Australian Government

Department of Health

Application Form

Alpha-1-Antitrypsin Genotyping

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

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

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):
Corporation name: The Royal College of Pathologists of Australasia
ABN: 52 000 173 231
Business trading name: The Royal College of Pathologists of Australasia

Primary contact name: REDACTED

Primary contact numbers
Business: REDACTED
Mobile: REDACTED
Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers
Business: REDACTED
Mobile: REDACTED
Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers
Business:
Mobile: REDACTED
Email: REDACTED

2. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

☐ Yes
☐ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Alpha-1-antitrypsin genotyping

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Alpha-1 antitrypsin (AAT) is a serine protease inhibitor (serpin) synthesised and secreted mainly by hepatocytes. The primary function of AAT is to protect lung tissue damage caused by proteolytic enzymes, such as neutrophil elastase, that are generated to attack inhaled pollutants/pathogens. The AAT protein is encoded by the *SERPINA1* gene, which expresses codominant alleles (Stoller 2018; Torres-Duran et al 2018). Alpha-1 antitrypsin deficiency (AATD) is a rare autosomal hereditary condition that results in decreased levels of circulating AAT, which then affects the lungs, liver, and sometimes, though rarely, the skin (e.g. necrotising panniculitis and vasculitis). In the lungs, AAT deficiency causes chronic obstructive pulmonary disease (COPD) (i.e. emphysema, persistent airflow obstruction, and/or chronic bronchitis) at a young age (Abboud et al 2011; Stoller 2018; Stoller et al 2017). Individuals with phenotypes associated with plasma AAT levels below the protective threshold of 11 µmol/L1 are considered to have *severe deficiency* of AAT and are at elevated risk for emphysema (Stoller 2018). The most common mutations are PI*Z (Glu342Lys) and PI*S (Glu264Val); however, there are more than 100 genetic variants of the *SERPINA1* gene have been described, most of which are rare and only some are associated with clinical disease (Gramegna et al 2018). A definitive diagnosis is of great importance in patients who might otherwise be misdiagnosed or missed altogether, allowing for earlier disease management, including preventive measures such as smoking cessation or prevention, and avoidance of exposure to environmental pollutants (Kueppers & Sanders 2017).

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Gene panel testing to identify alpha-1-antitrypsin (AAT) pathogenic variants in serum where the patient has respiratory symptoms indicative of AAT deficiency and abnormally low (<20 µmol/L[2]) alpha-1 antitrypsin levels or there is a demonstrated family history of AAT deficiency, requested by a specialist or consultant physician. Where the result after genotyping is inconclusive, sequencing of the *SERPINA1* gene to identify an AAT pathogenic variant should be conducted.

6. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

N/A

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

i. ☐ An amendment to the way the service is clinically delivered under the existing item(s)
ii. ☐ An amendment to the patient population under the existing item(s)

[1] Approximately 57 mg/dL using nephelometry and 80 mg/dL by radial immunodiffusion
[2] 110 mg/dL

iii. ☐ An amendment to the schedule fee of the existing item(s)
iv. ☐ An amendment to the time and complexity of an existing item(s)
v. ☐ Access to an existing item(s) by a different health practitioner group
vi. ☐ Minor amendments to the item descriptor that does not affect how the service is delivered
vii. ☐ An amendment to an existing specific single consultation item
viii. ☐ An amendment to an existing global consultation item(s)
ix. ☐ Other (please describe below):

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

(g) If yes, please advise:

N/A

7. What is the type of service:

☐ Therapeutic medical service
☒ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i. ☐ To be used as a screening tool in asymptomatic populations
ii. ☒ Assists in establishing a diagnosis in symptomatic patients
iii. ☒ Provides information about prognosis
iv. ☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☒ No

(b) If yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)
☐ No

N/A

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name:
Generic name:

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

☐ Yes
☒ No

If yes, please provide the following information (where relevant):
Billing code(s):
Trade name of prostheses:
Clinical name of prostheses:
Other device components delivered as part of the service:

(b) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

☐ Yes
☒ No

(c) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

☐ Yes
☒ No

(d) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

N/A

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: laboratory consumables
Multi-use consumables: Nil

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

The National Association of Testing Authorities (NATA) and the Royal College of Pathologists Australasia (RCPA) oversee the regulation of genetic testing for clinical purposes. Laboratories require accreditation by a joint NATA/RCPA process to ISO 15189, and specifically accredited to provide genetic testing. This accreditation process covers the technical aspects of the laboratory sequencing, analysis pipelines, curation (or interpretation) of results and production of the report to a clinical standard. This allows any accredited laboratory to provide equivalent variant analysis services to a minimum standard. There are no requirements for use of specific manufacturer's reagents, equipment or analysis pipelines.

Note: A non-commercial IVD is required to be regulated but not to be listed on the ARTG: testing using an IVD would be delivered only by Approved Practising Pathologists in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table.

Progenika Biopharma (a subsidiary of Grifols, Bilbao, Spain) markets an A1AT genotyping panel, which identifies 14 of the most prevalent known AATD mutations, representing approximately 99% of affected individuals. The Progenika panel was approved for use in the United States by the FDA in November 2017 (510(k) No: K171868[3]), and received CE marking in December 2016;[4] however, it is not currently registered on the Australian TGA.

It is likely that A1AT genotyping and *SERPINA1* sequencing would be performed in only a few centres of excellence in Australia and that these pathology laboratories would develop their own 'in-house' panels rather than using the commercially available product.

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: In-vitro diagnostic test
Manufacturer's name: N/A
Sponsor's name: N/A

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☒ Class III
☐ AIMD
☐ N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☐ Yes (if yes, please provide details below)
☒ No

ARTG listing, registration or inclusion number:
TGA approved indication(s), if applicable:

[3] https://www.fda.gov/medical-devices/510k-clearances/november-2017-510k-clearances
[4] https://www.grifols.com/en/view-news/-/news/fda-approval-of-genetic-test-for-alpha-1-deficiency-and-ema-approval-of-fibrin-sealant#

TGA approved purpose(s), if applicable:

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

☐ Yes (please provide details below)
☒ No

Date of submission to TGA:
Estimated date by which TGA approval can be expected:
TGA Application ID:
TGA approved indication(s), if applicable:
TGA approved purpose(s), if applicable:

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

☐ Yes (please provide details below)
☒ No

Estimated date of submission to TGA:
Proposed indication(s), if applicable:
Proposed purpose(s), if applicable:

