PI*Q0 saarbruecken		
c.1178C>T	PI*M heerlen	Impaired secretion (degradation) and severe plasma deficiency	<0.001% (heterozygous)
c.739C>T	PI*F	Impaired secretion and mild plasma deficiency	<0.001% (heterozygous)
c.839A>T	PI*P lowell	Impaired secretion (degradation) and mild plasma deficiency	<0.001% (PI*P lowell heterozygous)
	PI*P duarte		
	PI*Q0 cardiff	Truncated protein/intracellular degradation	
	PI*Y barcelona	Impaired secretion (degradation) and mild plasma deficiency	
c.863A>T	PI*S	Impaired secretion (degradation) and mild plasma deficiency	5–10% (carriers)

AAT = alpha-1 antitrypsin. Clinical significance as stated in the ClinVar database (Landrum et al., 2018). Orange = pathogenic; yellow = pathogenic/likely pathogenic; grey = conflicting interpretation.
Source: DCAR Table 24, which was based on Veith et al. 2019, and US FDA 2017.

Clinical utility

Change in management

The DCAR stated that the evidence describing the impact of testing on management decisions was of low to moderate quality.

Compared with healthy controls or carriers, PI*ZZ individuals had higher rates of ceasing or reducing smoking (Table 9). When informed at a young age (5–7 years), these individuals were more likely than were the general population to never smoke. In a US study, approximately 60% fewer PI*ZZ individuals identified themselves as smokers compared to PI*MZ individuals. However, rates of smoking among parents of children identified with a PI*S or PI*Z AAT variant by genetic screening at a young age were similar to controls. Severely deficient individuals (PI*ZZ) are more likely to engage in healthy behaviours such as exercise

and maintenance of a healthy weight and are more likely to have flu and pneumonia vaccinations[26].

Table 9 Summary of change in management results

Study Population	Findings	Knowledge of AATD status changed behavior / management
Thelin 1996, Sweden [27] Children screened for AATD as a part of the Swedish newborn screening program (1972–1974) and their parents	• Parents with AATD children had similar smoking rates to controls. • There was increased smoking in AATD fathers compared with controls. • There was a significant decrease of smoking in AATD individuals screened at birth, compared with matched controls. • AATD patients were more likely to be smokers if they had a parent who was a smoker.	Smoking: Yes (in children with PI*ZZ AATD) No (in parents of children with AATD)
Tanash, 2015, Sweden [28] Individuals followed up from Thelin 1996 above	• At 34 years of age, the frequency of never-smokers was significantly increased in AATD patients (PI*SZ and PI*ZZ), compared with controls (PI*MM). • Pack years* was not significantly different between genotype groups. PI*SZ and PI*ZZ never-smokers retained normal lung function.	Smoking: Yes (for PI*SZ and PI*ZZ compared to PI*MM)
Carpenter, 2007, USA [29] Individuals seeking an AAT genetic test kit Follow-up at 3 months	• Severely deficient individuals were more likely to make an attempt to quit, make a 24-hr quit attempt, find information on smoking cessation, use medication and participate in smoking cessation programs. • 59% of severely deficient patients reduced their smoking by 50% (compared with 14% of carriers and 15% of controls) • Adjusted odds ratio for achieving abstinence was 3.6 in the severely deficient group and 1.7 for carriers. • This study suggested that knowledge of severe AATD changes smoking behaviour, although this was not observed in carriers of an AATD variant allele.	Smoking: Yes (for PI*ZZ and PI*SZ) No (for PI*MZ)
Holm, 2018, USA [30] Patients enrolled in AlphaNet	• Individuals with the severe deficiency genotype PI*ZZ were less likely to be a current smoker, compared with PI*MZ or PI*SZ. • Carrier (PI*MZ) genotypes were at greater odds of unhealthy behaviour than were PI*ZZ. • PI*SZ had higher odds of lack of exercise and failure to maintain healthy weight (underweight and overweight). • Most participants had a pneumonia or flu vaccine (87.9% and 86.4% vaccinated, respectively).	Smoking: Yes (for PI*ZZ) No (for PI*MZ, PI*SZ, PI*??) Exercise and normal weight: Yes (PI*ZZ) No (PI*MZ, PI*SZ, PI*??) Vaccinated against pneumonia and flu? Yes (PI*ZZ, PI*SZ, PI*??) No (PI*MZ)

AATD = alpha-1 antitrypsin deficiency, PI*?? = genotype unknown to participant.
Note: *When 20 cigarettes are smoked each day for a whole year this is 1 'pack year'.
Source: DCAR, Table 26.

[26] Holm, K. E., et al. 2018. Genotype is associated with smoking and other key health behaviors among individuals with alpha-1 antitrypsin deficiency-associated lung disease. *Respir Med,* 143**,** 48-55.
[27] Thelin, T., et al. 1996. Primary prevention in a high-risk group: smoking habits in adolescents with homozygous alpha-1-antitrypsin deficiency (ATD). *Acta Paediatrica,* 85**,** 1207-1212.
[28] Tanash, H. A., et al. 2015. The Swedish α1-Antitrypsin Screening Study: health status and lung and liver function at age 34. *Annals of the American Thoracic Society,* 12**,** 807-812.
[29] Carpenter, M. J., et al. 2007. Does genetic testing result in behavioral health change? Changes in smoking behavior following testing for alpha-1 antitrypsin deficiency. *Annals of Behavioral Medicine,* 33**,** 22-28.
[30] Holm, K. E., et al. 2018. Genotype is associated with smoking and other key health behaviors among individuals with alpha-1 antitrypsin deficiency-associated lung disease. *Respir Med,* 143**,** 48-55.

