

Application Form

(New and Amended

Requests for Public Funding)

(Version 2.4)

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 in order 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.

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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 (RCPA)

ABN: Redacted

Business trading name: Redacted

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

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

Apolipoprotein B testing for high risk cardiovascular disease risk assessment

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)

Cardiovascular disease (CVD) is largely preventable and the evaluation of risk through a comprehensive clinical and diagnostic assessment of the patient allows for more effective management of modifiable risk factors. Individual risk factors such as high blood pressure and raised lipid levels are known to be associated with increased risk of CVD events.

Measurement of apolipoprotein B (apoB) may be most relevant in patients who are hypertriglyceridaemic owing to mixed hyperlipidaemia or as an isolated abnormality. This encompasses patients with metabolic syndrome, obesity, type 2 diabetes, chronic kidney disease, and familial hyperapobetalipoproteinaemia (hyperapoB). It is also helpful in diagnosing genetic hypocholesterolaemic lipid disorders, including familial hypobetalipoproteinaemia and abetalipoproteinaemia, where apoB levels are very low or absent.

ApoB together with cholesterol and triglyceride can be used to define hyperapoB, a heterogeneous condition associated with small dense LDL and a high risk of atherosclerotic CVD.

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)

ApoB is an essential and functional component of liver-derived very-low density lipoprotein (VLDL) and its metabolic remnants, intermediate density lipoprotein (IDL), LDL, as well as lipoprotein(a) [Lp(a)]. Plasma concentrations of apoB reflect the total number of atherogenic particles present in the circulation because each of these contains one molecule of apoB. Like LDL-cholesterol, an increased plasma concentration of apoB has been shown to be a key risk factor for the development of atherosclerotic CVD.

In a series of prospective epidemiological studies, plasma apoB (a measure of the number of VLDL, IDL, LDL, and Lp(a) particles), as measured by immunoassay, has been shown to be superior to LDL-cholesterol (a measure of the mass of cholesterol within LDL, IDL and Lp(a) particles) and non-HDL-cholesterol (a measure of the mass of cholesterol within VLDL, IDL, LDL, and Lp(a) particles) as markers of cardiovascular risk.

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)?

N/A

- 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)
- 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?

N/A

- 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)?

N/A

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

Insert PBAC submission item number here

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

N/A

Trade name: Insert trade name here

Generic name: Insert generic name here

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

N/A

- Yes
- No

(b) If yes, please provide the following information (where relevant):

N/A

Billing code(s): Insert billing code(s) here

Trade name of prostheses: Insert trade name here

Clinical name of prostheses: Insert clinical name here

Other device components delivered as part of the service: Insert description of device components here

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

N/A

Yes

No

(d) 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?

N/A

Yes

No

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

N/A

Insert sponsor and/or manufacturer name(s) here

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

Single use consumables:

Several assays are available for this test and all require single use consumables such as laboratory pipette tips.

This application does not endorse any one specific commercial product. The IVD will be subject to TGA processes and laboratory validation. A detailed listing of all products and their consumables is beyond the scope of this application. It should be noted that new products will continue to be developed using the same scientific principles.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

- 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: Various

Sponsor's name: Not applicable

- (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: Various

- 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?**

N/A

- Yes (please provide details below)
 No

Date of submission to TGA: Insert date of submission here

Estimated date by which TGA approval can be expected: Insert estimated date here

TGA Application ID: Insert TGA Application ID here

TGA approved indication(s), if applicable: If applicable, insert description of TGA approved indication(s) here

TGA approved purpose(s), if applicable: If applicable, insert description of TGA approved purpose(s) here

- 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?**

N/A

- Yes (please provide details below)
 No

Estimated date of submission to TGA: Insert date of submission here

Proposed indication(s), if applicable: If applicable, insert description of proposed indication(s)

Proposed purpose(s), if applicable: If applicable, insert description of proposed purpose(s) here