PART 4 – SUMMARY OF EVIDENCE

17. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*****
1.	Case-control (note cases and controls were not matched for smoking status) Saudi Arabia	Genotyping diagnosis of alpha-1 antitrypsin deficiency in Saudi adults with liver cirrhosis (Al-Jameil et al 2017)	300 adult patients with liver cirrhosis matched with 400 controls were RT-PCR genotyped for the common AAT deficiency alleles Z and S, with both groups undergoing IEF phenotyping. The genotype and phenotype results were 99% concordant, with 4 cases discordant. In 2 cases, the phenotype result of FM was discordant with an MM genotype result; however, a subsequent phenotype assay returned an MM result, which was consistent with the genotype result and indicated that a phenotyping error had occurred. It was noted that adult patients homozygous for AATD (ZZ) are at an elevated risk for developing liver cirrhosis.	http://clinchem.aaccjnls.org/content/52/12/2236.long	2017
2.	Cross sectional registry study Ireland	The Impact of Smoke Exposure on the Clinical Phenotype of Alpha-1 Antitrypsin Deficiency in Ireland: Exploiting a National Registry to Understand a Rare Disease (O'Brien et al 2015)	Cigarette smoking was the greatest predictor of impairment in FEV 1 and DLCO (%predicted) and the extent of emphysema correlated most significantly with DLCO. The rate of FEV_1 decline was similar in ex-smokers when compared to never-smokers. Passive smoke exposure in childhood resulted in a greater total pack-year smoking history. The majority of people, 30/34 (88%), reported a diagnosis of AAT helped them quit within a median time of 2 weeks.	https://www.tandfonline.com/doi/full/10.3109/15412555.2015.1021913	2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
3.	Level III-2 diagnostic evidence: a comparison with reference standard Europe	European screening for alpha1-antitrypsin deficiency in subjects with lung disease (Greulich et al 2017a)	11,648 subjects with respiratory symptoms that could be indicative of AATD from 13 countries. AAT determined by nephelometry and, if lower than 1.70 mg/dL in dried blood spot (equivalent to 1.04 g/L in serum), PCR was conducted to detect the PiS and PiZ alleles. Isoelectric focusing was used for confirmation of doubtful genotype results. Genotyping of 1,404 samples with AAT levels <1.70 mg/dL revealed 71 (5.06%) PiS, 151 (10.8%) PiZ, 1 (0.071%) PiSS, 8 (0.57%) PiSZ and 32 (2.28%) PiZZ. Phenotyping of 1,363 samples negative for the S and Z alleles or with PiS and PiZ genotype showed two (0.147%) PiZ(rare) and two (0.147%) Pi(null)(null).	https://onlinelibrary.wiley.com/doi/pdf/10.1111/crj.12310	2017
4.	Case-control Sweden	Survival in individuals with severe alpha 1-antitrypsin deficiency (PiZZ) in comparison to a general population with known smoking habits (Tanash et al 2017)	Survival of PiZZ individuals (n=1,585) from the Swedish National AATD Register was compared to randomly selected controls from the Swedish general population (n=5,999). Smoking habits were known for all subjects. During follow-up, 473 PiZZ subjects (30%), and 747 controls (12%) died, with PiZZ subjects having a significantly shorter survival time than controls (p<0.001). Of the 854 PiZZ ever-smokers (mean age 49 ± 13 years), 301 (35%) died compared to 445 (16%) of the 2,820 ever-smoking controls (mean age 47 ± 13 years) (p<0.001). Never-smoking PiZZ individuals had a similar life expectancy to the never-smoker controls. Early diagnosis of AAT deficiency is of utmost importance.	DOI: 10.1183/13993003.00198-2017	2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
5.	Cohort USA	Does genetic testing result in behavioral health change? Changes in smoking behavior following testing for alpha-1 antitrypsin deficiency (Carpenter et al 2007)	Identified smokers (N=199) from a larger study of genetic testing were surveyed 3 months following receipt of their AAT genotype. Smokers who tested severely AAT deficient were significantly more likely to report a 24-hr quit attempt (59%) than were those who tested normal (26%). Carriers had a 34% quit attempt rate. Severely AAT deficient smokers were more likely than both carriers and normals to seek information on treatment, use pharmacotherapy for smoking cessation, and report greater reductions in their smoking. However, there were no group differences in 3-month abstinence rates. Knowledge of severe AAT deficiency, but not carrier status, may motivate smokers toward cessation.	DOI:10.1207/s15324796abm3301_3	2007
6.	Case series/registry Ireland	Trends in diagnosis and smoking prevalence in Irish alpha-1 antitrypsin deficiency individuals (O'Connor et al 2013)	100 ZZ AATD individuals completed a detailed questionnaire in relation to their diagnostic experiences and clinical presentation. The mean age of symptom onset was 37.8 years ± 1.6; mean age of diagnosis was 44.1 years ± 1.6. 67% were past smokers, 32% never smokers, and 1% current smokers. Among the past smoker cohort 36% stopped smoking within the first 12 months of AATD diagnosis; 24% stopped after the first 12 months and 40% had stopped smoking prior to diagnosis. Early detection of symptomatic AATD correlates to an increase in smoking cessation rates.		2013

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
7.	Cohort USA	Clarification of the Risk of Chronic Obstructive Pulmonary Disease in α1-Antitrypsin Deficiency PiMZ Heterozygotes (Molloy et al 2014)	A comparison of 99 PiMM and 89 PiMZ non-index subjects recruited from 51 index probands who were confirmed PiMZ heterozygotes with COPD. There was no difference in lung function in never-smoking PiMM versus PiMZ individuals. FEV_1 was significantly lower in ever-smoking PiMZ individuals. PiMZ individuals were stratified into low-exposure (<20 pack-years of smoking) and high-exposure (≥20 pack-years of smoking). Cigarette smoke exposure was inversely proportional to quantitative measures of lung function. PiMZ individuals in the low-and high-exposure group had a greater degree of airways obstruction compared with PiMM individuals. Ever-smoking PiMZ heterozygotes had significantly reduced lung function and increased risk of COPD (p = 0.0004), whereas there was no increased risk in PiMZ never-smokers. Heterozygous PiMZ individuals had OR for COPD of 5.18. The unadjusted OR for COPD in ever-smoking PiMZ heterozygotes was 9.21. In never-smoking individuals the OR was not significantly increased (OR 0.24, p = 0.2).	https://www.atsjournals.org/doi/full/10.1164/rccm.201311-1984OC	2014

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
8.	Cohort Sweden	Health status and lung function in the Swedish alpha 1-antitrypsin deficient cohort, identified by neonatal screening, at the age of 37-40 years (Piitulainen et al 2017)	Cohort of PiZZ (n=120) and PiSZ (n=46) individuals followed up since birth, compared to age-matched control subjects from the population registry (n=164). 4% of the PiZZ, 2% of the PiSZ and 12% of the control subjects were current smokers (p=0.008), and 17% of the PiZZ, 9% of the PiSZ and 21% of the control subjects had stopped smoking. PiZZ current smokers had a significantly higher (ie, poorer) SGRQ[1] score than PiZZ never-smokers (p=0.032) and PiMM current smokers had significantly higher score (p<0.001) than PiMM never-smokers. The proportion of subjects with a FEV_1/FVC ratio of <0.70, indicating COPD, was significantly higher in the PiZZ current smokers than in the PiZZ never-smokers (p=0.001). Among the PiSZ and PiMM subjects, the differences in lung function between the smoking subgroups were insignificant. PiZZ current smokers were found to have signs of COPD before 40 years of age. Smoking is less common among the AAT-deficient subjects identified by neonatal screening than among their peers in the general population.	https://www.dovepress.com/getfile.php?fileID=34723	2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
9.	Case series/registry Germany	Exacerbations and duration of smoking abstinence are associated with the annual loss of FEV1 in individuals with PiZZ alpha-1-antitrypsin deficiency (Fahndrich et al 2017)	Longitudinal follow-up over 11 years (mean follow-up 4.89 years) from the German AATD registry of 100 individuals with post-bronchodilator FEV_1 measurements and 116 individuals with $TLCO^2$ measurements. Accelerated deterioration of FEV_1 was associated with occupational dust exposure ($p = 0.026$), shorter duration of smoking abstinence ($p = 0.008$), higher baseline FEV_1 ($p = 0.003$), higher annual exacerbation frequency ($p = 0.003$) and higher frequency of glucocorticoids intake ($p = 0.004$). Patients with an elevated decline in TLCO showed significant impaired health-related quality of life at baseline ($p = 0.039$) and lower AAT serum levels ($p < 0.001$) in multivariate analysis.	https://www.resmedjournal.com/article/S0954-6111(17)30153-1/pdf	2017
10.	Case series Canada	Clinical Experience with *SERPINA1* DNA Sequencing to Detect Alpha-1 Antitrypsin Deficiency (Maltais et al 2018)	*SERPINA1* DNA sequencing in the investigation of AATD for patients with: emphysema/severe COPD or having a family member with AATD. Patients with emphysema/severe COPD had one or more of the following features: 1) low serum level of alpha-1 antitrypsin (<1.2 g/L); 2) high clinical suspicion of AATD (smoking history <20 pack-years, predominant basal emphysema); or 3) a family history of AATD. DNA sequencing of *SERPINA1* was performed in 65 consecutive patients, with a mean turnaround time from blood sampling to final results of 11 days.	https://www.ncbi.nlm.nih.gov/pubmed/29182883	2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
11.	Guidelines	European Respiratory Society statement: diagnosis and treatment of pulmonary disease in α1-antitrypsin deficiency (Miravitlles et al 2017)	• The clinical impact of AATD is highly variable. Heterogeneity in lung disease is only partly explained by exposure to known risk factors, such as cigarette smoke. • Lung disease in AATD generally presents at a younger age than "usual" COPD and may be misdiagnosed as asthma. • The WHO recommends all patients with a diagnosis of COPD or adult-onset asthma should be tested for AATD. • The quantitative determination of AAT levels in blood is a crucial first test to identify AATD. • Quantitative deficiency must be supported by qualitative tests to identify the genetic mutation(s) causing AATD. • Genotyping allows a rapid and precise identification/exclusion of S and Z alleles and other variants. • Testing of relatives of identified patients should be considered after appropriate counselling.	https://erj.ersjournals.com/content/erj/50/5/1700610.full.pdf	2017