Therapeutic effectiveness (health benefit from change in management)

One non-systematic review and 4 observational studies were used to assess the effectiveness or impact of changes in management on health outcomes (Table 10). The quality of the non-systematic review is high while the risk of bias of observational studies is moderate to high.

Augmentation therapy is not publicly funded and is outside the scope of this report because it was found to be not cost-effective (MSAC Application 1530). In addition, since smoking cessation is a well-established treatment for slowing the progression of COPD, studies on the effectiveness of smoking cessation were not included.

Table 10 Included studies examining the effectiveness of change in management on health outcomes in patients with AATD

Study	Population	Findings
Senn et al., 2005 [31] non-systematic review	Patients with AAT deficiency in the lungs	Association between intermediate AATD and respiratory health parameters in subjects exposed to occupational inhalants was reported in some studies.
Tejwani et al., 2019 [32]	Patients with newly diagnosed severe AAT deficiency	Delayed diagnosis of AATD associated with worse COPD-related symptoms and functional status, and a trend towards worse airflow obstruction.
Tanash et al., 2017 [33]	34-year-olds screened for AATD as a part of the Swedish newborn screening program (1972–1974) and their parents	Quality of life not affected by genotype, despite some groups with higher symptom scores.
Von Ehrestein et al., 2002 [34]	International Study on Asthma and Allergies in Childhood (Munich and Dresden 1995–1996)	AATD children exposed to ETS had decreased pulmonary function compared with normal controls. Reductions largest for MEF_{50}, MEF_{25}, MMEF.
Seersholm et al., 2000 [35]	PI*MZ subjects from the Danish AATD registry and corresponding controls	AAT heterozygotes of phenotype PI*MZ are at increased risk of hospital admission for OPD if first-degree relatives of PI*Z index cases only; other, as yet unknown, genetic or environmental factors contribute to the development of lung disease.

AAT = alpha-1 antitrypsin, AATD = alpha-1 antitrypsin deficiency, COPD = chronic obstructive pulmonary disease, ETS = environmental tobacco smoke, MEF = maximum expiratory flow, MMEF = maximal mid-expiratory flow, OPD = obstructive pulmonary disease.
Source: DCAR, Table 27.

The limited evidence focused on the effect of receiving a positive genetic diagnosis for AATD and its effect on outcomes such as lung function, time to diagnosis, survival or life expectancy, occupational exposure to air pollutants, exposure to tobacco smoke and hospital admissions.

Results showed that there was a significant negative interaction between *SERPINA1* PI*MZ genotype, outdoor particulate matter ≤10 μm (PM_{10}) and occupational exposure to vapour, gases, dusts or fumes (VGDF) on lung function[36]. In PI*MZ carriers, associations between VGDF exposure and annual decline in forced expiratory flow (FEF) at 25–75% of forced vital

[31] Senn, O., et al. 2005. α1-Antitrypsin deficiency and lung disease: risk modification by occupational and environmental inhalants. *European Respiratory Journal,* 26**,** 909-917.
[32] Tejwani, V., et al. 2019. The impact of delayed diagnosis of alpha-1 antitrypsin deficiency: The association between diagnostic delay and worsened clinical status. *Respiratory Care,* 64**,** 915-922.
[33] Tanash, H. A., et al. 2017. Survival in individuals with severe alpha 1-antitrypsin deficiency (PiZZ) in comparison to a general population with known smoking habits. *European Respiratory Journal,* 50.
[34] Von Ehrenstein, O. S., et al. 2002. Lung function of school children with low levels of alpha1-antitrypsin and tobacco smoke exposure. *Eur Respir J,* 19**,** 1099-106.
[35] Seersholm, N., et al. 2000. Risk of hospital admission for obstructive pulmonary disease in alpha(1)-antitrypsin heterozygotes of phenotype PiMZ. *Am J Respir Crit Care Med,* 161**,** 81-4.
[36] Mehta, A. J., et al. 2014. Interactions between SERPINA1 PiMZ genotype, occupational exposure and lung function decline. *Occupational and Environmental Medicine,* 71**,** 234-240.

capacity ($FEF_{25-75\%}$) (-82 mL/s, 95% CI -125 to -39) and forced expiratory volume in 1 second over forced vital capacity (FEV_1/FVC) (-0.3%, 95% CI -0.6% to 0.0%) were observed ($P_{interaction}$ <0.0001 and $P_{interaction}$ = 0.03, respectively). VGDF-associated $FEF_{25-75\%}$ decline was observed only in smoking PI*MZ carriers ($P_{interaction}$ = 0.01).

Smokers with the PI*ZZ genotype had a shorter life expectancy compared to controls[37]. The risk of death was significantly higher in individuals with the PI*ZZ genotype compared to controls[38]. Factors significantly affecting the respiratory health of patients with severe AATD included exposure to occupational inhalants and passive smoking[39]. First-degree relatives of PI*Z index cases with the genotype PI*MZ had a higher risk of hospital readmission for COPD (RR: 3.4, 95% CI: 2.2 to 5.3) than did controls matched for birth date, gender and country of resident[40].

