1. Purpose of application

The Pathology Service Table Committee (PSTC) submitted an application in October 2010 requesting a Medicare Benefits Schedule (MBS) listing of genetic testing for mutations in the RET gene for:

(i) patients with symptoms of multiple endocrine neoplasia type II (MEN2), and
(ii) unaffected relatives of a patient with a documented RET mutation to determine the risk of disease.

The proposal is for two new MBS items to cover the use of diagnostic and predictive testing for mutations in the RET gene. Since the application was submitted, the PSTC was disbanded and the Royal College of Pathologists of Australasia agreed to be the sponsor.

The intervention is mutation testing for the RET proto-oncogene, whose mutations are associated with multiple endocrine neoplasia type II (MEN2A and B, and familial medullary thyroid cancer, FMTC) and the seemingly unrelated syndrome of congenital absence of the enteric ganglia (Hirschsprung disease).

MEN2 is autosomal dominant, which means that offspring with one affected parent have a 50% chance of having MEN2 themselves. Studies have shown that over 90% of people who have a RET mutation will develop MEN2. Mutation testing of the RET gene is therefore used as a means of diagnosing MEN2 in those with symptoms (distinguishing between those who have MEN2, and those who have the more common sporadic form of MTC), and also as a way of predicting which family members will develop MEN2, based on whether they carry the pathogenic mutation of the RET gene.

Given that specific genotype-phenotype relationships have become evident, the type of specific mutation found may also be used to determine the age at which a prophylactic thyroidectomy should be performed.

Testing of the RET gene for mutations occurs once a person has clinical features of MEN2, or in first or second degree family members, at genetic risk, of someone who has been diagnosed with MEN2. Testing occurs subsequent to genetic counselling.
RET mutation testing is currently standard practice offered in state and territory hospitals and private facilities.

2. **Background**
There has been no previous MSAC consideration of RET mutation testing. Although standard practice, RET genetic testing is a new application and is currently not MBS listed. Currently, patients can have their blood collected in public hospitals and the genetic test covered by the state health system. When patients are referred by a private facility, they are billed directly, as private health insurance generally provides a subsidy for testing only if the MBS also provide a rebate for the test. National surveys of medical genetic testing in 2006 and 2011 documented that the rate of RET genetic testing varied significantly in different States and Territories.

3. **Prerequisites to implementation of any funding advice**
RET genetic testing for mutations is in accordance with the relevant legislation set out in the new TGA Regulatory Framework (July 2010) for In vitro diagnostic medical devices (IVDs) products. Testing of the RET gene is currently only provided as an in-house IVD, and would be classified as a Class 3 in-house IVD.

Laboratories offering the test in house must have National Association of Testing Authorities (NATA) accreditation, with demonstrated compliance with the suite of standards on the validation of in-house IVDs, as published by the National Pathology Accreditation Advisory Council, for each test manufactured.

4. **Proposal for public funding**

**Proposed MBS item descriptors for RET mutation testing**

<table>
<thead>
<tr>
<th>Category 6 – Pathology services</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MBS [item number]</strong> Detection of germline mutations in the RET gene in patients with:</td>
</tr>
<tr>
<td>(a) medullary thyroid carcinoma</td>
</tr>
<tr>
<td>(b) adrenal phaeochromocytoma under the age of 50 years</td>
</tr>
<tr>
<td>(c) hyperparathyroidism plus a diagnosis of medullary thyroid cancer or phaeochromocytoma in a close relative</td>
</tr>
<tr>
<td>1 or more tests</td>
</tr>
<tr>
<td>Fee: $400</td>
</tr>
<tr>
<td>Prior to ordering these tests the ordering practitioner should ensure that the patient (or their parent/guardian in the case of children) has given informed consent. Testing can only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the treating practitioner, a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.</td>
</tr>
</tbody>
</table>

| **MBS [item number]** Detection of a known mutation in the RET gene in: |
| (a) asymptomatic first- or second-degree relatives, at genetic risk, of a patient with a documented pathogenic RET mutation |
| 1 or more tests |
| Fee: $200 |
| Prior to ordering these tests the ordering practitioner should ensure that the patient (or their parent/guardian in the case of children) has given informed consent. Testing can only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the treating practitioner, a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results. |
It is a requirement that all patients undergoing predictive testing should first receive genetic counselling and give informed consent (or assent in the case of children). It is also recommended that all patients undergoing diagnostic genetic testing should undergo genetic counselling. It is therefore suggested that the ordering of the genetic test for RET mutations should be limited to specialised genetic services that can provide accredited genetic counselling to patients and their family members.

Currently, there are only four¹ accredited pathology laboratories in Australia that offer RET mutation testing (RCPA 2012).