[1] SGRQ = St George respiratory questionnaire, [2] TLCO = transfer factor of the lung for carbon monoxide, COPD = chronic obstructive pulmonary disease

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

**** If the publication is a follow-up to an initial publication, please advise.*

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.	RCT Enrolling 96 participants United Kingdom	A Study of ALN-AAT02 in Healthy Participants and Participants With ZZ Type Alpha-1 Antitrypsin Deficiency Liver Disease	The purpose of this study is to evaluate the safety and tolerability of single or multiple doses of ALN-AAT02. The study will be conducted in 2 sequential phases in which Part A will be a single-ascending dose (SAD) phase in healthy participants, and Part B will be a multiple-ascending dose phase in participants with ZZ type alpha-1 antitrypsin deficiency (PiZZ) and biopsy-proven AAT deficiency-associated liver disease. Change from baseline in serum levels of AAT	NCT03767829	Commenced December 2018 Completion date June 2021
2.1.	Observational (registry), case series Enrolling 50,000 participants Procedure: Home finger stick testing for alpha-1 antitrypsin genotype USA	Alpha-1 Coded Testing (ACT) Study (ACT)	Genetic testing for alpha-1 antitrypsin deficiency is sometimes delayed despite established testing indications. All genetic tests have risks and possible benefits. The ACT study evaluates the population demographics, reasons for testing, and outcomes through a confidential testing program. Co-morbidities of alpha-1 antitrypsin deficiency other than lung and liver disease are being investigated.	NCT00500123	Ongoing, study commenced 2001 will finalise 2050 but reporting intermittently

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

****Date of when results will be made available (to the best of your knowledge).*

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

Royal College of Pathologists of Australasia (RCPA)

Human Genetics Society of Australasia (HGSA)

20. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

It should be noted that the RCPA provides other services used in the diagnostic workup of patients suspected of having AATD including:

- MBS item number 66635: Alpha-1-antitrypsin – quantitation;
- MBS item number 66638: Isoelectric focussing or similar methods for determination of alpha-1-antitrypsin phenotype in serum; and
- gene sequencing of the coding region of the *SERPINA1* gene (not an MBS item number).

Other professional bodies:

Royal Australasian College of General Practitioners

Royal Australasian College of Physicians - Paediatrics & Child Health Division and Adult Medicine Division (Respiratory Medicine)

Thoracic Society of Australia and New Zealand

21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

Alpha-1 Association of Australia

Lung Foundation Australia

22. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

N/A

23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

Name of expert 1: REDACTED

Telephone number(s): REDACTED

Email address: REDACTED

Name of expert 2: REDACTED

Telephone number(s): REDACTED

Email address: REDACTED

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease in terms of both morbidity and mortality:

Alpha-1 antitrypsin (AAT) is a serine protease inhibitor (PI) that is encoded by the *SERPINA1* gene and secreted into the plasma by the liver cells, then diffuses passively into the lung interstitium and alveolar lining fluid. The primary role of AAT is to protect lung tissue from proteolytic damage by inhibiting the action of neutrophil elastase (Craig & Henao 2018), which, if left unchecked, causes the destruction of lung matrix components, alveolar structures, and blood vessels (Kalfopoulos et al 2017).

AAT deficiency (AATD) is a clinically under-recognised and under-diagnosed inherited disorder affecting the lungs, liver, and in rare cases, the skin. The diagnostic delay (time between first symptoms and diagnosis) is estimated to be a mean of 5.6 years (median of 8 years). Factors contributing to under-recognition and diagnostic delay are a lack of awareness of the disease by healthcare providers and the belief that testing for AATD is not warranted due to a lack of effective therapies (Kalfopoulos et al 2017). However, clinical opinion indicates that the development of new treatment options requires the support of definitive genotyping.

Two co-dominant alleles of the *SERPINA1* gene determine the AAT phenotype, with the proteins encoded referred to by the prefix PI* (protease inhibitor*). There are four common alleles and four distinct phenotypes:

- **Normal phenotype**, PI*M[5]: the most common allele, encodes normal AAT, with PI*MM the most common homozygous allele;
- **Deficient phenotype**, PI*Z: the most common *pathogenic* allele caused by a single amino acid substitution resulting in functionally deficient AAT protein, accounting for 96% of known clinical cases of AATD. PI*MZ accounts for 10%-20% of carriers. Homozygous individuals (PI*ZZ) have severe AATD;
- **Deficient phenotype**, PI*S: a *pathogenic* allele caused by a single amino acid substitution resulting in functionally deficient AAT. PI*MS heterozygotes account for 50%-60% of carriers. It is usually only of clinical consequence in the compound heterozygous state with another pathogenic allele (e.g. PI*SZ) and when serum AAT levels are <11 µmol/L;
- **Null phenotype**, null alleles (may be designated PI*QO). Pathogenic alleles caused by transcriptional or translational errors that result in either no mRNA product or no protein production.(Craig & Henao 2018; Stoller 2018)
- **Dysfunctional phenotype**, a rare phenotype found in <0.1% of AATD characterised by normal amounts of AAT in plasma that does not function correctly, leading to decreased elastase inhibitory activity (Kalfopoulos et al 2017).

Estimates of serum levels of AAT for the most common genotypes and their associated risk of disease are summarised in

[5] M for "medium mobility" through an isoelectric gel, Z = slowest, S = slow

Table 1. The clinical phenotype of AATD is highly variable. AATD is a known genetic risk factor for the development of early onset chronic obstructive pulmonary disease (COPD), emphysema, persistent airflow obstruction, and/or chronic bronchitis (Stoller 2018; Stoller et al 2017). In most cases, a diagnosis of AATD is usually made only *after* a diagnosis of COPD or chronic liver disease, or after AATD diagnosis in a family member (Janciauskiene et al 2011); however, it is often *misdiagnosed* as COPD or non-responsive asthma (Carroll et al 2011).

