Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1512 – Apolipoprotein B testing for high risk cardiovascular disease risk assessment

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

Date of MSAC consideration: MSAC 77th Meeting, 28-29 November 2019

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of Apolipoprotein B (apoB) testing for high risk cardiovascular disease (CVD) risk assessment was received from the RCPA by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support the public funding of apolipoprotein B (apoB) testing for high-risk cardiovascular disease risk assessment on the basis that there was insufficient evidence for comparative effectiveness, safety and cost-effectiveness in the proposed populations. In addition, MSAC noted that the population who could benefit from apoB testing is potentially large, creating a potential leakage issue if there is utilisation outside the intent of the proposed MBS item.

Consumer summary

The Royal College of Pathologists of Australasia applied for public funding through the Medicare Benefits Schedule (MBS) for apolipoprotein B (apoB) testing. ApoB testing is intended to help a doctor and patient work out a person's risk of cardiovascular disease (CVD) – disease of the heart or blood vessels. It is important to know if someone is at high risk of CVD so that they can get the most appropriate treatment. Treatment might include medicines to lower a person's cholesterol levels (called lipid-lowering therapy) such as statins. It is also important to know which people do not need these medicines.

At the moment, doctors use several tests and calculations to work out a person's risk of getting CVD. These include lipid tests, which give information about a person's level of triglycerides and cholesterol (types of fat); HDL cholesterol (sometimes called the 'good cholesterol'); LDL cholesterol (sometimes called the 'bad cholesterol'); and non-HDL cholesterol (total cholesterol minus HDL cholesterol).

The application was for funding to use apoB testing in people with abnormal lipid test results who were not already using lipid-lowering medicines.

Some studies show that apoB might be more accurate than other lipid tests to predict the risk of CVD in some people. However, MSAC considered that there was not enough evidence to know exactly which people would benefit from having apoB testing, or whether a person's treatment would change based on their apoB level, and therefore whether it would be of health and financial benefit to consumers.

ApoB testing is performed on a blood sample so it is just as safe as other lipid tests. However, there was no information about the safety of changing people's treatment after an apoB test.

MSAC was also concerned that the financial impact might be more than the applicant estimated because more people than the applicant predicted might have the test.

MSAC's advice to the Commonwealth Minister for Health

MSAC did not support public funding for apoB testing to assess CVD risk because there was not enough evidence to show that it would help to distinguish between people who needed lipid-lowering medications and those who didn't, and whether there would be any benefit for consumers. The cost-effectiveness of apoB testing was also uncertain.

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

This application sought public funding of apoB testing to assess CVD risk in two populations of patients with dyslipidaemia who are currently not receiving lipid-lowering therapy. Correctly identified high-risk patients would receive appropriate pharmacotherapy, while pharmacotherapy could be avoided in patients correctly identified as being at only moderate or low risk.

MSAC noted that, in broader populations (that include patients already on lipid-lowering therapy), apoB provides a more direct measure of circulating atherogenic lipoproteins than low-density lipoprotein cholesterol (LDL-C). MSAC also noted that some studies (though not all) showed that apoB may be a slightly better predictor of risk than non-high-density lipoprotein cholesterol (non-HDL-C). However, MSAC considered that the proposed populations in this application are too restrictive and misaligned with populations typically recruited for clinical studies, resulting in limited evidence to support the clinical claims put forward in the application.

MSAC noted the proposed fee of $15 is higher than similar MBS items such as MBS item 66500 (quantitation of total cholesterol; $9.70) and MBS item 66536 (quantitation of HDL cholesterol; $11.05). As well as having a higher fee than existing items, the proposed item will be requested in addition to existing lipid profile evaluation items (MBS items 66500, 66503, and 66536) and represents an increased cost to the MBS.

MSAC noted that, although there are no additional safety issues associated with the use of apoB testing compared with current lipid testing (including non-HDL-C testing), the clinical safety of resultant changes in treatment (e.g. beginning or ceasing lipid-lowering therapy) has not been considered. MSAC considered that change in management from additional apoB testing would be most likely in patients at moderate absolute CV risk. However, MSAC noted that there are no guidelines to inform changes in treatment based on apoB levels.