5. Consumer Impact Statement
The public was invited to provide feedback on the draft protocol for undertaking this evaluation of RET mutation testing during October 2011. No public consultation responses were received from any relevant craft groups or consumer groups.

6. Proposed intervention’s place in clinical management
RET mutation testing is currently standard clinical practice but is not funded on the MBS. There is no specific alternative test to determine individual susceptibility to MEN2.

RET mutation testing is a part of the current clinical pathway. It was compared with a hypothetical algorithm that included a mix of historical treatment and current tests (other than the RET test), which outlines the approach to the diagnosis, surveillance and management of suspected MEN2 in a setting without genetic testing. Two clinical management algorithms were provided for RET mutation testing in index cases with an MTC and without an MTC, and for their close family members. The first clinical scenario is more common than the second, as an MTC is the first symptom in most MEN2 families due to its earlier and higher penetrance.

There were material differences between the algorithms outlining the ‘historical’ and ‘current’ clinical management strategies for MEN2 in the type of healthcare resources and the frequencies of their use. In the absence of RET mutation testing (the historical setting), all patients with an MTC at presentation or detected through initial investigations would be monitored for further clinical features of MEN2, despite there being a 75% chance of the MTC being sporadic. It was also assumed that, in the absence of genetic testing, their first-degree family members would receive annual surveillance for MEN2 features. Family members would undergo a total thyroidectomy once early signs of MTC are detected by elevated calcitonin levels.

In comparison, the main differences between this historical setting and the current setting (with RET mutation testing available) are:

i) the targeted use of lifelong surveillance in patients and family members who have a definitive diagnosis of MEN2 or RET mutation, or the avoidance of this requirement in those patients and family members without a RET mutation; and

ii) the use of prophylactic total thyroidectomy in family members with a confirmed RET mutation.

In the absence of RET mutation testing, all those who present with an early onset adrenal phaeochromocytoma or hyperparathyroidism (plus a diagnosis of MTC or phaeochromocytoma in a close relative) who are found not to have an MTC would be assumed not to have MEN2. Therefore, the index case and their family members would not
be screened or undergo surveillance. However, in the current setting where genetic testing is available, patients with this clinical profile who have a RET mutation would be diagnosed with MEN2 and therefore undergo prophylactic total thyroidectomy and lifelong surveillance. Their family members would also undergo cascade screening and those who also carry the RET mutation would undergo prophylactic thyroidectomy and lifelong surveillance.

7. Other options for MSAC consideration
Clinical trials comparing the health outcomes of patients diagnosed with the addition of RET mutation testing, versus without RET mutation testing, would now be considered unethical, as RET mutation testing has become standard clinical practice for patients suspected of having MEN2. Although the evidence identified is at risk of bias, studies controlling for confounding factors are highly unlikely to now be performed.

8. Comparator to the proposed intervention

The comparator for financial implications: RET mutation testing of patients suspected of having MEN2 or of their close family members is standard practice, not a technology to be replaced or added to. As a consequence, when determining the financial implications of RET mutation testing, the comparator was considered to be genetic testing paid for either by the patient or by the states and territories through the public hospital system.

The comparator for benchmarking the safety, effectiveness and cost-effectiveness: As RET mutation testing is a means of triaging biochemical screening and imaging (and has replaced pentagastrin-stimulated calcitonin measurements) in patients suspected of having MEN2 and their close relatives, the comparator selected was biochemical screening and imaging alone for the diagnosis of MEN2. The screening and imaging investigations that patients receive depend on their presenting feature.

There is no specific alternative test to determine individual susceptibility to MEN2. Without genetic testing the diagnosis of MEN2 would rely on tumour type and location, which is not possible to assess prospectively. However, close family members of someone with MEN2 would have lifelong surveillance to ensure early detection of disease. The comparison for first-degree relatives (and second-degree relatives in a cascade fashion) is therefore between genetic counselling and RET mutation testing in addition to a prophylactic thyroidectomy, lifelong thyroxine and lifelong surveillance in those who carry a RET mutation, versus genetic counselling and lifelong surveillance (with a total thyroidectomy and lifelong thyroxine after a rise in calcitonin levels) for all at-risk relatives.

The state and territory public health systems provide the genetic test (at no cost to the patient) if the patients are referred by public hospitals.

9. Comparative safety
No studies were available which specifically report on the safety of RET mutation testing. However, RET mutation testing enables the asymptomatic mutation carriers being recommended to undergo prophylactic total thyroidectomy, before clinical signs of an MTC appear, therefore, the safety of prophylactic total thyroidectomy was assessed using one historical controlled study (level III-3 interventional evidence) and eight uncontrolled case series (level IV interventional evidence).