Table 1 Genotypes, serum levels and risk of disease associated with AAT deficiency (Craig & Henao 2018; Kueppers & Sanders 2017; Stoller et al 2017)

Genotype	Serum level (mg/dL)	Risk of lung disease	Risk of liver disease	Explanatory information
MM	105-164 Normal	Background		The PI*M allele encodes normal AAT
MS	83-137	Background		
MZ	66-100 Low to normal	+	+	Some studies have found an increased risk of developing COPD due to exposure to cigarette smoke in individuals with the PI*MZ allele, although other studies have found no association
SS	73-106 Borderline normal to low	+/-		No conclusive evidence links 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.
SZ	49-66 Low	+ 20-50%		The PI*SZ allele has been associated with increased risk of COPD.
ZZ	20-45 Very low	+++ 80-100%	+++	The PI*Z allele leads to polymerisation in hepatocytes and less frequent binding to neutrophil elastase in the lungs.
Null/null	0 Absent	+++ 100%		Rare null alleles are characterised by absent circulating AAT due to transcriptional or translational errors.

The risk of developing COPD is highly dependent on genotype. Not all subjects will develop pulmonary disease and those who do vary in presentation and their subsequent decline. A meta-analysis of case-control studies reported an increased pooled odds ratio for COPD in PI*MZ heterozygotes compared with the normal PI*MM genotype (OR = 2.97, 95% CI [20.08, 4.26]) (Hersh et al 2004). Some studies have reported an elevated odds ratio for the development of COPD in PI*SZ individuals, whilst others have shown no effect (Miravitlles et al 2017). Targeted AATD screening of patients with COPD has indicated that between 1.0 – 4.5% have an underlying diagnosis of severe AATD (PI*ZZ), and that 75 to 85% of individuals with the PI*ZZ genotype will develop emphysema (Abramson et al 2015). In AATD adults, cigarette smoking is a major risk factor for the early development of fixed airflow obstruction leading to dyspnoea and COPD as it increases the elastase burden in the lung, thus increasing lung degradation. In individuals with the PI*SZ phenotype, cigarette smoking is a particularly important risk factor for the development of COPD, which rarely occurs in non-smokers with this phenotype (Stoller 2018).

AATD patients with concomitant asthma have a worse prognosis with bronchodilator response associated with greater decline in FEV^6_1 and poorer clinical outcomes (Gramegna et al 2018). Asthma patients with AATD have significantly more comorbidities including arterial hypertension, congestive heart failure, ischaemic heart disease, depression, chronic kidney disease, diabetes and lung cancer (all $p< 0.001$) when compared to non-AATD asthma or emphysema patients. In addition, AATD patients had significantly more consultations, and more frequent and longer hospitalisations compared to non-AATD COPD patients (Greulich 2017; Greulich et al 2017a).

To lessen the progression of lung disease it is recommended that patients implement complete cessation of smoking; avoid passive smoking and dusty occupational exposures, and vaccinate against influenza and pneumococcus. In addition, it is recommended that individuals with severe AATD undergo surveillance with pulmonary function tests, including spirometry with bronchodilators and diffusing capacity measurements, every 6-12 months (Stoller et al 2017). Clinical opinion notes that patients are unlikely to alter their behaviour without a definitive diagnosis.

[6] FEV = forced expiratory volume

A small proportion of AATD patients have an elevated risk of serious liver disease due to polymerisation and retention of AAT in hepatocytes, where the majority of AAT is produced (Craig & Henao 2018). In childhood, the most common manifestation of AATD-associated liver disease is jaundice, with hyperbilirubinemia and raised serum aminotransferase levels in the early postnatal period. Clinical presentation and progression is highly variable. In most AATD patients, liver damage progresses slowly, whilst in a small proportion of children with early hyperbilirubinemia liver destruction is accelerated leading to cirrhosis (Stoller et al 2017). A Swedish newborn screening study of 200,000 children found that of the 127 children identified with the PI*ZZ genotype, only 18% developed clinically recognised liver abnormalities (neonatal cholestasis, hepatomegaly and fatty liver) and 2.4% developed liver cirrhosis with death in childhood. No deaths were reported in other AATD genotypes, with the exception of one sudden infant death who was PI*SZ (Sveger 1988). A recent French registry study reported that of 153 children 81.9%, 8.1% and 10% were PI*ZZ, PI*SZ and other, respectively. Of these, half of the children had moderate liver disease. Of the 28 (18.3%) children with severe liver disease the majority were PI*ZZ (n=25) and 15 underwent liver transplantation, whilst one child died at 3 years of age (Ruiz et al 2019). The overall risk of severe liver disease in PI*ZZ children is low at approximately 2-3%, and those children who recover from early liver disease have a good prognosis. The risk of severe liver disease may be as high as 40% in the siblings of children with the PI*ZZ genotype who have severe liver disease, making cascade genotyping critically important (Stoller et al 2017).

Although liver disease in adults (cirrhosis and fibrosis) is associated with the PI*ZZ genotype, a greater number of PI*MZ (8.4%) patients have been noted in adults presenting with chronic liver failure compared to the general population (2%-4%). Liver disease in adult AATD patients is more common in men than women and may occur in the absence of a history of neonatal or childhood liver disease. Studies have reported that between 15% and 19% of individuals over age 50 years with AATD and the PI*ZZ genotype develop cirrhosis. In addition, the risk for developing hepatocellular carcinoma in adults with the PI*ZZ genotype is several times that of non-AATD liver cirrhosis patients, with an annual incidence of 1.5% in these patients (Stoller et al 2017).

To lessen the risk of liver disease it is recommended that patients minimise consumption of alcohol and vaccinate against hepatitis A and B. In addition, patients who have the PI*ZZ genotype should undergo periodic evaluation of liver function in order to detect liver disease, and those with established liver disease should undergo ultrasound examination of the liver to monitor for fibrotic changes and hepatocellular carcinoma every 6-12 months (Stoller et al 2017).

25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

The European Respiratory Society recommends that patients should be tested for AATD if they have:

- Early-onset (<40 years) COPD (emphysema, persistent airflow obstruction, and/or chronic bronchitis)
- Emphysema in the absence of a risk factor such as being a non-smoker;
- Emphysema with prominent basilar changes on a chest x-ray;
- A family history of AATD, COPD, emphysema, bronchiectasis, liver disease or panniculitis;
- Liver disease at any age, including obstructive jaundice in infancy (perinatal jaundice, cirrhosis, necrotising panniculitis or unexplained liver disease); or
- Anti-proteinase 3-positive vasculitis (Miravitlles et al 2017).

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

The diagnosis of AATD firstly requires the quantitative measurement of serum levels of the AAT protein, with a low concentration (<20 µmol/L) indicating a deficiency. A variety of techniques have been used to measure serum AAT concentration with the most commonly used technique being nephelometry. This is currently

funded using MBS item number 66635: Alpha-1-antitrypsin - quantitation in serum, urine or other body fluid - 1 or more tests. Fee: $20.10 Benefit: 75% = $15.10 85% = $17.10.

- By nephelometry, normal serum levels are 20-53 µmol/L or approximately 100-220 mg/dL
- Serum levels observed in AATD with lung disease are usually <20 µmol/L.

As AAT is an acute-phase protein, serum levels may fluctuate and levels may be increased in the following circumstances:

- Up to a fourfold rise as an acute phase reactant during episodes of acute inflammation, cancer, and liver disease in individuals without AATD;
- As an acute phase reactant during episodes of acute inflammation in heterozygotes for one *SERPINA1* pathogenic variant and those with mild AATD;
- In pregnancy and in women using oral contraceptives;
- In persons receiving blood transfusions or intravenous augmentation therapy (i.e., purified pooled human plasma AAT); and
- vaccination (Kueppers & Sanders 2017; Stoller et al 2017).

Even given these circumstances, serum levels of AAT of individuals with severe AATD (PI*ZZ) are unlikely to rise high enough to be considered in the normal range (Stoller et al 2017).