MSAC considered that the clinical validity of apoB *vs*. non-HDL-C in the requested populations is uncertain. No direct evidence was identified for population 1, and linked evidence showing the prognostic value of apoB to be similar to non-HDL-C was of low quality. MSAC noted that the included studies were in patients already receiving lipid-lowering therapies and were not directly assessing the prognostic value of apoB (information about apoB was extracted from studies on triglycerides). MSAC also noted that the baseline apoB levels in the included studies were lower than the levels considered 'abnormal' in Australian practice.

MSAC considered that the clinical utility of apoB *vs.* non-HDL-C is uncertain. No evidence of clinical utility, therapeutic efficacy or therapeutic effectiveness was identified for population 1. MSAC noted that no studies of clinical validity or clinical utility were identified for population 2.

MSAC therefore considered that the application presented insufficient evidence for clinical effectiveness of apoB testing. However, MSAC considered the literature search included in the application to be too restrictive, in particular the decision to only include studies from 2008 onwards. MSAC also noted that broadening the literature search, including broader patient populations, could have provided linked evidence from large prospective cohort studies providing evidence of comparative diagnostic performance (e.g. the Framingham Offspring Cohort study [1972], the Women's Health Study [2005], and the meta-analysis by Thanassoulis et al. [2014], which demonstrated that relative risk reduction from statin therapy was more closely related to reductions in apoB than to reductions in either LDL-C or non-HDL-C. However, MSAC noted, that these studies do not provide any further evidence of clinical validity or clinical utility in the proposed populations.

MSAC noted data presented in the applicant's pre-MSAC response from Welsh et al. (2019), a UK Biobank study of 502,639 participants (aged 37–73 years) who were recruited throughout the United Kingdom and followed up for six years. This study concluded that, in the general population, there was no meaningful improvement from the addition of apoB. However, among the subset of participants who were discordant with respect to apoB and LDL-C (n=63,520), only apoB was significantly associated with increased CVD risk (noting that this was a *post hoc* analysis). MSAC noted that apoB testing has potential value in this group of patients, but a new clinical management algorithm is needed to identify these patients.

MSAC considered that the economic evaluation presented was not informative, because of the limited clinical data available and lack of evidence regarding changes to management.

MSAC noted that the estimated financial impact was driven by an assumption that following routine lipid testing, approximately 10% of patients with mild to moderately elevated triglyceride concentrations would progress to apoB testing for a more precise CVD risk assessment, following routine lipid testing. However, MSAC noted that, based on the study by Welsh *et al.* (2019) and others, the proportion of patients progressing to apoB testing is more likely to be 15–20%. In addition, MSAC noted that an editorial discussing the Welsh et al. Biobank study stated that, because participants in the Biobank were volunteers and probably healthier than the general population, the proportion of patients with discordant results may be as high as 20–25%. Overall, MSAC considered that the financial estimates were uncertain, because the population who could potentially benefit is quite large, with a high risk of utilisation beyond the intent of the proposed MBS item.

MSAC also considered the restriction to once per lifetime testing to be inappropriate. MSAC noted that the applicant maintains that identifying previously low-risk untreated patients would require once in a lifetime apoB testing. However, MSAC considered that repeat testing over time may be required to reassess risk, whether or not the patient is being treated with lipid-lowering therapy.

MSAC acknowledged the applicant's advice in their pre-MSAC response that the European Society of Cardiology and European Atherosclerosis Society guidelines state that apoB analysis is recommended for risk assessment, particularly in people with high triglycerides; diabetes mellitus type 2, obesity or metabolic syndrome; or very low LDL-C.

However, MSAC also considered that while apoB may be a better predictor of CVD risk, it would be difficult and costly to re-engineer current models of risk prediction and care to change from LDL-C (or non-HDL-C) to apoB.

MSAC concluded that any future application should:

- identify markers/characteristics (e.g. triglycerides, obesity, diabetes) to define patients where apoB testing provides independent risk prediction beyond total and HDL cholesterol (e.g. from the UK Biobank study) and confirm these in an independent cohort
- limit the population to subjects at moderate absolute CVD risk based on traditional risk factors (the group in which change in management is most likely)
- include a better-defined clinical algorithm to identify the target population to benefit from apoB testing
- identify new and higher-level evidence to determine and support the clinical validity and clinical utility of apoB testing; and
- undertake an economic evaluation using a linked evidence approach.

4. Background

MSAC has not previously considered apoB testing for the assessment of high risk CVD risk assessment**.**

Currently apoB testing is not funded or reimbursed in the private or public setting in Australia for any clinical indication.