There were no safety concerns (either physical or psychological) raised in any of the articles identified for RET mutation testing.
Regarding the safety of prophylactic total thyroidectomy, one historical controlled study (level III-3 interventional evidence) showed similar rates of mortality due to surgical complications in those who underwent surgery prior to knowledge of the link between RET mutation status and MEN2, versus those who underwent surgery knowing their RET mutation status (one death in each cohort). Twelve case series (level IV interventional evidence) reported on the rate of adverse events following total thyroidectomy. Transient hypoparathyroidism was reported in five patients (36.4%) in 4 of the 12 case series.

Permanent hypoparathyroidism occurred in between 7.7% and 13.6% of patients from 4 of the 12 studies that reported adverse events after total thyroidectomy. Transient laryngeal nerve palsy was reported in between 4.5% and 5.9% of patients in 4 studies, and one case of permanent laryngeal nerve palsy was reported. Other complications included one case of arterial bleeding, one case of fluctuating thyroid hormone (at 1 year post-surgery) despite adequate compliance with thyroxine replacement, and one case of permanent unilateral Horner’s syndrome.

Overall, RET mutation testing is a safe procedure for patients, involving a simple blood test. In those who are found to be RET mutation carriers, the treatment recommended is a prophylactic thyroidectomy to avoid the risk of developing an MTC. This procedure is associated with a risk of hypoparathyroidism and laryngeal nerve palsy, which is usually transient. The risk of adverse events with prophylactic surgery is likely to be lower than when patients are treated at a later disease stage.

It is expected that the rate of surgical complications would be higher in those patients who undergo surgery at a later stage of disease, due to the more invasive surgery required to remove an MTC once the tumour has extended beyond the thyroid, although direct evidence was not available comparing the safety of prophylactic thyroid surgery against curative surgery.

10. Comparative effectiveness
Nine historical controlled studies (level III-3 interventional evidence) provided evidence showing that health outcomes are likely to be better for patients diagnosed with the addition of RET mutation testing.

Seven historical controlled studies reported on the incidence and severity of MTC in patients who underwent total thyroidectomy in the era prior to RET mutation testing compared with the era subsequent to the introduction of RET mutation testing. Those diagnosed and treated since RET mutation testing became available had almost half the risk of having an MTC at the time of surgery, compared with those whose treatment decisions were based on biochemical screening in the pre-RET mutation testing era (RR=0.53, 95% CI 0.32, 0.90). It is unknown whether any clinical benefit has occurred in index patients, or whether all the benefits found have been due to more effective management of family members.

One historical controlled study reported that age at diagnosis reduced for patients with MEN2A and FMTC between two surveys in Japan, one performed in 1996 (capturing data prior to the availability of RET mutation testing) and the other in 2002. Age at diagnosis in patients with MEN2B increased marginally, likely just through chance given the small sample; however, the MEN2B phenotype is more clearly diagnosed than the MEN2A, so genetic testing has probably had less impact on patients and their family members with or suspected of having MEN2B than MEN2A. Five additional historical controlled studies reported that the introduction of RET mutation testing resulted in the age at time of total
thyroidectomy being significantly reduced. One Australian study reported that the mean age decreased from 32 years to 16 years (Learoyd et al. 1997).

Both age at time of total thyroidectomy and severity of MTC are significant predictors of the risk of residual or recurrent disease (Schreinemakers et al. 2010). Six historical controlled studies reported a greatly reduced risk of persistence, recurrence or mortality in those who underwent total thyroidectomy with knowledge of their RET mutation status, compared with total thyroidectomy without this knowledge (RR=0.28, 95% CI 0.17, 0.45). However, this evidence is highly biased, as those in the historical cohort were followed up for longer time periods, allowing a greater chance of disease recurrence simply as a matter of time. Historical comparisons may also be confounded by changes in treatment over time. Finally, there is possible lead-time bias related to earlier diagnosis with RET mutation testing.

Assessment of individual components in an evidence linkage supported the conclusions based on direct evidence of the impact of testing on patient health outcomes. One historical controlled study and 3 case series reported instances of false positive results based on calcitonin levels, which led to patients either undergoing total thyroidectomy or being scheduled for surgery that was subsequently cancelled after a negative RET mutation status was identified.

One single case of an individual free from RET mutations, in a family with known mutations, who had an MTC was noted (Halling et al. 1997). It is unknown whether this could be considered a false negative RET mutation test or a coincidental finding of a spontaneous MTC in a RET-mutation-negative family member of an FMTC kindred. Although a true comparison of accuracy was not able to be performed given the lack of long-term clinical follow-up data to use as a reference standard for MEN2 diagnosis, the limited evidence available would suggest that diagnoses made with the addition of RET mutation testing are likely to be more accurate than those made on the basis of biochemical screening.