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.	Clinical effectiveness study	Brown WV et al. Should we use apoB for risk assessment and as a target for treatment? J Clin Lipidol 2010; 4: 144-151.	A discussion of methods for the assessment of lipoprotein-related risk and the most appropriate component of lipoproteins for optimally judging clinical risk.	Should we use apoB for risk assessment and as a target for treatment?	3 Dec 2010
2.	Clinical effectiveness study	de Nijs T, Sniderman A, de Graaf J. ApoB versus non-HDL-cholesterol: diagnosis and cardiovascular risk management. Crit Rev Clin Lab Sci 2013; 50: 163-171.	A study of the differences between LDL-C, non-HDL-C, and apoB and a summary of evidence relating to LDL-C, non-HDL-C, and apoB as predictors of cardiovascular risk and as targets for treatment. The study demonstrates that diagnosis of atherogenic dyslipoproteinaemias is a clinical priority.	ApoB versus non-HDL-cholesterol: Diagnosis and cardiovascular risk management.	4 Dec 2013
3.	Case-controlled study	McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-controlled study. Lancet 2008; 372: 224-233.	The study concluded that the non-fasting apoB/apoA-I ratio was superior to any of the cholesterol ratios for estimation of the risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages, and it should be introduced into worldwide clinical practice.	Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study.	22 Jul 2008
4.	Clinical effectiveness study	Pencina MJ, D'Agostino RB, Zdrojewski T, et al. Apolipoprotein B improves risk assessment of future coronary heart disease in the Framingham Heart Study beyond LDL-C and non-HDL-C. Eur J Prev Cardiol 2015; 22: 1321-1327.	Results from the Framingham Heart Study demonstrating that apoB improves risk assessment of future coronary heart disease compared with LDL-C or non-HDL-C, consistent with coronary risk being more closely related to the number of atherogenic apoB particles than to the mass of cholesterol within them.	Apolipoprotein B improves risk assessment of future coronary heart disease in the Framingham Heart Study beyond LDL-C and non-HDL-C.	31 Jan 2015
5.	Clinical effectiveness	Sniderman A, Couture P, de Graaf J. Diagnosis and	A review of the diagnostic algorithm for apoB	Diagnosis and treatment of	28 Apr

	ss study	treatment of apolipoprotein B dyslipoproteinemias. Nat Rev Endocrinol 2010; 6: 335-346.	dyslipoproteinaemias demonstrating the effectiveness of a treatment plan on the basis of a reduction of atherogenic lipoprotein particles rather than plasma lipids.	apolipoprotein B dyslipoproteinemias.	2010
6.	Clinical effectiveness study	Sniderman A, McQueen M, Contois J, Why is non-high-density lipoprotein cholesterol a better marker of the risk of vascular disease than low-density lipoprotein cholesterol. J Clin Lipidol 2010; 4: 152-155.	A discussion of methods for the assessment of cardiovascular risk concluding that information from non-HDL-C and apoB provides better risk assessment and a better target of therapy.	Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study	3 Dec 2010
7.	Case controlled study	Sniderman AD et al. Discordance analysis of apolipoprotein B and non-high density lipoprotein cholesterol as markers of cardiovascular risk in the INTERHEART study. Atherosclerosis 2012; 225: 444-449.	Results from the INTERHEART study using discordance analysis to compare non-HDL-C and apoB and demonstrating superiority of apoB for cardiovascular risk analysis.	Discordance analysis of Apolipoprotein B and non-high density lipoprotein cholesterol as markers of cardiovascular risk in the INTERHEART study	28 Apr 2010
8.	Case controlled study	Sniderman AD, Islam S, Yusuf S, McQueen MJ. Is the superiority of apoB over non-HDL-C as a marker of cardiovascular risk in the INTERHEART study due to confounding by related variables? J Clin Lipidol 2013; 7: 626-631.	Results from the INTERHEART study demonstrating the superiority of assessing apoB compared with non-HDL-C and the importance of the atherogenic apoB-containing lipoproteins in cardiovascular risk.	Is the superiority of apoB over non-HDL-C as a marker of cardiovascular risk in the INTERHEART study due to confounding by related variables?	10 Dec 2013
9.	Clinical effectiveness study	Sniderman AD, Lamarche B, Contois JH, de Graaf J. Discordance analysis and the Gordian Knot of LDL and non-HDL cholesterol versus apoB. Curr Opin Lipidol 2014; 25: 461-467.	A study using discordance analysis demonstrating that cardiovascular risk is more closely related to the number of atherogenic particles than to the total mass of cholesterol within them.	Discordance analysis and the Gordian Knot of LDL and non-HDL cholesterol versus apoB	24 Oct 2014
10.	Clinical effectiveness study	Sniderman AD, Pencina M, Thanassoulis G. Limitations in the conventional assessment of the incremental value of predictors of cardiovascular risk. Curr Opin Lipidol 2015; 26: 210-214.	Study demonstrating that for correlated predictors describing different aspects of the same variable such as non-HDL-C and apoB or LDL-C and LDL particle number, discordance analysis offers a simple valid alternative to capture and compare the	Limitations in the conventional assessment of the incremental value of predictors of cardiovascular risk.	19 Apr 2015