Translation issues

Key issues relating to the translation of the evidence to the economic model are firstly, the applicability of diagnostic yield evidence to clinical practice in Australia is uncertain as the 14-variant panel is not available and will need to be developed. Which set of variants laboratories choose to include in their development of 14-variant tests is not fixed, although variant prevalence can be estimated using the 14 variants on the Progenika panel. Secondly, rates of disease progression included in the Markov models were based on US registry data, which mainly include patients with the PI*ZZ genotype. There are limited data about the decline in lung function for other genotypes. Thirdly, the diagnostic yields used in the economic model were derived from populations less enriched than the population in the proposed clinical management algorithm. Additionally, diagnostic yields in the Australian population are unknown. Improved diagnosis is assumed to support the adoption of lifestyle interventions to better manage disease progression. The major impact is on the rates of smoking among patients with a positive genetic diagnosis. There is uncertainty about how a positive genetic diagnosis of AATD may affect rates of smoking among patients already diagnosed with lung conditions such as COPD.

12. Economic evaluation

A cost-utility analysis was presented comparing genetic testing with IEF (Table 11).

[37] Tanash, H. A., et al. 2017. Survival in individuals with severe alpha 1-antitrypsin deficiency (PiZZ) in comparison to a general population with known smoking habits. *European Respiratory Journal,* 50.
[38] Piitulainen, E., et al. 2017 Health status and lung function in the Swedish alpha 1-antitrypsin deficient cohort, identified by neonatal screening, at the age of 37-40 years. *International Journal of COPD,* 12**,** 495-500.
[39] Senn, O., et al. 2005. α1-Antitrypsin deficiency and lung disease: risk modification by occupational and environmental inhalants. *European Respiratory Journal,* 26**,** 909-917.
[40] Seersholm, N., et al. 2000. Risk of hospital admission for obstructive pulmonary disease in alpha(1)-antitrypsin heterozygotes of phenotype PiMZ. *Am J Respir Crit Care Med,* 161**,** 81-4.

Table 11 Summary of the economic evaluation

Perspective	Australian health system; includes resource use supported by the Government.
Patient	Abnormally low (<20 µmol/L) AAT concentration and symptoms suggestive of AATD, such as early-onset (<40 years) COPD, adult-onset asthma, liver disease at any age, antiproteinase 3-positive vasculitis, or those with a family history of AAT deficiency.
Intervention	Variant panel testing for the 14 most common AATD pathogenic variants and subsequent sequencing in the base analysis.
Comparator	AAT protein phenotyping with IEF (MBS item 66638)
Economic evaluation	Cost–utility analysis
Source of evidence	Literature and clinical feedback during contracted assessment
Time horizon	50-year time horizon in the base case Sensitivity analyses include a time horizon of 10 and 25 years
Outcomes	Quality-adjusted life years/life years gained
Methods used to generate results	Cohort expected value analysis using decision tree and Markov models for: (a) true positive, adopting lifestyle change (b) false negative, non-adopter of lifestyle change, (c) AATD negative patients
Health states	FEV_1 ≥50% predicted, FEV_1 <50% predicted, Lung transplant, Dead
Cycle length	1 year
Discount rate	5% used for base; 3.5% and 7% sensitivity analyses
Software used	Microsoft Excel 2010

AAT = alpha-1 antitrypsin; AATD = alpha-1 antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; IEF = isoelectric focusing; MBS = Medicare Benefits Schedule; QALY = quality-adjusted life year.
Source: DCAR, Table 4.

The overall costs and outcomes, and incremental costs and outcomes (quality-adjusted life years (QALYs) as calculated for the intervention and comparator in the model, and using the base case assumptions, are shown in Table 12. The cost-effectiveness of other decision options available to MSAC are also presented, including clearly separating out the increment of sequencing on panel testing. The incremental cost-effectiveness ratio (ICER) per extra proband detected is also presented to facilitate comparisons to other germline testing applications previously considered by MSAC.

The ICER per extra QALY for the base case (14-variant panel testing and sequencing) is $35,756 per QALY over 50 years. Using costs and diagnostic yield estimates from the DCAR, the ICER per extra proband detected is calculated to be $391 for the 14-variant panel alone, and $43,728 for sequencing after the 14-variant panel – giving an overall ICER per extra proband detected for the base case of $4,607.

Table 12 Economic outcomes for affected individual testing: incremental benefit of sequencing after the 2- and 14-variant panels, against IEF

Scenario	Cost (discounted)	Incremental cost	QALYs (discounted)	Incremental QALY	ICER ($ per extra QALY gained)	Diagnostic yield	Incremental probands detected	ICER ($ per extra proband detected)
IEF (comparator)	$17,316	-	23.03	-	-	0.2452 × 0.815 = 0.199838	-	-
14-variant panel alone	$17,333	$16	23.04	0.01	$3,119	0.2452 × 0.982 = 0.2407864	0.240786 – 0.199838 = 0.0409484	$16 / 0.0409484 = **$391**
Sequencing after 14-variant panel		$209-$16 = $193				0.2452 – 0.2407864 = 0.0044136	0.0044136	$193 / 0.0044136 = **$43,728**
14-variant panel ± sequencing (**base case**)	$17,526	$209	23.04	0.01	$35,756	0.2452	0.2452 – 0.199838 = 0.045362	$209 / 0.045362 = **$4,607**
2-variant panel alone	$17,352	$36	23.03	0.00	Cost increase with no improvement in effectiveness	0.2452 × 0.815 = 0.199838	0.199838 – 0.199838 = 0	Undefined
Sequencing after 2-variant panel		$198-$36 = $162				0.2452 – 0.199838 = 0.045362	0.045362	$162 / 0.045362 = **$3,571**
2-variant panel ± sequencing	$17,514	$198	23.04	0.01	$33,818	0.2452	0.2452 – 0.199838 = 0.045362	$198 / 0.045362 = **$4,365**