As the treatment option (thyroidectomy) is the same, irrespective of early or late identification of MEN2, and has proven effectiveness, it is unlikely that studies assessing the comparative effectiveness of thyroidectomy in an ‘earlier (RET-mutation-tested)’ versus ‘later (non-RET-mutation-tested)’ MEN2 diagnosed population are necessary or will be conducted.

Patients who are asymptomatic gene carriers are likely to undergo prophylactic total thyroidectomy on the basis of this knowledge. Prophylactic surgery is associated with having a lower stage of MTC disease at time of surgery, compared with surgery performed on the basis of calcitonin levels.

Overall, clinical management with the addition of RET mutation testing would appear to have superior effectiveness and at least non-inferior safety, compared with diagnosis and treatment of MEN2 without knowledge of RET mutation status.

**Key results**
There is evidence that RET mutation testing has allowed patients to undergo total thyroidectomy at an earlier age, and at an earlier stage of MTC disease, than before the introduction of RET mutation testing.

**Key uncertainties**
Both age and stage of disease at the time of surgery may be considered surrogate outcomes for survival. Longer term patient-relevant outcomes such as rates of mortality and disease
recurrence were reported and were highly in favour of RET mutation testing; however, these results were confounded by different lengths of follow-up in the testing and non-testing study arms.

There is also a high risk of bias in the results due to the comparison against historical cohorts. This type of comparison means that it is unknown to what extent other factors might have influenced the results; for example, if significant advances in surgical methods or surveillance for features of MEN2 have occurred over the same time period as the introduction of RET mutation testing, it would be difficult to correctly attribute the clinical benefits. Lead-time bias may also occur related to earlier diagnosis with RET mutation testing.

**Overall conclusion with respect to comparative clinical effectiveness**

All the evidence regarding the comparative clinical effectiveness of RET mutation testing was at high risk of bias. This evidence suggested that the addition of RET mutation testing allows identification of patients at risk of MEN2 at a younger age, allowing prophylactic surgery to occur at a younger age and at a less advanced stage of MTC disease. As age and disease stage are predictors of MTC disease recurrence, it is probable that earlier identification will reduce the risk of disease recurrence in MEN2 patients. Assuming that the findings from the evidence base remain consistently in the same direction, even if the size of this effect is confounded by longer lengths of follow-up in the control arm and differences in patient care over time, the comparative clinical effectiveness of the addition of RET mutation testing would be superior to biochemical screening and imaging.

11. **Economic evaluation**

Economic evaluations were conducted for:

(i) RET mutation testing in potential index cases:

   (a) MTC and
   (b) phaeochromocytoma under 50 years of age; and

(ii) RET mutation testing in index cases and additional familial genetic testing in first-
     or second-degree relatives of:

   (c) patients presenting with MTC and
   (d) patients younger than 50 years of age presenting with phaeochromocytoma.

These were the four evaluations required by the DAP. All four evaluations compare the proposed MBS listings for RET mutation testing against a hypothetical scenario of medical surveillance before RET mutation testing was available. (This comparator is referred to as ‘hypothetical’ because RET testing is currently available but funded through state hospital budgets).

ESC noted that the second pair of evaluations does not include an analysis of the incremental cost-effectiveness of familial testing compared with testing in potential index cases alone.

**RET mutation testing in index cases alone**

The economic evaluation presented for genetic testing in potential index cases alone was a cost-minimisation, as there is no evidence to suggest that health outcomes for the index case will be affected by genetic testing. The inputs into this model related to the costs of genetic testing and monitoring (consultation, biochemical tests and imaging) for additional MEN2 clinical features. Resources used were based on the surveillance regimen described by the Genetics Subcommittee of the PSTC and current MBS fees.
In each of the two evaluations in this scenario, the models run over 30 years and show accumulated healthcare costs from a societal perspective using a discount rate of 5% per year. The results indicated that cost savings occur within 5 years of testing a patient for RET mutations. Over the course of 30 years, savings of approximately $535 per MTC patient tested, or $1,458 per phaeochromocytoma patient tested under 50 years of age, would be expected compared with a scenario where testing was not available.