			independent information contained by each predictor.		
11.	Evidence-based analysis	Sniderman AD, Toth PP, Thanassoulis G, Furberg CD. An evidence-based analysis of the National Lipid Association recommending non-HDL-C and apoB. J Clin Lipidol 2016; 10: 1248-1258.	An evidence-based analysis of the National Lipid Association recommendations concerning non-HDL-C and apoB indicating that apoB is a more accurate marker of cardiovascular risk than non-HDL-C and lipid management would be improved by inclusion of apoB along with lipoprotein lipids in routine clinical care.	An evidence-based analysis of the National Lipid Association recommendations concerning non-HDL-C and apoB.	30 Sep 2016
12.	Meta-analysis	Thanassoulis G, Williams K, Ye K, et al. Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials. J Am Heart Assoc 2014; 3: e000759 doi: 10.1161/JAHA.113.000759.	Meta-analysis using both a frequentist and Bayesian approach, demonstrated relative risk reduction across seven major placebo-controlled statin trials was more closely related to reductions in apoB than to reductions in either non-HDL-C or LDL-C.	Relations of Change in Plasma Levels of LDL-C, Non-HDL-C and apoB With Risk Reduction From Statin Therapy: A Meta-Analysis of Randomized Trials.	16 Apr 2014
13.	Clinical effectiveness study	Sniderman AD, Islam S, McQueen M, et al. Age and cardiovascular risk attributable to apolipoprotein B, low-density lipoprotein cholesterol or non-high-density lipoprotein cholesterol. J Am Heart Assoc 2016; 5: e003665 doi: 10.1161/JAHA.116.003665.	Results from the INTERHEART Study (t different ages in 11,760 controls and 8,998 myocardial infarction cases) demonstrating that the risk of cardiovascular events associated with apoB particles is greater in younger compared to older individuals; consistent with greater relative benefit from LDL-lowering therapy in younger compared to older individuals and supports use of therapy in younger individuals with elevated lipids.	Age and Cardiovascular Risk Attributable to Apolipoprotein B, Low-Density Lipoprotein Cholesterol or Non-High-Density Lipoprotein Cholesterol	16 Oct 2016
14.	Clinical effectiveness study	Wilkins JT, Li RC, Sniderman A, et al. Discordance between apolipoprotein B and LDL-cholesterol in young adults predicts coronary artery calcification. J Am Coll Cardiol 2016; 67: 193-201.	Results from the CARDIA Study of 2,794 participants (mean age: 25 +/- 3.6 years); with complete baseline cardiovascular disease (CVD) risk factor data, including apoB and year 25 (Y25) coronary artery calcium (CAC) score. Compared with the lowest apoB tertile, higher odds of developing Y25 CAC were seen in the middle and high tertiles. High apoB and low	Discordance Between Apolipoprotein B and LDL-Cholesterol in Young Adults Predicts Coronary Artery Calcification: The CARDIA Study.	