Individuals with low levels of AAT (<20 µmol/L) should undergo phenotype characterisation using polyacrylamide gel isoelectric focusing (IEF) electrophoresis of serum. As described previously, electrophoretic AAT protein variants are designated by letters based on their migration pattern. The normal AAT protein (PI*M) migrates in the middle of the isoelectric field. The abnormal AAT deficiency protein (PI*Z) migrates most slowly. The limitations of IEF include inability to interpret an atypical electrophoretic pattern resulting from rare AAT protein variants and absence of AAT protein resulting from a *SERPINA1* pathogenic null allele (Stoller et al 2017). IEF is currently funded under MBS item number 66638: Isoelectric focussing or similar methods for determination of alpha-1-antitrypsin phenotype in serum - 1 or more tests. Fee: $49.05 Benefit: 75% = $36.80 85% = $41.70.

For individuals where IEF does not identify an abnormal AAT protein, or for those who have normal levels of AAT but a high clinical suspicion of AATD, then sequencing of the *SERPINA1* gene should be conducted looking for null or rare variants (Stoller et al 2017).

Figure 1 describes the current clinical algorithm for the diagnosis of alpha-1 antitrypsin deficiency without genotyping.

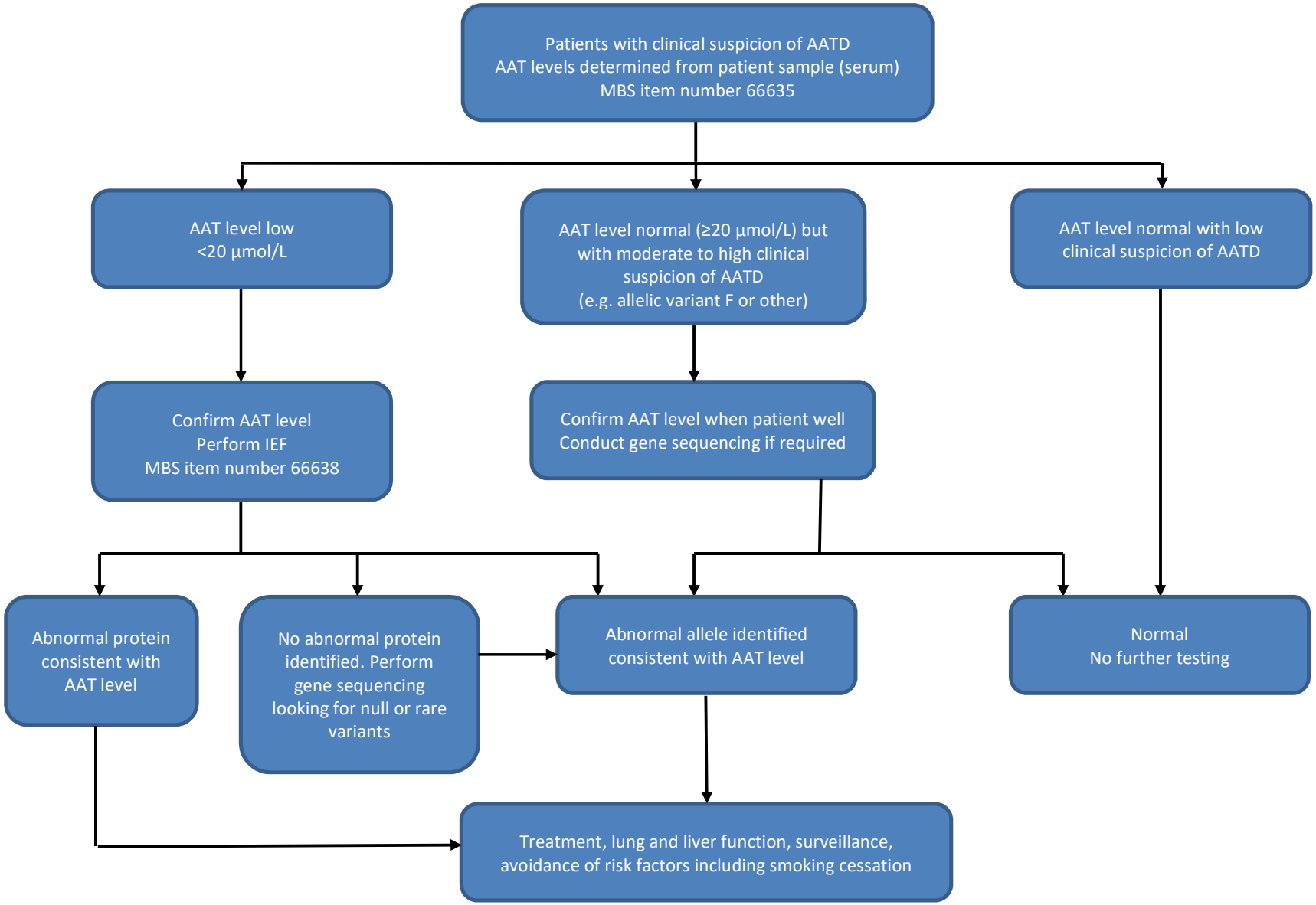

Figure 1 Algorithm for the diagnosis of alpha-1 antitrypsin deficiency without genotyping (Stoller 2018) AAT = alpha-1 antitrypsin, IEF = isoelectric focusing

PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

As described above, individuals suspected of being AATD should undergo measurement of AAT serum levels. The Thoracic Society of Australia and New Zealand recommend that genotyping should be performed in individuals with reduced serum levels of AAT (<20 µmol/L) (Abramson et al 2015), negating the need to conduct IEF.. For genotyping a DNA sample needs to be obtained, usually from a blood sample or a buccal swab (which may be preferable in children). In allele-specific genotyping, a fragment of the AAT gene is amplified by real-time PCR with specific oligonucleotide primers. Fluorescent labelled probes are used to identify the PCR product and determine the genotype by melting curve analysis. Exome sequencing, which requires complete study of the DNA sequences of the 4 encoding exons (II, III, IV, V) of the AAT gene, consists of amplification of the 4 exons by polymerase chain reaction (PCR) followed by cycle sequencing of the PCR products (Belmonte et al 2017).

At least 60 deficient mutations have been described. They comprise single point mutations, truncated (nonsense, frameshift and splicing) mutations, deletions of single codons and larger deletions. Most of them are located in the four coding exons of the gene. The most common deficient variants are named Z (G/A, Glu342Lys, in exon V) and S (A/T, Glu264Val, in exon III) (Janciauskiene et al 2011); however, genotyping is of greatest value when used to diagnose patients with variants not detected by IEF. Progenika Biopharma (a subsidiary of Grifols, Bilbao, Spain) markets an A1AT genotyping panel, which identifies 14 of the most prevalent known AATD mutations, including the Mmalton variant, representing approximately 99% of affected individuals (see Figure 4). The TaqMan technology currently used by Queensland Pathology to detect 4 SNPs would not be suitable to detect 14 SNPs due to high costs; however, technology that is amenable to multiplexing, such as Agena MassARRAY or NGS, would entail similar costs for 4 or 14 SNPs (personal communication SA Pathology).

For those patients with a high clinical suspicion of AATD where genotyping does not identify a pathogenic variant, DNA sequencing of the *SERPINA1* gene is recommended. It has been estimated that with the introduction of panel genotyping, the number of patients proceeding to sequencing of the SERPINA gene genetic testing may be reduced by up to 60 percent (Veith et al 2019).

It is likely that A1AT genotyping and *SERPINA1* gene sequencing would be performed in only a few centres of excellence in Australia and that these pathology laboratories would develop their own 'in-house' panels rather than using the commercially available product.

It should be noted that, unlike phenotyping by IEF, genotyping allows for cost-saving batching of samples, allowing for large runs of patient samples. With decreasing costs of genotyping it is expected that, over time, AATD genotyping will represent significant cost-savings to the health system.

28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

N/A

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

N/A

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

Once off diagnostic test.