5. Prerequisites to implementation of any funding advice

ApoB concentrations can be measured via immunoassay conducted by approved pathology practitioners in National Association of Testing Authorities (NATA) accredited laboratories.

The applicant claims that apoB can be measured by automated, readily available commercial immunoassays currently used in clinical laboratories.

The National Pathology Accreditation Advisory Council (NPAAC) advised MSAC that the test is well established with an external quality assurance program (EQA) available.

6. Proposal for public funding

The proposed MBS item descriptor, updated at ESC, is presented in Table 1. The fee includes the equipment and resources associated with conducting the apoB immunoassay.

Table 1 Proposed MBS item descriptor, updated with ESC proposed amendments (in red)

Category 6 – Pathology Services
Item 6650X Quantitation of apoB in patients with: (a) triglycerides ≥3 mmol/L AND <10 mmol/L; OR (b) total cholesterol >7.5 mmol/L AND clinical evidence of cholestatic liver disease where there is the possibility of the presence of the abnormal lipoprotein X. ~~One test per lifetime~~ Fee: $15, Benefit 75% = $11.25 (in-hospital / admitted patient), 85% = $12.75 (out-of-hospital / outpatient)

This application seeks to limit the population to be tested for apoB to two dyslipidaemic groups:

- Population one: Patients with "moderate hypercholesterolaemia" defined as having triglycerides greater than, or equal to 3 mmol/L and less than 10 mmol/L (i.e. 266 to 885 mg/dL); or
- Population two: Patients with hypercholesterolaemia and cholestasis defined as having total cholesterol of greater than 7.5 mmol/L (i.e. more than 290 mg/dL) and cholestatic liver disease where there is the possibility of the presence of the abnormal lipoprotein X.

The Critique stated that the contracted assessment (CA) provided little justification or explanation of clinical need for apoB testing in the requested populations. It was also unclear if the proposed populations consist of patients who are not receiving lipid-lowering therapy, or who are already on-treatment (or both).

In the pre-MSAC response, the applicant clarified that apoB testing is intended to assess CVD risk in patients who are currently not receiving lipid-lowering therapy. The applicant highlighted that the following recommendation for lipid analyses for CVD risk estimation from the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias should be noted:

"ApoB should be considered as an alternative risk marker whenever available, especially in individuals with high TG: ApoB analysis is recommended for risk assessment, particularly in people with high TG, DM2, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG, DM, obesity, or very low LDL-C."(ESC & EAS 2019; Mach et al. 2019).