LDL-C or non-HDL-C discordance was associated with Y25 CAC in adjusted models demonstrating a dose-response association between apoB in young adults and the presence of midlife CAC independent of baseline traditional CVD risk factors.

- | | | | | | |
|-----|-----------------------|--|--|--|-------------|
| 15. | Meta-analysis | Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. <i>Circ Cardiovasc Qual Outcomes</i> 2011; 4: 337-345 | This conventional meta-analysis demonstrates a hierarchy of risk among the markers with apoB > non-HDL-C > LDL-C. Accordingly, it supports much previous work that indicated apoB and non-HDL-C were superior to LDL-C. | A Meta-Analysis of Low-Density Lipoprotein Cholesterol, Non-High-Density Lipoprotein Cholesterol, and Apolipoprotein B as Markers of Cardiovascular Risk | 14 Apr 2011 |
| 16. | Case-controlled study | Sniderman AD, Hogue J-C, Bergeron J, et al. Non-HDL cholesterol and apoB in dyslipidaemia. <i>Clin Sci</i> 2008; 114: 149-155. | A study of 1771 patients in a lipid clinic examining variance of non-HDL-C in comparison with apoB. The results indicated that there is substantial variance of apoB for given values of non-HDL-C in many dyslipidaemic patients. | Non-HDL cholesterol and apoB in dyslipidaemia | 2008 |

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.	For yet to be published research that may have results relevant to your application, insert the type of study design in this column and columns below	For yet to be published research that may have results relevant to your application, insert the title of research (including any trial identifier if relevant) in this column and columns below	For yet to be published research that may have results relevant to your application, insert a short description of research (max 50 words) in this column and columns below	For yet to be published research that may have results relevant to your application, insert a website link to this research (if available) in this column and columns below	For yet to be published research that may have results relevant to your application, insert date in this column and columns below
2.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
3.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
4.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
5.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
6.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
7.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
8.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
9.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date

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):**

The Royal College of Pathologists of Australasia (RCPA)

- 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 the comparator services, so no others would be impacted by the medical service. However, these organisations may be relevant to the proposed medical service: Pathology Australia, Public Pathology Australia, Australasian Association of Clinical Biochemists.

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

Australian Atherosclerosis Society, Cardiac Society of Australia and New Zealand, Endocrine Society of Australia and National Heart Foundation

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

Not applicable

- 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

Justification of expertise: Redacted

Name of expert 2: Redacted

Telephone number(s): Redacted

Email address: Redacted

Justification of expertise: 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), INDICATION, 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:

CVD encompasses four major areas including coronary heart disease, cerebrovascular disease, peripheral artery disease and aortic atherosclerosis, thoracic or aortic aneurysms. CVD is common in the general population with a lifetime risk approaching 50% in persons aged 30 y without known CVD. In 2012 and 2013, CVD was estimated to result in 17.3 million deaths worldwide on an annual basis. Coronary heart disease accounts for one third to one half of the total cases of CVD.

Clinical risk factors include high blood pressure, high cholesterol, overweight and obesity, physical inactivity, low fruit and vegetable intake, alcohol and smoking. Nine in 10 adult Australians have at least one risk factor for CVD and one in four (25%) have three or more risk factors.

Despite increases in longevity and decreases in age-specific death rates from CVD, chronic heart disease (CHD), and stroke since 1975, CVD and its related complications remain highly prevalent. In one cohort of over 1.9 million persons aged 30 years or older free of known baseline CVD who were followed for a median of six years, the majority of initial CVD presentations were neither myocardial infarction nor stroke. These presentations, which included angina, heart failure, peripheral arterial disease, transient ischemic attack, and abdominal aortic aneurysm, along with some less common manifestations, represented 66% of the initial CVD presentations.