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

The results of genetic tests may require genetic counselling in order to allow predictive testing of asymptomatic family members; however, despite the increasing number of genetic tests listed, there remains no rebate for genetic counselling on the MBS. Patients with AATD due to a mutation that

polymerises inside hepatocytes will require extensive follow-up of liver function. For current smokers, smoking cessation strategies, which may include counselling, should be offered.

32. If applicable, advise which health professionals will primarily deliver the proposed service:

Testing would be provided by Approved Practising Pathologists in line with other tests on the MBS Pathology Table.

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

N/A

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Patients should be referred by a respiratory specialist or consultant physician.

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

Testing would be delivered only by NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table. Interpretation of results would be provided by an approved practising pathologist or medical scientist.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select <u>ALL</u> relevant settings):

- ☐ Inpatient private hospital (admitted patient)
- ☐ Inpatient public hospital (admitted patient)
- ☐ Private outpatient clinic
- ☐ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms - GP
- ☐ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☐ Private day surgery clinic (admitted patient)
- ☐ Private day surgery clinic (non-admitted patient)
- ☐ Public day surgery clinic (admitted patient)
- ☐ Public day surgery clinic (non-admitted patient)
- ☐ Residential aged care facility
- ☐ Patient's home
- ☒ Laboratory
- ☐ Other – please specify below

Specify further details here

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

N/A

37. Is the proposed medical service intended to be entirely rendered in Australia?

- ☒ Yes
- ☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

See Figure 1.

The quantitative measurement of serum AAT levels by nephelometry should be the first step in the diagnosis of AATD. Measurement of serum levels of AAT cannot be considered diagnostic of AATD, and in fact may be misleading (Kueppers & Sanders 2017). Individuals found to have low levels of serum AAT should then undergo phenotype characterisation by isoelectric focusing (IEF) (Belmonte et al 2017). IEF is a time-consuming technique and difficult technique that requires specific expertise, and is characterised by a low sensitivity, as it does not recognise the 'null' variant (without any phenotypic expression) and M-like alleles (Janciauskiene et al 2011). IEF is useful when phenotyping normal alleles (PI*MM) or the loss of the most common alleles (PI*S and PI*Z); however, genotyping is necessary to characterise certain rare or the null allele (Joly et al 2011). In addition, phenotyping by IEF, unlike genotyping, cannot be batch processed.

The appropriate comparator for genotyping of AATD individuals is therefore IEF.

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☒ Yes (please list all relevant MBS item numbers below)
☐ No

Item 66635: Alpha-1-antitrypsin - quantitation in serum, urine or other body fluid - 1 or more tests
Fee: $20.10 Benefit: 75% = $15.10 85% = $17.10

Item 66638: Isoelectric focussing or similar methods for determination of alpha-1-antitrypsin phenotype in serum - 1 or more tests
Fee: $49.05 Benefit: 75% = $36.80 85% = $41.70

Item 66639: A test described in item 66638 if rendered by a receiving APP - 1 or more tests
Fee: $29.20 Benefit: 75% = $21.90 85% = $24.85

40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

See Figure 1.

For many patients, a phenotypic diagnosis by IEF would be sufficient (PI*S and PI*Z patients) and the medical services and treatment received after IEF are similar to those that many patients would experience after genetic testing (see Q42). However, IEF does not detect null alleles (i.e. no detectable α1-AT in the blood) and M-like alleles, and the interpretation of rare alleles is difficult (Miravitlles et al 2010), with genotyping or gene sequencing required to diagnose these patients.

41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

☐ In addition to (i.e. it is an add-on service)
☒ Instead of (i.e. it is a replacement or alternative)

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

Genetic testing should completely replace IEF in patients with low levels of AAT. In addition, genetic testing has been reported to greatly reduce the number of individuals who undergo sequencing of the SERPINA gene (by up to 60%) (Veith et al 2019).

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

Figure 2 describes the clinical algorithm for the diagnosis of alpha-1 antitrypsin deficiency with genotyping replacing IEF in those patients with low levels of AAT (<20 µmol/L) as determined by MBS item number 66635. The goal of testing is to identify individuals and at-risk families for whom interventions might confer benefit, and to especially identify those individuals where there is a mismatch between phenotype as determined by IEF and levels of AAT (i.e. where the underlying genotype does not correlate with phenotype).

The most important result of genetic testing is to promote risk modification behaviour in patients. The diagnosis of AATD in adults is associated with a greater willingness to attempt quitting and greater success in quitting smoking. Recent evidence indicates that MZ individuals who smoke are at increased risk for airflow obstruction, with the Z allele the single most frequent genetic risk factor for airflow obstruction. In addition, the rate of lung function decline in smokers with AATD-COPD is considerably higher than that seen in AAT-replete COPD, indicating that correct identification and behaviour modification is imperative in these patients. The most sensitive and specific (99%) method for identification of specific alleles is genetic testing. Correct identification using genetic testing of individuals carrying the Null genotype is of utmost importance. It is particularly important to identify family members at risk i.e. asymptomatic first-degree relatives of AATD individuals, in order to promote risk modification behaviour, especially smoking avoidance, and adequate monitoring. Identification of AATD at birth is associated with a lower rate of smoking initiation (Sandhaus et al 2016).

In addition, genetic testing will identify not only individuals who are homozygous for the most common abnormal AAT genes, but also those who are heterozygous, enabling informed reproductive options for those individuals wishing to have children.

It should be noted that a recent application[7] for the public funding of weekly infusions of purified human alpha1-proteinase inhibitor (A1-PI) for the treatment of AATD was not supported by the MSAC. Although the MSAC acknowledged that there was a large unmet clinical need for this therapy, concerns were raised regarding the lack of evidence describing the measurement of the effectiveness of A1-PI treatment using CT density. In addition, MSAC noted that there are no statistically significant differences between A1-PI and placebo in relation to mortality, exacerbation of COPD, hospitalisation due to COPD exacerbation, QoL, FEV1, exercise capacity or carbon monoxide diffusion capacity.

This current application is concerned with identifying AATD individuals in order that they can put in place a regimen of behaviour modification *before* they become symptomatic with conditions such as COPD.

[7] Application No. 1530 – Purified human alpha1-proteinase inhibitor for the treatment of alpha1-proteinase inhibitor deficiency, leading to chronic obstructive pulmonary disease
http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1530-public