**RET mutation testing in potential index cases and family members of test-positive index cases**

A cost-utility analysis was undertaken as the ability to identify RET-mutation-positive family members via testing allowed for prophylactic thyroidectomy treatment and therefore both health costs and outcomes in family members are affected. The inputs into this model related to the costs of genetic testing, monitoring (biochemical/imaging etc.) and thyroidectomy (surgical, hospital and pharmaceutical). The health states, which are applicable to family members only, included: healthy (no surgery/surveillance); healthy (pre-surgery, with surveillance); healthy (no MTC) post-thyroidectomy (incorporating adverse effects of surgery); symptomatic MTC; and death. Health outcomes were measured as accumulated quality-adjusted life-years (QALYs).

The cost-utility model ran over a ‘lifetime’ time horizon (70 years). However, results for shorter time horizons (10, 20 and 50 years) were also presented. An annual discount rate of 5% was applied to both costs and health outcomes.

The results of both base case analyses (i.e. the analysis of potential index cases with MTC plus familial testing, and of potential index cases younger than 50 years of age presenting with phaeochromocytoma plus familial testing) indicated that availability of genetic testing ‘dominates’ (i.e. it results in both improved health outcomes and cost-savings), compared with the alternative scenario where RET mutation testing is not available.

**Sensitivity analyses**

Sensitivity analyses suggested that the base-case economic conclusions for all four economic evaluations are relatively robust.

With respect to diagnostic RET mutation testing in suspected index cases presenting with MTC, a positive net cost might be expected if i) high test costs ($1,150) are applied or ii) diagnostic yield increases substantially (i.e. testing only occurred in patients with suspected familial disease). With respect to diagnostic testing in suspected index cases presenting with phaeochromocytoma, the costs of testing are most sensitive to test price.

The cost-utility model incorporating both diagnostic testing and familial screening was highly robust where the index cohort presents with MTC. Adoption of RET mutation testing remained the dominant economic strategy (vs a hypothetical model of biochemical screening) across all analyses of alternative test price, diagnostic yield, uptake rates and relative risk (RR) of health outcomes below 0.97.

The cost-utility model incorporating both diagnostic testing of index cases presenting with phaeochromocytoma and predictive testing of their family members, was also relatively robust. Genetic testing remained the dominant economic strategy across alternative values of test price, and diagnostic yield. When uptake rates of testing or screening were reduced to 15% a relatively low ICER ($485/QALY) is obtained.
In the two cost-utility analyses, the base case estimate of relative risk (RR) for health outcomes is 0.25, however this is highly uncertain. In either model if the RR of MTC recurrence is increased to 1.0, then genetic testing has negative outcomes and is either dominated (resulting in neither health benefits nor savings) in the model where index patients present with MTC, or associated with a cost-saving of $4,721/QALY lost in the model where index patients present with phaeochromocytoma. However, the assumption of zero clinical benefit may be considered unreasonable and not consistent with the available evidence. Where the index cohort present with MTC, any RR less than 0.97 results in genetic testing remaining dominant (gaining QALYs and saving money), and this applies to any RR less than 0.43 in the model where index cases present with phaeochromocytoma.

**Key uncertainties**
The lack of direct comparative evidence and the hypothetical nature of the economic comparisons mean that the actual quantification of both incremental costs and outcomes in the economic models are not expected to be particularly accurate. Furthermore, the model structure is simplistic and incorporates generalised assumptions that do not capture the distribution of patient age or risk profiles. For this reason the assumptions and inputs in the base case have been selected to be conservative with respect to the cost-effectiveness of RET. However, broad-ranging sensitivity analyses nevertheless demonstrate that cost-effectiveness is maintained across a range of clinical scenarios.

**Overall conclusion with respect to comparative cost-effectiveness**
Despite the shortcomings of the model, the robust nature of the findings that RET mutation testing results in cost savings and health outcome benefits when model inputs are varied over a wide range of possibilities is reassuring. On this basis the conclusion that RET mutation testing and subsequent targeted surveillance (in comparison with broader and increased reliance on imaging/biochemical surveillance) is cost-effective is reasonably certain.

**12. Financial/budgetary impacts**
Diagnostic RET mutation testing was estimated to occur in 130–260 patients in 2013, increasing to 147–294 in 2015. The estimate of the population suspected of having MEN2 was based on those diagnosed with MTC (approximately 5–10% of all thyroid cancers) (Keatts & Itano 2006). An annual increase in thyroid cancers (and MTCs) of 6.3% was projected based on the average annual increase in thyroid cancer in Australia 2005-09. One diagnostic RET test is required per patient.

The likely number of eligible family members who elect to have RET mutation screening tests is estimated to be 150–359 in 2013, increasing to 169–406 in 2015. One predictive RET mutation test would be required per eligible family member. These estimations were based on the following assumptions:

- Between 25% and 30% of diagnostic RET mutation tests identify a patient with a mutation (Raue & Frank-Raue 2010).
- Each index patient has 11.5 first- or second-degree relatives eligible for predictive RET mutation testing (Suthers et al. 2006).
- Of eligible relatives, 40% accept familial testing (Suthers et al. 2006); i.e., uptake of the test occurs in 4.6 family members per index case.