While CVD remains the leading cause of death in most developed countries, mortality from acute myocardial infarction (MI) has decreased by up to 50 percent since the 1990s. Among 49 countries in Europe and northern Asia, over 4 million persons die annually from CHD. In the United States, approximately 1.5 million persons suffer a heart attack or stroke annually, resulting in over 250,000 deaths. In Australia, CVD was the main cause for 480,548 hospitalisations in 2013/14 and played an additional role in another 680,000 hospitalisations. It affects 4.2 million Australians and claimed an estimated 45,392 Australians (nearly 30% of all deaths) in 2015 - deaths thought largely preventable.

Many risk factors for CVD are modifiable by preventive measures. In the worldwide INTERHEART study of patients from 52 countries, nine modifiable factors accounted for over 90 percent of the population-attributable risk of a first myocardial infarction MI: smoking, dyslipidaemia, hypertension, diabetes, abdominal obesity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol consumption, and regular physical activity.

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:

Measurement of apoB would be relevant in patients who are mild-moderately hypertriglyceridaemic owing to mixed hyperlipidaemia or as an isolated abnormality. This encompasses patients with metabolic syndrome, obesity, type 2 diabetes, chronic kidney disease, and familial hyperapoB.

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):

A lipid profile would typically be undertaken as part of routine biochemical testing for cardiovascular risk assessment. This testing would include measurement of total cholesterol, HDL-cholesterol, triglyceride,

calculated LDL-cholesterol (using the Friedewald equation), along with calculation of non-HDL-cholesterol.

In normolipidaemic patients and those with type IIa and IIb hyperlipoproteinaemia there is high correlation between non-HDL-cholesterol and apoB as VLDL constitutes only a small minority of the apoB-containing particles. However, marked variance between apoB and non-HDL-cholesterol is found in type I (chylomicronaemia), III (dysbetalipoproteinaemia), and V (chylomicronaemia and excess VLDL) hyperlipoproteinaemia, where the number of LDL particles is typically low. Moreover, the correlation between non-HDL-cholesterol and apoB is low in type IV hyperlipoproteinaemia, a heterogeneous disorder, in those with moderate hypertriglyceridaemia (≥ 3 mmol/L) when compared with mild hypertriglyceridaemia (< 3 mmol/L).

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

ApoB testing requires a venepuncture to be performed on the patient for the collection of a blood sample that is referred to a pathology laboratory for biochemical analysis.

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

Various immunoassays are available for apoB testing using similar scientific principles and no single commercial or trademark product is endorsed in this application.

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?

Not applicable

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):

The medical service would be limited to patients with conditions associated with the presence of small dense LDL and hyperapoB, rare genetic hypocholesterolaemic disorders (e.g. familial hypobetalipoproteinaemia and abetalipoproteinaemia), and in patients with cholestatic liver disease where there is the presence of the abnormal lipoprotein X.

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

Not applicable

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

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

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

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

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

Testing would be delivered only by Approved Pathology Practitioners in 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.

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 Approved Pathology Practitioners in Accredited Pathology Laboratories (as defined in MBS Pathology table).

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):

- Inpatient private hospital
- Inpatient public hospital
- Outpatient clinic
- Emergency Department
- Consulting rooms
- Day surgery centre
- 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:

Not applicable

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

- Yes
- No – please specify below

Specify further details here

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):**

The comparator for apoB is non-HDL-cholesterol, which can be calculated by subtracting HDL-cholesterol from total cholesterol at no additional expense beyond the standard lipid panel.

Non-HDL-cholesterol is superior to LDL-cholesterol in assessing CVD risk, because it better estimates the LDL particle number. In terms of analytical error, non-HDL-cholesterol involves two measurements. Total cholesterol is relatively well standardised, and assays are precise. However, direct HDL-cholesterol assays are problematic, and bias and imprecision are likely to impact the clinical accuracy of non-HDL-cholesterol calculation.

Although apoB and non-HDL-cholesterol are highly correlated, they measure different entities. Non-HDL-cholesterol is not equivalent to apoB as a marker of cardiovascular risk. If apoB is high, but non-HDL-cholesterol is normal, cardiovascular risk is high. If non-HDL-cholesterol is high, but apoB is normal, cardiovascular risk is not high. Approximately 1 in 6 individuals would have clinically significant discordance between these measures.