ICER = incremental cost-effectiveness ratio, IEF = isoelectric focusing, QALY = Quality-adjusted life years.
Note: the increments for panel alone and panel ± sequencing are relative to IEF, whereas the increments for sequencing-after-panel are relative to panel alone.
Source: Department's calculations expanding Rejoinder Table 6, as endorsed by ESC.

The DCAR did not include cascade testing items CCCC, DDDD, or EEEE in its economic analyses.

The DCAR's sensitivity analyses found that assumptions about diagnostic accuracy, proportion adopting lifestyle changes, FEV_1 decline rates and smoking rates have the largest impact on model results. Key drivers of the model are summarised in Table 13.

Table 13 Key drivers of the economic model

Description	Method/Value	Impact
AATD pathogenic variant prevalence	Diagnostic yield estimates were based on international studies, with a range of serum thresholds used for testing eligibility. Prevalence and diagnostic yield in the Australian target population are highly uncertain. Prevalence rates of 19.6% and 30.6% were included as sensitivity estimates.	High impact. An AATD prevalence of 19.6% resulted in an ICER of $49,346 per QALY, whereas a prevalence of 30.6% generated an ICER of $24,885 per QALY.
Diagnostic accuracy	PASC noted that Australian laboratories will need to develop their own panels for testing. Based on the literature and claims made by the applicant, a sensitivity of 98% was included for the 14-variant panel test when detecting the 14 most common pathogenic variants; with sequencing this increases to 100%. The IEF test was assumed to have the same diagnostic yield (20%) and sensitivity (82%) as the 2-variant panel test for detecting the 14 most common AATD variants. Commercial IEF kits target common variants; however, gels could be formulated to improve diagnostic accuracy. Sensitivities may differ, so a 90% sensitivity scenario was included for IEF.	High impact. If IEF sensitivity is increased from 82% to 90%, then the ICER would increase to $72,873. Changes in panel sensitivities had less impact on the ICER.
Proportion adopting lifestyle changes	The base analysis assumed that 60% of patients adopt smoking cessation upon being genetically diagnosed with AATD, which was reasonable given the smoking rates of patients with MZ and ZZ genotypes reported in Holm et al. 2018 (7.1% and 2.4%, respectively).	High impact. A lifestyle change adoption rate of 90% resulted in an ICER of $21,201 per QALY, whereas a rate of 30% generated an ICER of $79,424 per QALY.
FEV_1 rates of decline for non-panel variants	The decline in FEV_1 assumptions were based on US registry data, which mainly include patients with the PI*ZZ genotype. Other variants may result in similar disease progression; however, there is limited data on the decline in lung function across these variants, given they are not widespread. High and low FEV_1 declines were included in the sensitivity analysis.	High impact. The use of low and high FEV_1 decline estimates, which could be associated with some non-panel variants, had a large impact on the estimated ICER. At a lower smoker FEV_1 decline of 70 ml/year for AATD+ patients, the ICER increased to $127,741 per QALY.
Smoking prevalence and lifestyle adoption	The base case assumed 7% smoking prevalence among adult patients with AATD presenting with COPD or other indications. There is considerable uncertainty about smoking rates among COPD patients and those who test genotype-positive for AATD. Clinical feedback during the assessment indicated COPD patients would cease smoking with or without receiving genotype-positive AATD diagnoses.	High impact. If the rate of smoking in COPD patients was 3% in the absence of AATD diagnosis, then the estimated ICER increased to $93,072 per QALY. If smoking prevalence was 25%, then the ICER decreased to $4,717 per QALY.
Cost of the test	Costs for the 14- and 2-variant panels are proposed to be $100 and $78, respectively. The cost was varied by 10% in sensitivity analyses. The applicant noted that *SERPINA1* sequencing is offered by Queensland Health for $260. Sensitivity analyses were included with these testing costs.	Moderate impact. Changing the 14-variant panel cost from $90 to $100, varied the ICER from $34,049 to $37,464 per QALY. Varying the cost of sequencing by 10% had a larger impact, given the cost per test is $260 and a large percentage (76%) of inconclusive panel tests will require sequencing.
Disease management costs for COPD	Disease management costs based on a UK study were used in the economic model. The proportions of mild, severe and very severe cases are varied by 20% for each COPD state in a series of sensitivity analyses.	Low impact. This variation had limited impact on economic results. Differences in testing costs and lung transplant costs had a larger impact on the ICER.

AATD = alpha-1 antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years.
Source: DCAR Table 6, including additions by ESC.