The extent of uptake in eligible family members is uncertain, with lower uptake (of one or two relatives per index patient) previously reported in the Australian context (Suthers 2008b). The effect of this uncertainty on the financial and budgetary impact is explored in sensitivity analyses.
The cost of diagnostic RET mutation testing used in the base-case estimates was $400, and $200 for familial RET mutation testing. These costs were based on the median quote for RET mutation testing of the 6 exons most commonly examined (exons 10, 11 and 13–16) provided by the pathology laboratories currently providing this service, and are substantially lower than the price previously estimated in the DAP. The financial and budgetary impacts using the DAP-based costs were provided in the assessment report. It was assumed that all testing is provided in an outpatient setting and, as such, the MBS will cover 85% of the cost of the test.

The total estimated cost to the MBS, based on an estimated number of 130–260 diagnostic and 150–359 predictive RET mutation tests performed in 2013, is $109,654, increasing to $123,906 in 2015 based on 147–294 diagnostic and 169–406 screening RET mutation tests performed.

Under the current arrangements, some patients who are referred through the public system receive genetic counselling services and testing at no direct cost. With the listing of RET mutation testing on the MBS, assuming that most patients would receive testing as outpatients, Medicare would pay 85% of the scheduled fee and a patient contribution of 15% plus any ‘gap’ charges or out-of-pocket expenses associated with billing above the Schedule fee when bulk-billing is not applied. Patients who may be eligible for the Medicare Safety Net, and those whose pathology service bulk-bills tests listed on the MBS, may not be required to contribute a co-payment (Table 1 of the assessment report). However, an unknown proportion of patients may qualify for the Medicare Safety Net, in which case 100% of the scheduled fee is paid by the MBS. Allowing for application of the Medicare Safety Net, the overall true costs to the Commonwealth health budget would lie between the total costs to the MBS and the total combined costs of RET mutation testing, i.e. up to $129,005 in 2013 and $145,772 in 2015.

A cost saving would be observed in the state and territory systems due to transfer of testing services to the MBS; however, the costs of genetic counselling services provided in hospitals would continue as per current arrangements.

Table 2  Total costs of RET mutation testing

<table>
<thead>
<tr>
<th>Year</th>
<th>2013&lt;sup&gt;a&lt;/sup&gt;</th>
<th>2014&lt;sup&gt;a&lt;/sup&gt;</th>
<th>2015&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic RET mutation testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of diagnostic RET mutation tests&lt;sup&gt;b&lt;/sup&gt;</td>
<td>130–260</td>
<td>138–277</td>
<td>147–294</td>
</tr>
<tr>
<td>Estimated expenditure on diagnostic RET mutation testing&lt;sup&gt;c&lt;/sup&gt;</td>
<td>$52,071–$104,141</td>
<td>$55,351–$110,702</td>
<td>$58,838–$117,676</td>
</tr>
<tr>
<td>Patient co-payment&lt;sup&gt;d&lt;/sup&gt;</td>
<td>$7,811–$15,621</td>
<td>$8,303–$16,605</td>
<td>$8,826–$17,651</td>
</tr>
<tr>
<td>Estimated MBS expenditure&lt;sup&gt;e&lt;/sup&gt;</td>
<td>$44,260–$88,520</td>
<td>$47,048–$94,097</td>
<td>$50,012–$100,025</td>
</tr>
<tr>
<td><strong>Familial (predictive) RET mutation testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relatives eligible for testing</td>
<td>374–898</td>
<td>398–955</td>
<td>423–1,015</td>
</tr>
<tr>
<td>Number of relatives tested</td>
<td>150–359</td>
<td>159–382</td>
<td>169–406</td>
</tr>
<tr>
<td>Estimated expenditure on predictive RET mutation testing&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$29,941–$71,857</td>
<td>$31,827–$76,384</td>
<td>$33,832–$81,197</td>
</tr>
<tr>
<td>Patient co-payment&lt;sup&gt;d&lt;/sup&gt;</td>
<td>$4,491–$10,779</td>
<td>$4,774–$11,458</td>
<td>$5,075–$12,179</td>
</tr>
<tr>
<td>Estimated MBS expenditure&lt;sup&gt;e&lt;/sup&gt;</td>
<td>$25,450–$61,079</td>
<td>$27,053–$64,927</td>
<td>$28,757–$69,017</td>
</tr>
</tbody>
</table>
### Yearly Costs