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

- Yes (please provide all relevant MBS item numbers below)
 No

66500 Total cholesterol; 66536 Quantitation of HDL cholesterol

- 40. Define and summarise the current clinical management pathways 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):**

The clinical management pathway after the comparator (non-HDL-cholesterol calculated by subtracting HDL-cholesterol from total cholesterol) would include lifestyle measures to address known CVD risk factors which would include cessation of smoking, control of blood pressure, diet modification, decreased alcohol intake, increasing physical activity along with weight loss, together with appropriate lipid-lowering therapy. ApoB testing would be indicated in patients who were found to have mild-moderate hypertriglyceridaemia (≥ 3 and < 10 mmol/L), consistent with the presence of atherogenic small dense LDL particles. It is also helpful in the diagnosis of rare genetic hypocholesterolaemic disorders (e.g. familial hypobetalipoproteinaemia and abetalipoproteinaemia), and in patients with cholestatic liver disease, where there is the presence of the abnormal lipoprotein X.

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

- Yes
 No

- (b) If yes, please outline the extent of which the current service/comparator is expected to be substituted:**

It is expected that 5-10% of patients identified by the presence of mild-moderately elevated triglyceride levels (≥ 3 mmol/L) would progress to apoB for more precise cardiovascular risk assessment.

- 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):**

Currently patients assessed as having high non-HDL-cholesterol are advised on lifestyle adjustments measures and offered therapies for prevention to reduce CVD risk.

ApoB testing will more accurately identify patients with hyperapoB than current non-HDL-cholesterol evaluation and allow for more targeted medical advice and therapy. It is valuable in distinguishing patients who may be managed with advice on lifestyle factors in the first instance from those requiring immediate lipid-lowering therapy.

ApoB measurement will be a useful diagnostic tool should there be a suspicion of the presence of lipoprotein X, an abnormal lipoprotein that occurs in cholestatic liver disease.

ApoB testing will allow for appropriate treatment of patients with genetic hypocholesterolaemic lipid disorders (e.g. familial hypobetalipoproteinaemia and abetalipoproteinaemia), where apoB levels are very low or absent, and where appropriate treatments such as supplementation with fat soluble vitamins are required.

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):

ApoB testing is clinically superior when compared to non-HDL-cholesterol. The benefits relate to the ability of apoB to more accurately identify patients with hyperapoB, diagnosing genetic hypocholesterolaemic lipid disorders, and should there be a suspicion of the presence of lipoprotein X, an abnormal lipoprotein that occurs in cholestatic liver disease than non-HDL-cholesterol, which allows for more targeted medical advice and therapy, thereby reducing the morbidity and mortality associated with CVD.

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:

Equivalent (non-inferior) safety to other blood tests for Total cholesterol and HDL-cholesterol
Superior safety for assessment of high CVD risk
Superior safety for assessment of other dyslipidaemias.

Clinical Effectiveness Outcomes:

Quantitative testing rather than qualitative evaluation of hyperapoB
Identifies patients that otherwise might not receive therapy
Prevention of coronary events
Prevention of poor health outcomes of other dyslipidaemias

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

170,000

Hypertriglyceridaemia in adults is estimated to be present in 14% of adult Australians i.e. approx. 2.5 million people.

In 2011–12, 13.9% of people aged 18 years and over had high triglyceride levels (TG \geq 2 mmol/L). High triglycerides were more common among men (19.0%) than women (9.0%). The proportion of people with high triglycerides steadily increased with age until middle adulthood, before gradually declining in older age. Overall, rates were highest among those aged 45–54 years (18.5%) (ABS).

MBS item number statistics indicate that last year 1.7 million Australians were tested for HDL-cholesterol (MBS 66536) and 800,000 for triglycerides/total cholesterol (MBS 66500). It is estimated that 5-10% would need apoB testing. It is recognised that MBS statistics do not capture all triglycerides/total cholesterol test numbers due to coning or aggregation into a group of tests. However, based on the current HDL-cholesterol statistics, the upper limit estimation would suggest a population of approximately 170,000 for apoB testing.