7. Summary of public consultation feedback/consumer Issues

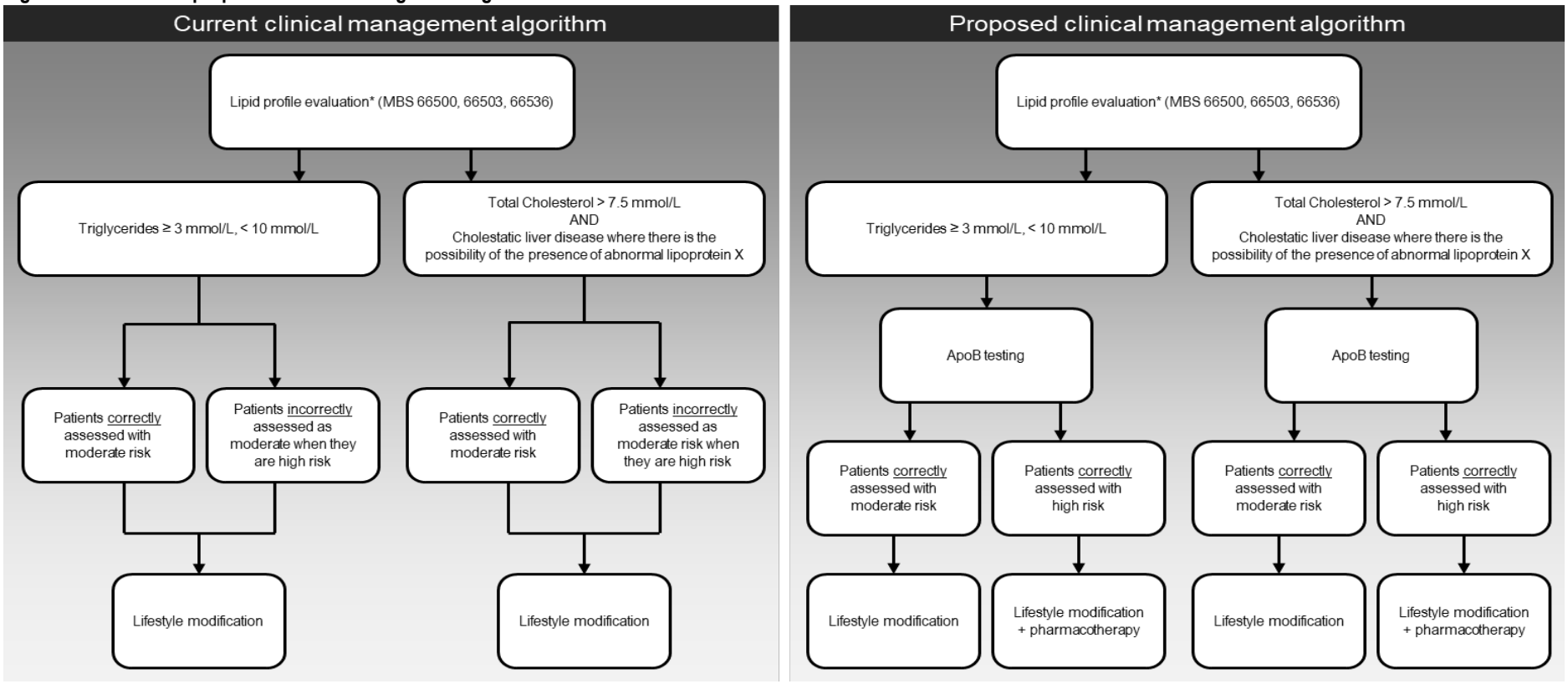
Three organisations and one specialist provided positive feedback in support of this application.

8. Proposed intervention's place in clinical management

The proposed test is an *ex vivo* quantitation of apoB in serum or plasma (from blood).

The clinical management algorithm proposed in both the CA and the PICO Confirmation is presented in Figure 1. ApoB testing will occur in addition to routine lipid profiling including non-high-density lipoprotein cholesterol (non-HDL-C).

Figure 1 Current and proposed clinical management algorithms.



*This includes testing for triglycerides, total cholesterol, HDL-C, and non-HDL-C via calculation

9. Comparator

The CA stated that the comparator for apoB testing is non-HDL-C testing, i.e. calculation of non-HDL-C serum concentrations by subtracting HDL-C from total cholesterol. Non-HDL-C concentrations are used as a measure of risk for development of cardiovascular disease, in addition to other lipid profile indicators. The Critique stated it would be more accurate to say that the main comparator is standard care, consisting of no further lipid evaluation as apoB testing is performed in addition to routine lipid profile evaluation (including LDL-C, non-HDL-C and total cholesterol).

The relevant MBS item numbers were considered in the CA to be 66536 and 66503. MBS item 66500 was considered to not be relevant, as it only applies to a single test for one of 29 available blood markers.

10. Comparative safety

Three studies were identified from the systematic literature search. All three studies met the search criteria for apoB testing of Population 1. No studies were identified for Population 2.

Test adverse events
ApoB testing is proposed for blood specimens already collected from dyslipidaemic patients. No additional venepuncture nor changes to blood collection protocols are required for the purpose of the proposed index test. Potential harms associated with apoB testing are therefore non-inferior to current lipid pathology practice. This applies to both proposed target Populations 1 and 2.

Adverse events from change in management
Intermittent apoB testing for patient monitoring purposes is out of scope of this CA as the applicant recommended a once-in-a-lifetime test frequency. Potential harms associated with apoB testing for target Populations 1 and 2 are assumed to be non-inferior to current lipid pathology practices, including non-HDL-C.

The Critique stated that MSAC may wish to consider if apoB testing could be associated with risks to the patient following a reallocation of therapy (e.g. treatment inappropriately prescribed or withheld).

11. Comparative effectiveness

No direct evidence was identified from the systematic literature search. Evidence was only provided assessing prognostic value of apoB testing in population 1 (Table 2). No clinical evidence was identified for Population 2.