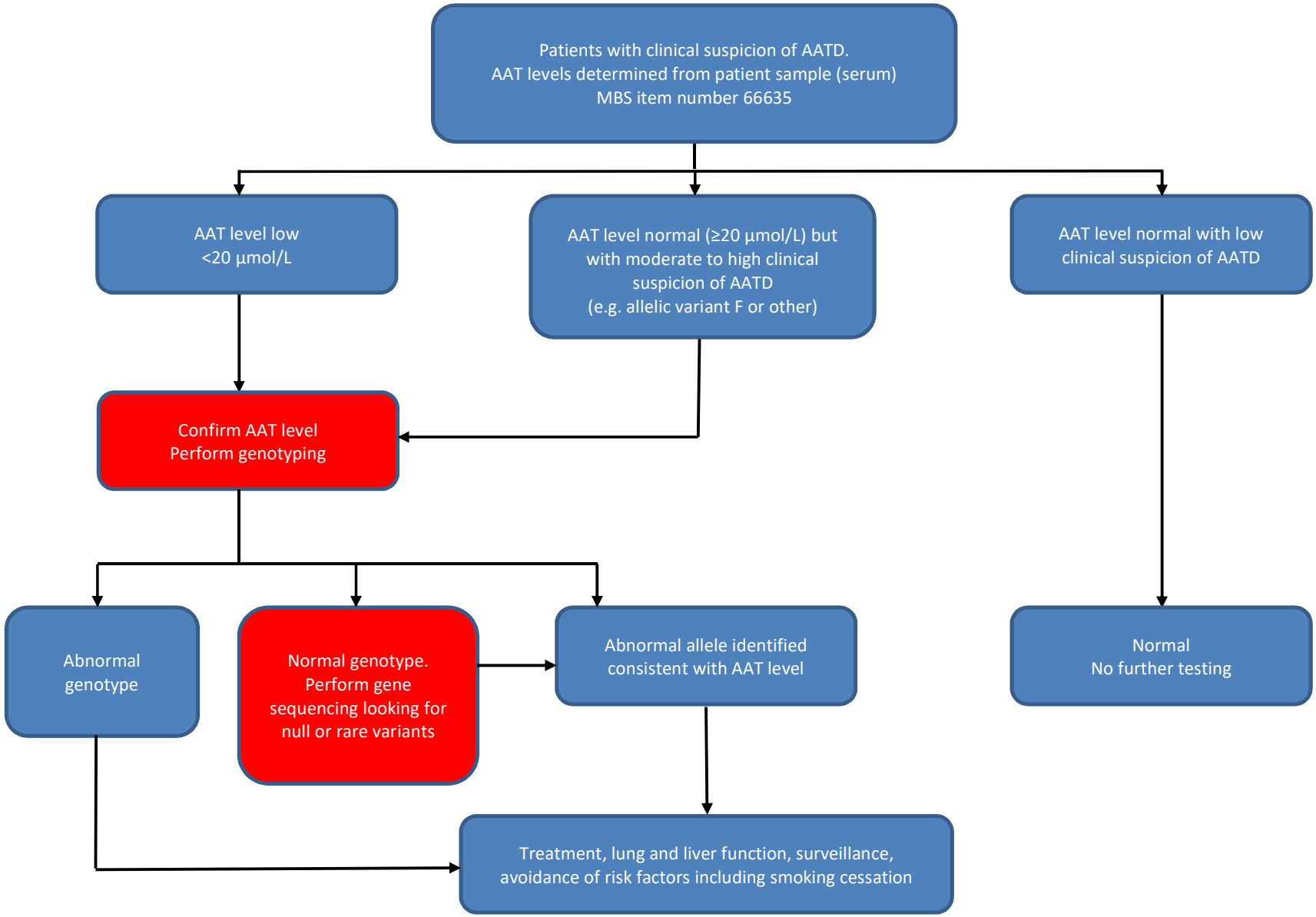

Figure 2 Algorithm for the diagnosis of alpha-1 antitrypsin deficiency with genotyping (Stoller 2018) AAT = alpha-1 antitrypsin

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Many studies have identified under-recognition of AATD in symptomatic patients. A 5 to 8-year delay between the first symptom and recognition of AAT deficiency has been found in studies performed over a span of 18 years (to 2013), indicating that under-recognition persists despite extensive educational efforts and the publication of evidence-based guidelines for diagnosis and management of AATD (Stoller 2018).

Genetic testing is superior compared to the comparator, IEF and may result in considerable downstream cost-savings to the health system. For many patients, a phenotypic diagnosis by IEF would be sufficient (PI*S and PI*Z patients); however, IEF does not detect null alleles and M-like alleles, and the interpretation of rare alleles is difficult (Miravitlles et al 2010). Genotyping or gene sequencing is required to diagnose these patients.

Access to AAT testing is a key factor to early diagnosis and treatment before the condition manifests in associated debilitating conditions. It should be noted that the World Health Organization recommends testing of all COPD patients, and the European Respiratory Society and American Thoracic Society Guidelines recommend the testing of all symptomatic adults with persistent airway obstruction (Greulich & Vogelmeier 2016). Genotyping for the two specific alleles (PI*S [p.Glu264Val] and PI*Z [p.Glu342Lys]) using QT-PCR has almost 100 per cent analytical sensitivity and specificity (Janciauskiene et al 2011). As such, AATD genotyping delivers certainty of diagnosis and may provide potential parents with reproductive options including prenatal genetic testing, especially for women who are homozygous or a carrier for the Z or a null mutation. The partners of these women should also be screened for variants by targeted DNA analysis. Knowledge of AAT mutation status has been demonstrated to motivate patients to modify behaviour by reducing or ceasing exposure to tobacco smoke and minimising exposure to other environmental pollutants (Abboud et al 2011).

AATD is a systemic disease with extra-respiratory clinical manifestations that might benefit from a specific management with positive impact on clinical outcomes and patients' quality of life. AATD is both a genetic disease with increased risk of affected children and a chronic condition with possible impact on family planning and patients' life priorities (Gramegna et al 2018).

Management of symptomatic lung disease is the same as that for COPD, including smoking cessation, inhalers, and pulmonary rehabilitation. However, it should be noted that the rate of lung function decline in smokers with AATD-COPD is considerably higher than that seen in AAT-replete COPD (Sandhaus et al 2016). Definitive identification of AATD may allow for the infusion of plasma-derived AAT to restore physiological levels. This augmentation therapy is the only disease-specific treatment for AATD, and although very expensive it has demonstrated a significant slowing of the progression of emphysema as measured by CT density change compared to placebo (0.79 g/L/year p=0.002) (Edgar et al 2017). There is evidence that augmentation therapy brings benefits (slowed rate of FEV_1, decline and decreased mortality) for those individuals with moderate obstructive pulmonary impairment (FEV_1 35–60% predicted) than for those with severe airflow obstruction (Gramegna et al 2018).

The greatest health benefit of genotyping may not be mediated through changes in clinical management; however, a definitive diagnosis allows preventive strategies such as behaviour modification to be put in place *before* patients become symptomatic. An accurate diagnosis facilitates the physician's ability to actively intervene with measures such as smoking cessation and perhaps augmentation therapy, and it will also help provide a better understanding of the natural history of the disease (McElvaney 2015). Smoking cessation is a clear recommendation supported by good quality evidence.

44. Please advise if the overall clinical claim is for:

☒ Superiority
☐ Non-inferiority

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety outcomes:

- Adverse events from obtaining a sample for testing
- Psychological or physical harms from testing or not testing to the proband
- Psychological or physical harms from cascade testing or not testing on relatives of the proband

Clinical Effectiveness/utility Outcomes:

- Analytical validity
- Clinical validity
- Clinical utility
    - Change in clinical management for proband
    - Change in clinical management for relatives (cascade testing)
    - Change in patient outcomes
        - Quality of life
        - Morbidity
        - Mortality
        - Number of and length of hospital stays
- Cost-effectiveness

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

AATD is inherited in an autosomal recessive manner. If both parents are heterozygotes (e.g., PI*MZ), each sibling of an affected individual has a 25% chance of being affected (PI*ZZ), a 50% chance of being a carrier (PI*MZ), and a 25% chance of being an unaffected non-carrier (PI*MM). If an individual with AATD has children with a reproductive partner who is affected or a carrier, their offspring will be obligate heterozygotes (carriers) for the pathogenic variant (Stoller et al 2017).

Under-diagnosis of AATD is a global issue. There is a paucity of Australian prevalence and incidence data. A recent worldwide analysis of cohort studies; however, identified eight AAT cohort studies conducted in Australia that reported a prevalence for the severe PI*ZZ genotype of 1 in 5,572, equating to a total of 4,126 (95% CI [2,894–5,695]) affected individuals (Blanco et al 2017). In a much earlier study by de Serres et al (2003), reviewed 12 Australian control cohort studies (i.e. unselected populations without symptoms of AATD e.g. blood donors, newborns, hospital patients, school or college students etc) with a total of n=6223 individuals. Four of these studies described the epidemiology in Aboriginal and eight Caucasian populations, when the total population in Australia was 19,169,074. In the Aboriginal population, the mean frequency for the PI*S allele was 26.0 (18.0–37.0) per 1,000 and the mean gene frequency for PI*Z was 0.8 (0.04–5.4) per 1,000. In the Caucasian population the mean gene frequency for the PI*S and PI*Z alleles was 44.5 (40.8–48.5) and 13.4 (11.4–15.7) per 1,000, respectively. Overall, for Australia, the weighted mean gene frequency for the PI*S and PI*Z alleles was 44.4 (40.7–48.5) and 13.4 (11.4–15.7) per 1,000, respectively. Noting that there was a very high PI*S gene frequency for the Aboriginal Elco population in the Northern Territory that was not identified in two other Aboriginal populations (de Serres et al 2003).