**Source: Australian Bureau of Statistics and Medicare Statistics.*

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

Once

On average patients are tested and follow up could be managed with Total cholesterol/triglycerides and/or HDL-cholesterol testing. Occasional retesting of apoB may be required.

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

One

On average patients are tested once, but occasional re-testing may be required.

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

170,000

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:

Uptake in the next three years could result in all of the at-risk population using the test in diagnosis. This could be projected at 10% of 2.5 million patients with hypertriglyceridaemia i.e. 250,000.

Leakage to populations not targeted by the service would be restricted by the item descriptor.

PART 8 – COST INFORMATION

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

ApoB testing is likely to cost \$15 to perform

Equipment and resources	Per test
Kit, probes, reagents, ancillary reagents	4.00
Labour medical (consultant pathologist)	2.00
Labour scientific	3.00
Labour on costs	2.00
Depreciation, overheads	1.00
Admin, IT	3.00
Total	\$15.00

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

On arrival in lab, less than 24 h

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.

Cost (\$15 plus \$2 margin)

Category (proposed category number) – (proposed category description)
<p>Proposed item descriptor</p> <p>Quantitation of apoB in patients with Triglycerides ≥ 3 mmol/L AND < 10 mmol/L4 OR Total cholesterol > 7.5 mmol/L AND clinical evidence of cholestatic liver disease</p> <p>Fee: \$17</p>

PART 9 – FEEDBACK

The Department is interested in your feedback.

54. How long did it take to complete the Application Form?

4 hours

55. (a) Was the Application Form clear and easy to complete?

- Yes
 No

(b) If no, provide areas of concern:

There is no orderly flow of some questions.

As examples:

Responses to Q9 could be re-stated as:

- Pharmaceutical / Biological (**Go to Q10**)
 Prosthesis or device (**Go to Q11**)
 No (**Go to Q12**)

Q15 is written as if it is a new question and should be answered when this is related to Q14(b). It could be re-numbered as 14(c).

56. (a) Are the associated Guidelines to the Application Form useful?

- Yes
 No

(b) If no, what areas did you find not to be useful?

Insert feedback here

57. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

- Yes
 No

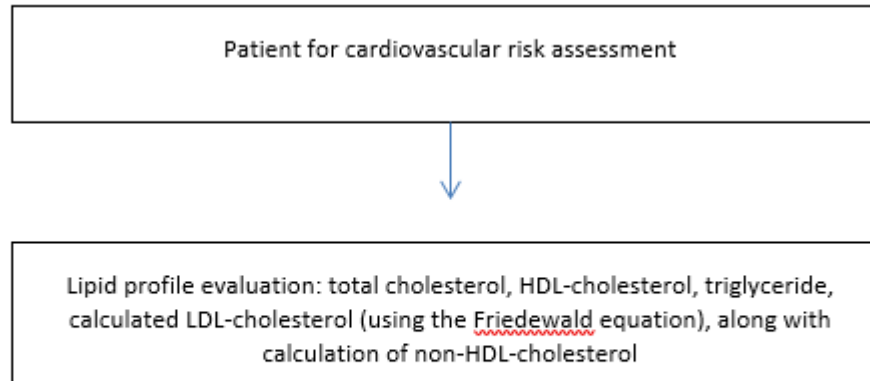
(b) If yes, please advise:

The form could be better tailored for Pathology items that are not technology-specific (i.e. not a single TGA product) and already have established rules in the MBS (Approved Pathology Practitioners; accredited laboratories; referrals by registered medical practitioners).