Table 2 Summary of findings for the linked evidence comparison of apoB testing, relative to non-HDL-C testing, in dyslipidaemic patients with assumed pre-test CVD probability (prevalence) of 16-74% in Population 1

	Participants	Quality of evidence[a]	Findings for index test	Findings for comparator	Importance
Accuracy	No evidence identified				
Prognostic value	Patients receiving lipid-lowering drugs; N = 8,647	⊕⊙⊙⊙	Having apoB concentrations between 82.3 to 83.5 mg/dL poses a high risk (17.2 - 22% likelihood) of CVD outcomes within 5 years	Having non-HDL-C concentrations between 118.2 to 119.6 mg/dL poses a high risk (17.2 - 22% likelihood) of CVD outcomes within 5 years	Prognostic value of apoB is identical to non-HDL-C. Poor quality data and lack of evidence linkages point to critical uncertainties with the clinical validity of apoB testing when compared against non-HDL-C testing.
Impact on clinical management	No evidence identified				

[a] GRADE Working Group grades of evidence (Guyatt et al., 2013)
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Clinical claim

On the basis of the benefits and harms reported in the evidence base (summarised above), it is suggested that, relative to non-HDL-C testing, the proposed apoB testing service has assumed non-inferior safety and uncertain clinical effectiveness. However, the Critique stated that this was based on incomplete review of the clinical literature. Specifically, the studies identified in the review were of poor quality, and the statistical methods were not appropriate for the assessment of prognostic accuracy.

In the pre-MSAC response, the applicant agreed with the Critique that the clinical claim was based on an incomplete review of the literature. The applicant highlighted a UK study by Welsh et al. 2019 (n=502,639) with six years follow-up, which indicated that for a subset of participants who were discordant with respect to apoB and LDL-C (n=63,520), only apoB was significantly associated with increased CVD risk. Based on these results apoB is more suitable for untreated risk assessment, which will probably occur more than once in a person's lifetime, whilst non-HDL-C measurements may suffice during routine patient management. The applicant stated this addressed the concerns raised by ESC in terms of the financial impact of the item number and the potential for leakage.

12. Economic evaluation

A cost-consequence analysis was conducted despite the issues with the clinical evidence. A summary of the key characteristics of the economic evaluation is given in Table 3.

Table 3 Summary of the economic evaluation

Perspective	Direct health care costs
Comparator	Lipid profile evaluation using non-HDL cholesterol
Type of economic evaluation	Cost-consequences
Sources of evidence	Systematic review, proposed MBS item descriptor
Time horizon	NA, the model duration is only until test results are available (i.e. <1 year)
Outcomes	Number of patients with apoB results
Methods used to generate results	Decision tree
Discount rate	None, time horizon is <1 year
Software packages used	Microsoft Excel 2016

This analysis showed that the funding of apoB would result in a cost of $15 per apoB test result. The CA stated that the impact of a known apoB value on risk stratification and subsequent treatment and health-related quality of life is unknown. The Critique stated that notwithstanding limitations in the quality of the evidence identified in the CA, a cost-consequence model to determine the cost per additional apoB test performed is not a relevant or useful approach to estimating the value provided by apoB testing.

13. Financial/budgetary impacts

The financial implications to the MBS (inclusive of safety net implications) resulting from the proposed listing of apoB testing for high-risk cardiovascular disease risk assessment are summarised in Table 4. The financial estimates were based on the assumption that 10% of patients with mild to moderately elevated triglyceride concentrations would progress to apoB testing for more precise cardiovascular risk assessment. This was based on the 5-10% estimate provided by the College in the application, which was based on the restrictive definition of the at-risk population, which were put in place to reduce/prevent leakage. The Critique also included financial estimates of apoB testing where it assumed 50% of patients would receive an additional general practitioner consultation (MBS item 23) for those who would receive apoB testing after HDL-C testing.