The rejoinder conducted a further sensitivity analysis to re-examine the DCAR's assumption of equivalent diagnostic yields for IEF and the 2-variant panel. If the ratio of diagnostic yields between IEF and the 2-variant panel observed by Snyder is applied to the diagnostic yield observed for the 2-variant panel by Ottaviani, then the hypothetical diagnostic yield for IEF in the Ottaviani population is 21.4%. A sensitivity analysis using this diagnostic yield for IEF produced a higher ICER for genetic testing, of $52,875 per QALY gained.

13. Financial/budgetary impacts

The DCAR used a market share approach to estimate utilisation of genetic testing, assuming 70% of IEF is replaced by genetic testing. The flow of patients and diagnostic yield assumptions used in the DCAR's financial calculations are presented below (Figure 4).

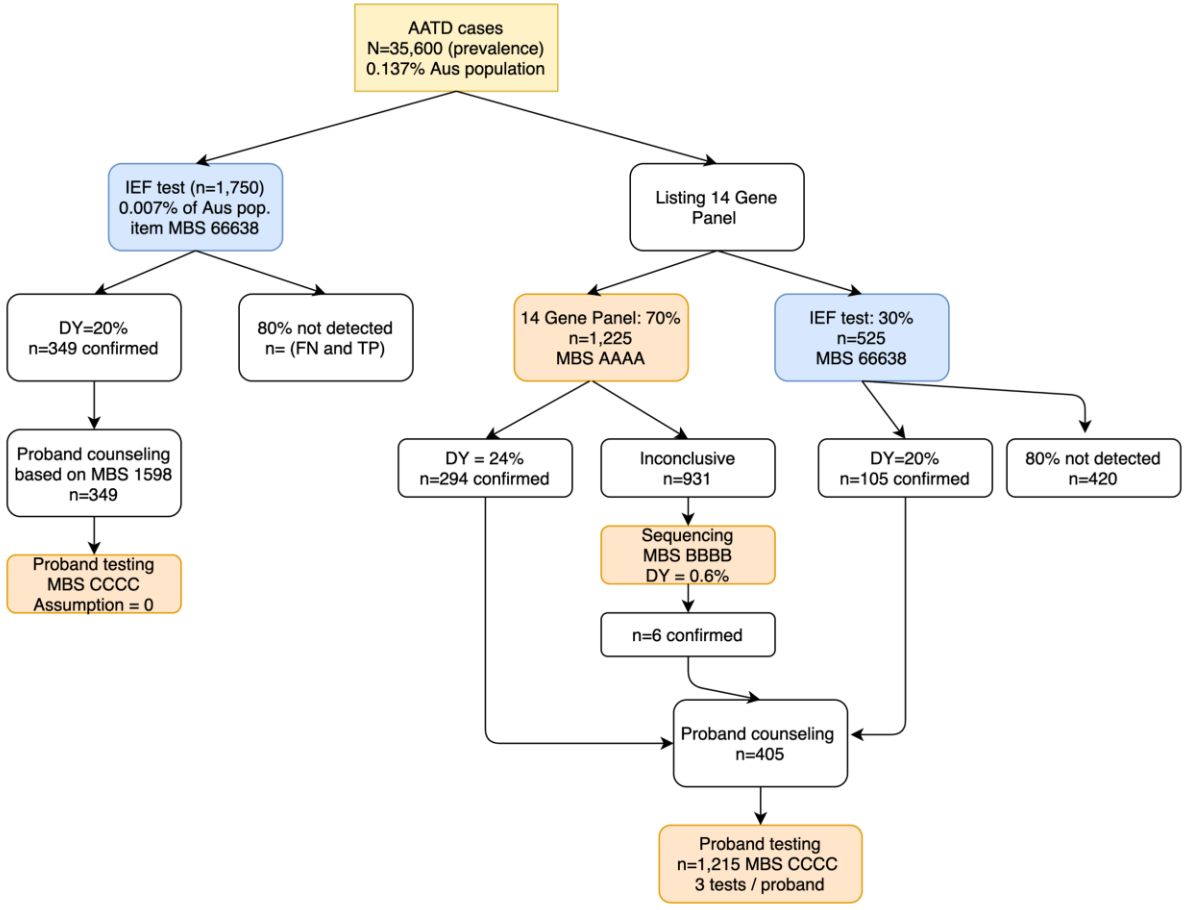

Figure 4 Flow of patients and diagnostic yield assumptions used in the financial analyses
Source: ESC

In the pre-ESC response, the applicant disagreed with the DCAR's assumption of 70% market share substitution of IEF by genetic testing, stating that it is unclear why only 70% of IEF tests will be substituted by 14-variant panel testing instead of the proposed 100%. The applicant stated that IEF will be superseded by genetic testing, with Australian laboratories currently disinvesting themselves from this technology, and that a more appropriate base case analysis would be 100% genetic testing, followed by a one-way sensitivity analysis of 70%.

The 5-year budget impact underpinned by the DCAR's assumptions is presented in Table 14. Net costs are limited to the MBS and increase from $573,462 in 2022 to $603,869 in 2026. The budget impact analysis is most sensitive to the assumed number of panel tests conducted.