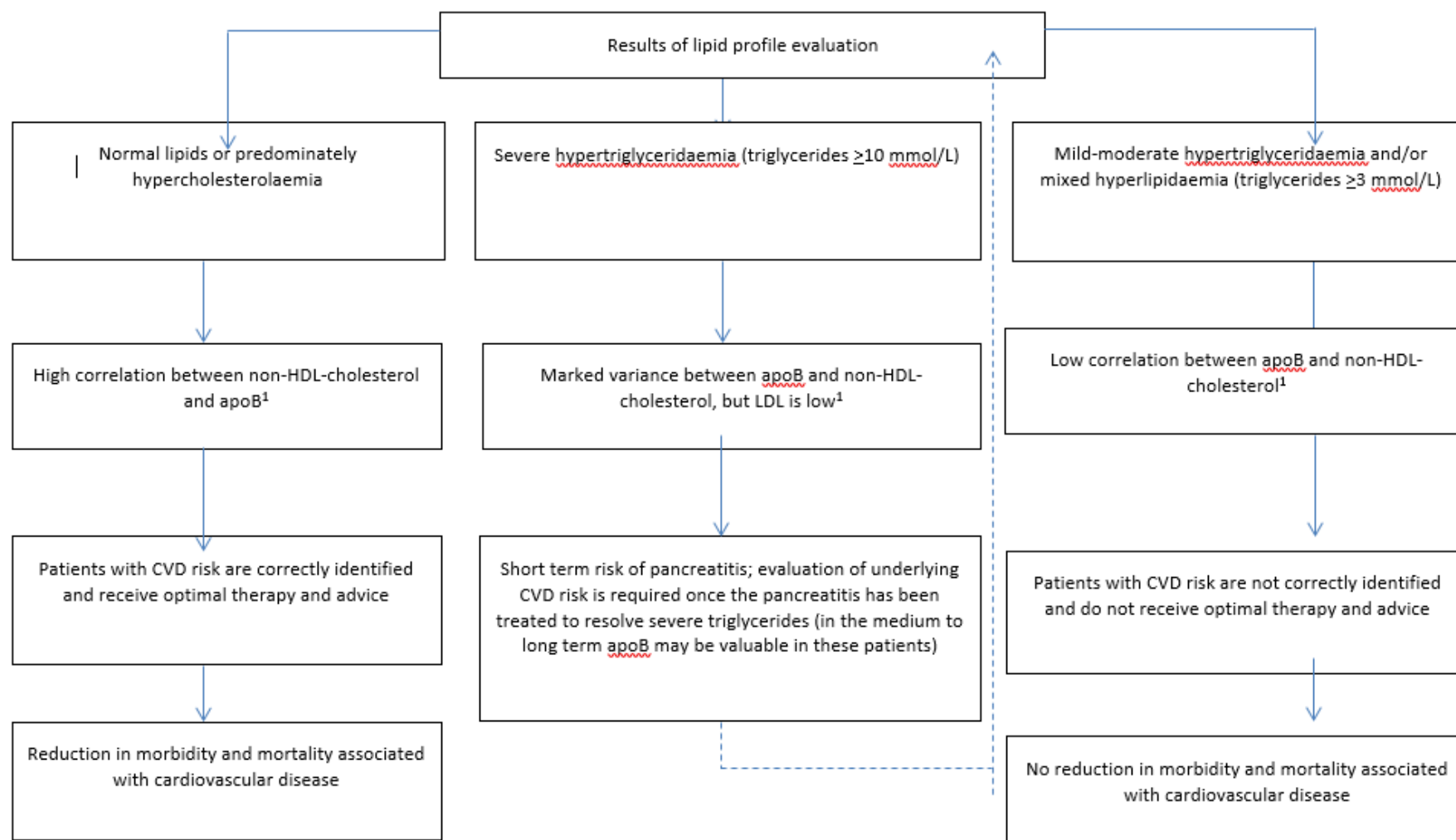
MSAC Application for Apolipoprotein B testing

Flowcharts

Q26 Clinical pathway before intervention



Q40 Clinical pathway after comparator (without apoB testing)



1. Sniderman Allan D, Hogue J-C, Bergeron J, et al. Non-HDL cholesterol and apoB in dyslipidaemia. [Clin Sci. 2008; 114: 149-155.](#)