Table 4 Total costs to the MBS associated with apoB testing for high-risk cardiovascular disease risk assessment

	2019	2020	2021	2022	2023
Cost to MBS due to increase in apoB testing					
Number of services (population 1)	83,797	84,072	84,347	84,622	84,898
Sub-total cost (population 1)	$1,068,414	$1,071,921	$1,075,428	$1,078,936	$1,082,447
Number of services (population 2)	738	750	763	775	787
Sub-total cost (population 2)	$9,408	$9,567	$9,725	$9,882	$10,038
Number of services (overall)[a]	84,535	84,823	85,110	85,398	85,685
Sub-total cost (overall)	$1,077,822	$1,081,488	$1,085,153	$1,088,819	$1,092,484
Reduction in cost to MBS due to reductions in other services					
Sub-total cost	$0	$0	$0	$0	$0
Total cost (without GP consult)	$1,077,822	$1,081,488	$1,085,153	$1,088,819	$1,092,484
Critique's values					
Total cost (with 50% GP consult)[b]	**$2,692,442**	**$2,701,599**	**$2,710,755**	**$2,719,912**	**$2,729,069**
CA Rejoinder's values					
Total cost (with 100% GP consult)[b]	**$4,307,059**	**$4,321,720**	**$4,336,355**	**$4,351,016**	**$4,365,652**

[a] *Based on assumption that 10% of patients would receive apoB testing (Applicant stated 5-10%)*
[b] *Assumption*

In the pre-MSAC response, the applicant stated that based on Welsh et al., the estimate is actually more likely to be 15-20% (ESC & EAS 2019; Mach et al. 2019; Welsh et al. 2019). *MSAC noted that if the upper estimate (20%) is used this would approximately double the financial impact of apoB testing to the MBS.*

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Population too restrictive	Population definition is too restrictive and misaligned with patient populations typically recruited for clinical studies. Pre-ESC applicant response is contradictory. It acknowledged that evidence for utility of apoB testing exists in broader populations but requested that the PICO remains unchanged. Consider widening the population and extend the search to earlier published studies.
Insufficient evidence for clinical effectiveness	Insufficient evidence to support the service in the proposed populations.
Clinical safety of resultant changes in treatment not considered	Safety of testing is unlikely to be an issue, but the impact of changing risk profile with apoB assessment should be considered.
Restriction to one-off testing inappropriate	Restriction is not justified, and not clinically intuitive.
Economic evaluation not informative	Economic evaluation not informative to MSAC decision-making without a measure of clinical benefit (change in treatment, risk stratification, quality of life).
Potential for leakage	Broader population who would potentially benefit from apoB testing is quite large, creating potential for leakage.

ESC Discussion

ESC noted that after the PICO was ratified in November 2018, there was ongoing consultation between the applicant and the assessment group to refine the proposed populations. It was suggested to the applicant that broadening the population to include patients receiving statin therapies would improve the overall evidence base for apoB testing in a monitoring setting. However, the applicant chose to limit the application to once per lifetime apoB testing in two populations (see Section 2. Purpose of application).

ESC considered that apoB has a role in identifying high-risk patients who are not currently being treated; this would include not only patients with cholestatic liver disease (for which there are many aetiologies) but also those with fatty liver disease who often do not receive statins. However, the applicant did not clearly state that the proposed populations are undertreated, and did not provide any evidence as to how undertreated they are, or how they are treated and whether apoB testing would make a difference. ESC noted that overtreatment would also be a problem because of the side effect profile of statins.

ESC considered that, although the two chosen populations are appropriate because test results could influence clinical management, a broader population would need to be included to generate sufficient evidence for MSAC decision-making.

ESC noted the applicant's clinical claim that apoB provides a more direct measure of circulating atherogenic lipoproteins and is therefore superior to LDL-C (low-density lipoprotein cholesterol) and non-HDL-C as a marker of cardiovascular (CVD) risk. ESC noted that there are data to support apoB being a better marker of risk and atherogenic outcomes because of its 1:1 relationship with atherogenic lipoprotein particles.

ESC noted that LDL-C estimation is already MBS listed.

In relation to population 1, ESC noted that cut-offs for triglyceride in the diagnosis of hypertriglyceridaemia are inconsistent between laboratories. However, ESC considered that this would not have much impact on this application.

ESC noted that there are no studies that identify a total cholesterol cut-off for population 2.

ESC considered that the restriction to one test per lifetime is not clinically appropriate given the dynamic nature of cholesterol levels. ESC considered that there may be clinical value in ongoing monitoring of apoB after medical therapy and over time.

ESC noted issues raised by consumer consultation: a lack of clarity around population selection (i.e. whether selection is based on clinical utility or higher clinical need) could confuse consumers; most people with some degree of CVD risk will already be receiving lipid-lowering therapy; the impact of testing on patient self-management has not been considered; patients may be subjected to unnecessary changes in therapy; lack of evidence about effectiveness could lead to patient complacency or undue anxiety; and there was limited discussion of apoB testing's use in primary care setting.