Table 14 Budget impact of AAT genetic testing listing, 2022–2026

Costs to the MBS	2022	2023	2024	2025	2026
IEF tests without listing (66683)	$72,975	$73,924	$74,885	$75,858	$76,844
Counselling costs	$46,929	$47,539	$48,157	$48,783	$49,417
Total MBS costs without listing	**$119,904**	**$121,462**	**$123,041**	**$124,641**	**$126,261**
IEF tests with listing (66683)	$21,893	$22,177	$22,465	$22,757	$23,053
Panel tests (AAAA)	$104,125	$105,479	$106,850	$108,239	$109,646
Sequencing tests (BBBB)	$205,724	$208,398	$211,108	$213,852	$216,632
Cascade tests (CCCC)	$103,263	$104,606	$105,966	$107,343	$108,739
Counselling costs	$258,361	$261,720	$265,122	$268,569	$272,060
Total MBS costs with listing	**$693,366**	**$702,379**	**$711,510**	**$720,760**	**$730,130**
Net MBS costs to government	**$573,462**	**$580,917**	**$588,469**	**$596,119**	**$603,869**

AATD = alpha-1 antitrypsin deficiency, IEF = Isoelectric focusing, MBS = Medicare Benefits Schedule
Source: DCAR Table 7.

The estimated utilisation and financial impact of cascade testing for reproductive partners (DDDD) and fetuses (EEEE) is provided below (Table 15), noting that this table also differs from Table 14 in that it assumes an 80% market share for genetic testing.

Table 15 Budget impact of cascade testing, including reproductive partners and fetuses

Description	2022	2023	2024	2025	2026	Row Ref.	Source or calculation
Australia population	26,020,973	26,359,245	26,701,915	27,049,040	27,400,678	A	ABS
Affected individuals tested	1,750	1,773	1,796	1,819	1,843	B	A × 0.007%, Australian population
14-variant panel tests (AAAA)	1,400	1,418	1,437	1,455	1,474	C	B × 80%, assumption†
Probands identified by panel testing	336	341	345	349	354	D	C × 24%, 14-variant panel DY
Affected individuals proceeding to sequencing (BBBB)	1,064	1,078	1,092	1,106	1,120	E	C – D, 14-variant panel negative or unspecified population
Probands identified by sequencing	7	7	7	7	7	F	E × 0.6%, sequencing DY
Number of probands identified by affected individual testing	**343**	**347**	**352**	**357**	**361**	**G**	**D + F, probands identified by affected individual testing**
FDRs tested (CCCC)	**1,029**	**1,042**	**1,056**	**1,070**	**1,084**	H	G × 3, assuming 3 FDRs tested per proband
Positive FDRs expected	515	521	528	535	542	I	H × 50%, assuming 50% DY in FDRs
Total number of probands	858	868	880	892	903	J	D + F + I, number of probands identified by affected individual testing and cascade testing of FDRs
Reproductive partners tested (DDDD)	**669**	**677**	**686**	**696**	**704**	K	J × 78%, assuming 78% of patients are in a reproductive relationship‡
Positive reproductive partners expected	*72*	*73*	*74*	*75*	*76*	L	K × 10.67%, sum of S- and Z-containing genotype frequencies in Australia (DCAR, Table 13)
Fetuses tested (EEEE)	***1***	***1***	***1***	***1***	***1***	M	L × (12.1/1000), assuming CBR of 12.1 per 1000
Total cascade testing volume	***1,699***	***1,720***	***1,743***	***1,767***	***1,789***	N	H + K + M, total cascade testing volume (i.e. FDRs, reproductive partner and fetuses)
Total cost of cascade testing	***$144,415***	***$146,200***	***$148,155***	***$150,195***	***$152,065***	O	N × $85, assuming all use the 14-variant panel

AATD = Alpha-1 Antitrypsin Deficiency, ABS = Australian Bureau of Statistics, CBR = Crude birth rate (i.e. births per 1000 estimated resident population per year), DY = diagnostic yield, FDR = first-degree relatives.
† = assumes 80% market share (rather than the 70% used in the base case)
‡ = maximum 78% partnership rate suggested based on most recent ABS data for household structure.
Source: based on Rejoinder Table 1, with calculations modified by the Department (italics) to assume the diagnostic yield in reproductive partners is comparable to that in the general Australian population, and to reflect the clinical management algorithm under which fetal testing would take place.