<table>
<thead>
<tr>
<th>Year</th>
<th>2013&lt;sup&gt;a&lt;/sup&gt;</th>
<th>2014&lt;sup&gt;a&lt;/sup&gt;</th>
<th>2015&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total combined cost of RET mutation testing</strong>&lt;sup&gt;i&lt;/sup&gt;</td>
<td>$129,005</td>
<td>$137,132</td>
<td>$145,772</td>
</tr>
<tr>
<td>Lower limit</td>
<td>$82,011</td>
<td>$87,178</td>
<td>$92,670</td>
</tr>
<tr>
<td>Upper limit</td>
<td>$175,999</td>
<td>$187,087</td>
<td>$198,873</td>
</tr>
<tr>
<td><strong>Total patient co-payment</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td>$19,351</td>
<td>$20,570</td>
<td>$21,866</td>
</tr>
<tr>
<td>Lower limit</td>
<td>$12,302</td>
<td>$13,077</td>
<td>$13,901</td>
</tr>
<tr>
<td>Upper limit</td>
<td>$26,400</td>
<td>$28,063</td>
<td>$29,831</td>
</tr>
<tr>
<td><strong>Total cost to the MBS</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>$109,654</td>
<td>$116,562</td>
<td>$123,906</td>
</tr>
<tr>
<td>Lower limit</td>
<td>$69,710</td>
<td>$74,101</td>
<td>$78,770</td>
</tr>
<tr>
<td>Upper limit</td>
<td>$149,599</td>
<td>$159,024</td>
<td>$169,042</td>
</tr>
</tbody>
</table>

<sup>a</sup> Projected incidence of thyroid cancer based on the average annual incidence during 2005–09 of 6.3%

<sup>b</sup> Estimated based on a 5–10% incidence of medullary thyroid cancer in all thyroid cancers

<sup>c</sup> Assuming that the cost of the diagnostic RET mutation test is $400

<sup>d</sup> Assuming that most patients are outpatients and Medicare pays 85% of the scheduled fees, with no Medicare Safety Net concessions or bulk-billed pathology service

<sup>e</sup> Assuming that all services are provided in an outpatient setting such that Medicare pays 85% of the scheduled fees, with no allowance for additional MBS if some patients qualify for the Medicare Safety Net

<sup>f</sup> Estimated based on the identification of a positive hereditary mutation in the RET gene in 25–30% of tests performed; each patient was assumed to have, on average, 11.5 first- or second-degree relatives eligible for familial screening

<sup>g</sup> Assuming an uptake rate of 40% in eligible family members

<sup>h</sup> Assuming that the cost of the predictive RET mutation test is $200

<sup>i</sup> Assuming that all patients qualify for the Medicare Safety Net, then the total cost to the MBS would equate to the total combined cost of RET mutation testing

Sensitivity analyses assuming upper estimates around disease incidence and a 100% uptake rate of familial screening were undertaken to provide an extreme upper limit of the predictable financial costs. The estimated cost of RET mutation testing to the MBS under these limits increased to $272,568 in 2015.

The proposed MBS item descriptors require that appropriate genetic counselling be provided to the patient prior to diagnostic testing or familial screening; further counselling may be required upon receipt of the test results. Genetic counselling services have not been accounted for in the financial and budgetary estimates, as the current distribution of counselling services is unlikely to change, with little impact expected to the overall health budget, MBS, and state and territory systems.

The assessment report indicated that listing RET mutation testing on the MBS is not expected to have any impact on the costs of the overall Australian healthcare system considered in its entirety. The practice of genetic testing and counselling is routine in diagnostic and familial screening of patients in a manner unchanged by the proposed listing and at a similar cost, which is currently borne by state government hospital budgets.

### 13. Key issues for MSAC from ESC

**Main issues around the proposed eligible population for public funding and/or the proposed main comparator**

ESC discussed the wording of the proposed item descriptor and agreed that the service should be restricted to ‘specialists’ rather than a ‘treating practitioner’. This change in wording is to avoid GP’s from ordering the test without supportive genetic counselling. ESC discussed options for remote patients, however it agreed that due to the small percentage of the population affected by hereditary mutations of the RET gene, it was appropriate to keep it as a specialist only item.
ESC was concerned that as genetic counselling was a prerequisite for the test, there should be an MBS item to address this, however ESC accepted that at present genetic counselling is conducted under state and territory government, not federal, auspices.