ESC agreed with the Critique that standard care is the appropriate comparator.

ESC noted that in the current clinical management algorithm, current lipid estimates may incorrectly assess patients to be at moderate CVD risk when they are actually at high risk. The application proposes that adding apoB testing will allow correct identification of patients

at high risk. However, ESC considered that the choice of proposed populations resulted in the clinical data being insufficient to support this claim.

ESC noted that literature searches were restricted to 2008–2019. ESC agreed with the Critique that the literature review was too restrictive, and noted that relevant studies would have been published before 2008.

ESC considered it likely that the pre-specified populations are too restrictive and misalign with patient populations typically recruited for clinical studies. Restriction to these populations may lead to exclusion of patients who would otherwise benefit from apoB testing.

ESC agreed with the Critique that, overall, the included studies provide insufficient information to answer the research question. ESC also agreed with the Critique that it would have been more appropriate to broaden the scope of the literature search to include large cohort prospective studies using regression analysis to determine the association between apoB and CVD, and then assess the applicability of that evidence to the intended population. Relevant studies include: the Framingham study; a study by Thanassoulis et al. (2014), which demonstrated that relative risk reduction from statin therapy was more closely related to reductions in apoB than to reductions in either LDL-C or non-HDL-C; and the Women's Health Study (Ridker et al., 2005), which showed apoB to be a better predictor of CVD in women than LDL-C or non-HDL-C.

ESC noted that the following evidence was sought for the linked evidence analysis:

- Clinical validity: apoB testing compared to non-HDL-C in terms of positive predictive value, negative predictive value, prognostic value, and morbidity and mortality of CVD
- Clinical utility: apoB testing compared to non-HDL-C in terms of the impact on clinical management.

ESC noted that evaluation of the prognostic power/clinical validity of apoB testing in population 1 was based on two studies that performed a baseline apoB and non-HDL-C test, and follow-up observation on the incidence of new CVD events (Bhatt et al 2019, Zhao et al 2016). ESC noted that no studies of clinical utility, therapeutic efficacy or therapeutic effectiveness in population 1 were identified.

ESC agreed that because apoB testing is performed on the same blood specimen as other lipid tests, there are no additional safety issues associated with the apoB test itself. However, ESC noted that potential harms of changes in management resulting from changing a patient's risk category (e.g. treatment inappropriately prescribed or withheld) were not considered.

ESC noted that the two studies assessing prognostic value of apoB testing in population 1 both showed that apoB and non-HDL-C performed similarly in predicting subsequent CVD risk and morbidity over the duration of the trial. However, ESC noted that assessment of these outcomes was not the primary intention of either trial. ESC agreed with the Critique that poor quality data and lack of evidence linkages lead to critical uncertainties about the clinical validity of apoB testing compared with non-HDL-C testing.

ESC considered cost-consequence analysis to be appropriate given the limited data available. However, ESC noted that the outcomes of the economic model related only to the incremental cost of an apoB test and the number of patients with known apoB values. No

assumptions were incorporated into the model structure; modelling to final outcomes was not considered feasible due to applicability concerns (poor overlap between studies and the proposed populations), heterogeneity in the included studies, uncertain comparative effectiveness (risk stratification, health-related quality of life) and uncertain impact on patient management.

ESC noted that the main driver of the estimated financial impact was an assumption that 10% of patients with mild to moderately elevated triglyceride concentrations would progress to apoB testing for more precise cardiovascular risk assessment. This was based on a value of 5–10% provided by the applicant. However, because the source of this proportion was unclear, ESC considered the financial estimates to be uncertain.

ESC considered it appropriate that estimates of the total cost to the MBS should include an additional GP consultation; in practice, apoB testing would only be ordered after other lipid tests so an additional GP consultation would be necessary for all patients.

ESC noted that the population who would potentially benefit from apoB testing is quite large, which creates a potential leakage issue.

ESC considered that there is insufficient evidence of incremental benefit of the addition of apoB testing to that currently performed to justify the additional cost.

ESC considered that genetic tests currently under development could have better predictive value for CVD risk than for current tests with the addition of apoB testing, and will require separate assessment once data becomes available.

15. Other significant factors

Nil.

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

The applicant had no comment.

17. Further information on MSAC

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