Other studies have estimated the prevalence of AATD as between one in 2,857 and one in 5,097 in USA, and between one in 2,175 and one in 5,164 in Spain (Barrecheguren et al 2016). A cross-sectional study conducted in Germany reported a prevalence of 23.73 per 100,000 in all age groups, and 29.36 per 100,000 in those ⩾30 years (Greulich et al 2017b). MZ heterozygotes occur in approximately 2%–3% of the Caucasian population and is associated with only a slight increased risk of development of COPD in smokers. The MS genotype has a prevalence of 4%–11% in Europe and is not a risk factor for disease (Abboud et al 2011). A large population-based screening performed in Ireland on 3,000 subjects identified 42 ZZ, 44 SZ and 430 MZ individuals, a prevalence estimation greater than previously thought. These figures would result in an estimated prevalence in Ireland of severe (PI*ZZ), intermediate (PI*SZ) and mild (PI*SS) AATD of 1 in 2,104, 1 in 424 and 1 in 341, respectively, with allele frequencies of 0.0938 for the Z mutation and 0.0518 for the S mutation. The majority of AATD individuals with the Z and S alleles were undetected prior to this study (Carroll et al 2011). Stoller et al (2017) summarised the prevalence of AATD genotypes (Table 2).

Table 2 Prevalence of AATD genotypes in AATD individuals (Stoller et al 2017)

Genotype	Prevalence (%)			Genetic prevalence in Australian population (de Serres et al 2003)
	Worldwide	North America	Europe	
MM	96.3	93.0	91.1	Not applicable
MS	2.7	4.8	6.6	1 in 12
MZ	0.8	2.1	1.9	1 in 40
SS	0.08	0.1	0.3	1 in 507
SZ	0.02	0.1	0.1	1 in 841
ZZ	0.003	0.01	0.01	1 in 5,584*
Null/null	Rare	Rare	Rare	Rare

47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

Once per lifetime diagnostic test.

48. How many years would the proposed medical service(s) be required for the patient?

Once per lifetime diagnostic test.

49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

In the first full year it is likely that the prevalent AATD Australian population will undergo AAT genotyping in addition to first-degree relatives who will undergo cascade testing.

The number of services provided by MBS item number 66638 (IEF) may be indicative of the number of patients likely to access AAT genotyping. The MBS statistics below show a relatively steady number of services provided over the previous 5-years, with an average number of services of 1,655; however, it is not possible to identify if each service represents a single patient as some patients may have undergone repeat testing, or if services represent cascade testing.

		State								Total
		NSW	VIC	QLD	SA	WA	TAS	ACT	NT	
		Services	Services	Services	Services	Services	Services	Services	Services	Services
66638	2014/2015	304	197	314	154	152	56	6	3	1,186
	2015/2016	461	191	329	195	243	289	8	1	1,717
	2016/2017	644	209	396	174	197	284	5	4	1,913
	2017/2018	623	103	424	152	207	279	7	1	1,796
	2018/2019	673	100	371	172	238	93	13	4	1,664
	Total	2,705	800	1,834	847	1,037	1,001	39	13	8,276

Figure 3 Number of services provided by MBS item number 66638 by year and state, July 2014- June 2019

Currently at least two laboratories in Australia offer AAT genotyping: Pathology NSW Health and Pathology Queensland (Queensland Health). In 2019, Pathology Queensland conducted 2,269 tests for AAT genotyping (4 SNPs) and seven *SERPINA1* sequencing tests (personal communication Queensland Health). With the introduction of a broader genotyping service encompassing 14 SNPs it is expected that the number of *SERPINA1* sequencing tests will reduce dramatically (by up to 60%). Based on the numbers provided by Queensland this would equate to approximately 4 patients per year who would require sequencing.

50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

It would be expected that the number of tests (both index and cascade) will decrease in years 2 and 3, once the prevalent population had been tested in year 1 of MBS listing.

There may be some leakage with physicians testing all patients with symptoms of COPD in order to identify and underlying cause of the COPD.

PART 8 – COST INFORMATION

51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

Genotyping is usually conducted after serology has identified abnormal levels of AAT. Currently at least two laboratories in Australia offer AAT genotyping: Pathology NSW Health and Pathology Queensland (Queensland Health). Pathology Queensland currently use Taqman QT-PCR using specific primers to detect only the two most common mutations (4 different alleles: MS, MZ) at a cost of $78, whilst the cost of genotyping in NSW is $80 (personal communication Pathology Queensland).

Progenika Biopharma (a subsidiary of Grifols, Bilbao, Spain) markets an A1AT genotyping panel, which identifies 14 of the most prevalent known AATD mutations, representing approximately 99% of affected individuals (Figure 4). This panel is currently offered in Spain via private franchises for €200 (A$324) per test; however, profit margins and economies of scale would differ in an Australian market. In Australia it is likely that an 'in-house' IVD would be developed by pathology laboratories using technology that is amenable to multiplexing, such as Agena MassARRAY or NGS to test for the 14 SNPs as per the 'Spanish panel', with an associated cost of approximately $100.

Queensland Health currently offer *SERPINA1* sequencing for $260 (personal communication Pathology Queensland).

	Allelic variant	Most frequently associated alleles
1	c.187C>T	Pi* I
2	c.194T>C	Pi* M procida
3	c.226_228delTTC	Pi* M malton
4	c.230C>T	Pi* S iiyama
5	c.552delC	Pi* Q0 granite falls
6	c.646+1G>T	Pi* Q0 west
7	c.721A>T	Pi* Q0 bellingham
8	c.739C>T	Pi* F
9	c.839A>T	Pi* P lowell
10	c.863A>T	Pi* S
11	c.1096G>A	Pi* Z
12	c.1130dupT	Pi* Q0 mattawa
13	c.1158dupC	Pi* Q0 clayton
14	c.1178C>T	Pi* M heerlen

Figure 4 Allelic variants and associated alleles included in the Progenika Biopharma A1AT genotyping panel

52. Specify how long the proposed medical service typically takes to perform:

The turnaround time for genotype testing is typically one week; however, this will be dependent on numbers tested and the prioritisation of testing.

Gene sequencing may take between 2-6 weeks, depending on laboratory workload; however, the literature has reported a mean turnaround time of 11-days (Maltais et al 2018).

53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Category 6 (Pathology Services) – Group P7 Genetics
Proposed item descriptor: AAAA Gene panel testing to identify alpha-1-antitrypsin (AAT) pathogenic variants where the patient has respiratory symptoms indicative of AAT deficiency and abnormally low (<20 µmol/L) alpha-1 antitrypsin levels as determined by item number 66635, or there is a demonstrated family history of alpha-1 antitrypsin deficiency, requested by a specialist or consultant physician. Maximum one test per lifetime. **Fee**: $100

Category 6 (Pathology Services) – Group P7 Genetics
Proposed item descriptor: BBBB Sequencing of the *SERPINA1* gene to identify an alpha-1-antitrypsin (AAT) pathogenic variant where the result after genotyping using item number BBBB is inconclusive, requested by a specialist or consultant physician. Maximum one test per lifetime. **Fee**: $260

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