ESC noted that future cost offsets due to slower disease progression are not included in the DCAR's financial impact assessment.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Clinical utility is possible but uncertain	Detecting a gene variant may affect the health behaviours and clinical decisions of the person tested, which may then translate to health benefits. The benefit of early detection may be greatest for cascade testing (before clinical disease is apparent), although evidence in this population was generally lacking. Few individuals receive cascade testing under the current pathway.
Safety is probably non-inferior	The limited evidence suggests that it is reasonable to assume non-inferior safety to the reasonable comparator of isoelectric focusing (IEF).
2- or 14-variant panel for AAAA	The 14-variant panel appears to have higher diagnostic yield compared to the 2-variant panel alone, but when each is combined with sequencing the overall diagnostic yield should be similar; the choice of approach may therefore depend on which testing pathway has the lower overall cost. Neither panel detects wildtype genotype conclusively, so if there is leakage to patients with a broader spectrum of disease than that defined by the MBS descriptor, this could result in more requests for sequencing. If the 14-variant panel is chosen, then there is a need to determine the prevalence and clinical validity of *SERPINA1* variants in the Australian population and develop an Australia-specific 14-variant panel.
Consider retaining IEF	MSAC may wish to consider if there is any value retaining IEF as a prior test to the panel, noting the applicant states that IEF is becoming an obsolete test in Australia. The ability of IEF to detect wildtype protein phenotype would prevent unnecessary subsequent referral to gene sequencing. The applicant states that few Australian labs have IEF capability, but it appears that it may be part of international clinical algorithms that include panel testing (e.g. Ottaviani 2020).
Economic model presented is uncertain	The economic model presents an ICER with a base case of $35,000/QALY for identification of a proband. The main drivers of the ICER are smoking prevalence, FEV_1 decline and lifestyle changes, which can change the ICER from $20,000/QALY to more than $100,000/QALY. • The diagnostic yield from Ottaviani 2020 may not accurately reflect the Australian population. ESC considered the uncertainty related to these diagnostic yield estimates to be problematic because it drives the economic model. • A detailed overview of applicability and translation issues was presented. Uncertainty is correctly quantified in the DCAR, and may not be further reduced in the absence of new studies. • Health benefits for the cascade testing population are not included (DDDD, EEEE).
Budget impact is uncertain	The financial cost to the MBS is estimated to be $435k per year (excluding counselling costs, and assuming 70% market share substitution), which is a net financial cost of $363k per year above current testing. If the market share substitution is increased to 100%, then the net cost to the MBS is estimated to be $195k per year. Changing assumptions needed because of insufficient data about diagnostic yield can substantially change the budget impact. Cost offsets due to earlier diagnosis and slower progression in the affected population are not included, primarily as there are no specific treatments available.
Analysis of cascade testing	The DCAR did not further analyse the health benefits of cascade testing. Including the analysis of cascade testing of first- and second-degree relatives was suggested by PASC noted in its ratified PICO.

ESC discussion
ESC noted that this application was seeking new Medicare Benefits Schedule (MBS) items for variant panel testing for common *SERPINA1* gene variants, followed by sequencing the *SERPINA1* protein-coding regions if the panel test is negative or inconclusive, as happens with non-panel variants and in individuals who do not have a variant. The *SERPINA1* gene encodes the alpha-1 antitrypsin (AAT) protein, whose insufficiency can result in AAT deficiency (AATD).

ESC noted that consumer feedback supported the application. Without genetic testing, many adults are misdiagnosed with late-onset asthma.

ESC noted the clinical claim that early detection of AATD genotypes can lead to patients more readily making lifestyle changes, such as limiting alcohol and smoking, that will reduce damage to the lungs and liver, or clinical interventions such as vaccination to reduce the rates of infections.

ESC noted that five MBS items are proposed:

- AAAA is for panel testing to identify the 14 most common pathogenic variants (as requested by the applicant) in the *SERPINA1* gene.
    - PASC requested a 2-variant panel also be considered as an option for AAAA, as such a panel is more readily defined and available, and it may be more cost-effective.
- BBBB is for *SERPINA1* gene sequencing if AAAA does not identify a pathogenic variant.
- CCCC is for cascade testing of first- and second-degree relatives of probands.
- DDDD is for panel testing to identify the 14 (or 2) most common *SERPINA1* pathogenic variants in the reproductive partner of probands identified using AAAA, BBBB or CCCC.
- EEEE is for panel testing of the pregnant patient to identify the 14 (or 2) most common pathogenic variants of *SERPINA1* in their fetus.

ESC noted that the two most common variants in Australia are the PI*S (44.4/1,000) and the PI*Z (13.4/1,000) alleles. People with PI*Z have a more severe phenotype. ESC considered that Australian laboratories would need to determine the most common pathogenic variants in Australia (and their pathogenicity and penetrance) to inform an Australia-specific 14-variant gene panel, if the 14-variant panel is supported.

ESC noted the following issues with the proposed MBS items:

- Patients with rare non-functioning protein variants (but with a ‘normal’ AAT concentration) would not be accommodated by the algorithm as currently proposed. To include them, the AAAA descriptor would need to be amended to indicate an abnormally low (<20 μmol/L) serum AAT concentration as an optional indication for testing rather than a requirement. However, doing so would significantly increase the eligible patient cohort for a likely greatly reduced diagnostic yield as a proportion of the increased number of patients tested.
- MSAC could consider including:
    - practice note (PN.0.23) in all proposed items requiring appropriate genetic counselling before the test is requested, to ensure consistency with other listed genetic items.
    - practice note to ensure that the testing methodology used is appropriately sensitive to detect the clinically relevant *SERPINA1* variants that are most

common in the Australian population, consistent with the practice notes for MBS items 73345–73350. PASC proposed using "sufficient diagnostic range and sensitivity to detect at least 95% (if 2-variant panel) or 99% (if 14-variant panel) of pathogenic SERPINA1 variants likely to be present in the patient", based on the reported frequencies of these alleles amongst other populations.
    - "applicable once per lifetime" (AAAA and BBBB), to both reduce the risk of unnecessary claiming and ensure consistency with other similar listed tests.
    - "applicable once per variant per lifetime" in cascade item CCCC to both reduce the risk of unnecessary claiming and ensure consistency with other similar listed tests.
- Proposed item CCCC may not be needed, given item AAAA already includes access to genetic testing for those with a demonstrated family history of AAT deficiency. The Boolean logic in proposed item AAAA may also need to be clarified as to whether the family history clause is connected to or independent of the serum AAT concentration clause. PASC also suggested that cascade testing not be restricted to first-degree relatives, as the clinical utility was expected to be greater for this predictive testing in relatives than for affected individuals.
- The proposed item AAAA will identify 95% (if 2-variant panel) or 99% (if 14-variant panel) of patients who have a pathogenic variant. Neither panel will be able to conclusively establish wildtype genotype in the considerable proportion of affected individuals who have no variant. The proposed fee for the 2-variant panel ($78) is cheaper than that of the 14-variant panel ($100), however opting for the 2-variant panel would increase the proportion of patients requiring gene sequencing through proposed item BBBB.

ESC noted that isoelectric focusing (IEF), the comparator, is becoming an outdated test and few laboratories still offer it. ESC also noted that cascade testing is not commonly performed in the relatives of probands who were identified using IEF, though is proposed for the relatives of probands who were identified using genetic testing.

ESC advised that MSAC may wish to consider retaining IEF as a prior test to the panel, as the ability of IEF to detect wildtype protein phenotype would prevent unnecessary subsequent referral to gene sequencing.

ESC considered that genetic testing had non-inferior safety to IEF, and that false negatives resulting from variant panel testing or sequencing are rare.

ESC noted that the clinical trial data were presented using a linked evidence approach. ESC noted that the diagnostic accuracy of the 14-variant panel was high among two studies – clinical sensitivity and specificity is 98.2% and 100%, respectively (k = 1, clinical population), test sensitivity and specificity are both 100% (k = 1, highly enriched population).

ESC noted that there was high variability in the DCAR's estimates of diagnostic yield, depending on how the study population was selected for testing, including the serum AAT threshold used. In some studies, the lower AAT threshold may lead to overestimated diagnostic yields of variants. In contrast, it is anticipated that the PICO population is more enriched than the populations of the included studies, leading to underestimates of diagnostic yield. In addition, based on the comparative prevalences of PI*S and PI*Z variants in the countries of the included studies (mostly European countries) versus those in Australia, most reported diagnostic yields are likely underestimates. ESC noted the rejoinder's correction to

the AAT threshold used by the key study Ottaviani et al. 2020[41] (from 14.7 µmol/L to 20.8 µmol/L) means the study is more closely aligned with the PICO than stated in the DCAR. ESC noted the DCAR conclusion that IEF has a similar diagnostic yield to 2-variant panel testing.

ESC noted that the evidence of clinical utility for AAT genetic testing related to changes in patients' behaviour (smoking, exercise, vaccination against pneumonia and flu). There is no publicly funded intervention or therapy for AATD, as the November 2018 MSAC meeting found therapy for AATD in adults with severe emphysema to be insufficiently cost-effective (MSAC application 1530).

ESC noted the translation issues with the diagnostic performance and yield from the literature. A 14-variant panel is not currently available in Australia, and the transformation of improved overall diagnostic accuracy to any improved health outcomes is uncertain. ESC also noted the uncertainties in the rates of smoking among patients who receive a positive genetic diagnosis, the selection of utility values, and the use of US registry data as model inputs.

ESC noted that, in its pre-ESC response, the applicant claimed that the diagnostic yields should be 67% for IEF, 95% for the 14-variant panel, and 100% for sequencing. ESC considered the rejoinder's response that the diagnostic yield of the 14-variant panel should be 24.1% (from the Ottaviani (2020) paper), to be more reasonable, as diagnostic yield is not the proportion of true positives that are detected (i.e. sensitivity), but the proportion of all tested individuals who test positive, and a negative (or inconclusive) panel test result does not rule out all variants, but rather it means further testing is needed (via sequencing). However, ESC also considered that this estimate of diagnostic yield from the Ottaviani (2020) paper may not accurately reflect that of the proposed Australian population tested as defined by the proposed item descriptor, which also has implications for the incremental diagnostic yield following referral for gene sequencing. ESC considered the uncertainty related to these diagnostic yield estimates to be problematic because it drives the economic model.

ESC noted the incremental cost-effectiveness ratio (ICER) of $35,000 per QALY, and considered the estimated utility gain to be small.

ESC noted the additional economic analyses presented for its consideration by the Department (see Table 12). ESC recommended that MSAC consider this table as presenting a more comprehensive set of cost-effectiveness results for the 2- and 14-variant gene panels, with and without subsequent sequencing, and thus informing a wider range of decision options, including sequencing alone, without a panel triage.

ESC noted that, in its pre-ESC response, the applicant queried why the financial estimates used a market share of 70% substitution of IEF, rather than 100% as genetic testing is proposed to completely replace IEF. ESC considered that the DCAR's financial impact of $363,000 per year and the applicant's revised financial impact of $194,000 per year could indicate the maximum and minimum likely impact, respectively. ESC noted that the financial impact did not include other future cost offsets due to decreased disease progression.

[41] Ottaviani, S., et al. 2020. Molecular diagnosis of alpha1-antitrypsin deficiency: A new method based on Luminex technology. *Journal of Clinical Laboratory Analysis,* 34.

15. Other significant factors

Nil

16. Applicant comments on MSAC's Public Summary Document

The College does not agree with MSAC's interpretation of the evidence, and will work with MSAC and the Department to resolve this.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website