ESC discussed the comparator used in the economic evaluations, noting it was not current practice. While the rationale for using a historic comparator to answer the question of is the test worthwhile compared to no test appears sound, ESC discussed whether it only answered part of the question. ESC proposed considering the merit of an additional economic analysis using current practice in public hospitals as the comparator. ESC also noted that what was referred to as a historical comparator was better described as a hypothetical comparator since it was a mix of historical treatment pre-RET mutation testing, but included some current tests not available prior to RET mutation testing, meaning the evaluation results (including cost savings) are also hypothetical.

ESC discussed whether the scope and test type should be specified in the descriptor of the genetic test – most common exons versus full screen. ESC concluded that leaving the particular test methodology to pathologists and the pathology accreditation process was the best way to ensure the item would be kept current, as more exons or better testing processes may be identified in the future.

Main issues around the evidence and conclusions for safety
ESC agreed that the safety of this test is comparable to that of any other peripheral blood test. No safety concerns raised in any literature were identified regarding RET mutation testing. ESC had concerns regarding the sensitivity and specificity of the test. ESC was most concerned that false-positive readings could lead to unnecessary thyroidectomies and subsequent inappropriate thyroidecetomies in familial members from the index case.

ESC accepted that there was comparative safety of the total prophylactic thyroidectomy. One historical study found similar rates of mortality due to surgical complications in those who underwent surgery prior to knowledge of the link between RET mutation status and MEN2 versus those who underwent surgery knowing their RET mutation status.

ESC noted that there was expected to be a higher risk of surgical complication in patients who underwent surgery at a late stage of identificaiton of the disease due to the more invasive surgery needed to remove MTC once the tumour had extended beyond the thyroid. 12 case series were provided regarding the rates of adverse events due to total thyroidectomy, and ESC accepted that on the sum of this evidence there were no undue concerns about the safety of the introduction of a RET mutation testing item onto the MBS.

Main issues around the evidence and conclusions for clinical effectiveness
ESC questioned whether familial cancers are likely to be diagnosed after 50 years of age. ESC felt the average age of entry stated as 40 years was too high considering the majority of patients would be diagnosed well before 50.

ESC noted that population (c) from the first MBS item descriptor had not been included in the CMA of index cases and that the age profile used in the economic evaluation also did not match that stipulated in the item descriptor for population (a).

ESC agreed that the initial test to identify the index case will need to be more sensitive and specific with the familial test than only needing to identify the exons found in the index case. DNA testing is currently used by the four Australian labs who undertake this work, and it is
unlikely that a more sensitive or specific test could be used, as this was the methodology used to identify the RET exons in the first place. Although there are other testing methodologies used overseas to identify RET mutations with varying levels of sensitivity and specificity, they usually use DNA testing as the gold standard.

Main issues around the evidence and conclusions for cost effectiveness

ESC questioned whether the correct incremental cost-utility analysis had been undertaken to inform MSAC deliberations on the addition of RET mutation testing of family members to the testing of suspected index cases. (This is directly relevant to the second proposed MBS item descriptor, which related to testing of family members).

ESC noted that neither of the two economic evaluations involving familial genetic testing compared the incremental costs and outcomes of testing both potential index cases and family members with the testing of index cases alone. However, it is possible to obtain these results from the information and results presented in the contracted assessment report (see Table 1 below). For MTC, testing family members in addition to suspected index cases increases the cost of genetic testing by $789,352 and results in 203 QALYs gained in family members (mutation testing in index cases does not affect health outcomes in index cases). This gives a cost-utility result of $3,888 per QALY gained. For phaeochromocytoma with index cases less than 50 years of age, the corresponding result is $10,115 per QALY gained.

Table 1: Incremental cost-utility analysis of testing suspected index cases and family members compared with testing suspected index cases alone, 30 year time horizon

<table>
<thead>
<tr>
<th></th>
<th>Index cases alone (1)</th>
<th>Index cases and family members (2)</th>
<th>Difference (2) – (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MTC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost(^{(a)})</td>
<td>$88,037</td>
<td>$877,389</td>
<td>$789,352</td>
</tr>
<tr>
<td>QALYs(^{(b)})</td>
<td>0</td>
<td>203</td>
<td>+203</td>
</tr>
<tr>
<td>Inc cost/QALY gained</td>
<td></td>
<td></td>
<td>+$3,888</td>
</tr>
<tr>
<td><strong>Phaeochromocytoma (index cases &lt; 50 years of age)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost(^{(c)})</td>
<td>$51,953</td>
<td>$517,234</td>
<td>$465,281</td>
</tr>
<tr>
<td>QALYs</td>
<td>0</td>
<td>46</td>
<td>+46</td>
</tr>
<tr>
<td>Inc cost/QALY gained</td>
<td></td>
<td></td>
<td>+$10,115</td>
</tr>
</tbody>
</table>

Sources:
(a) Contracted Assessment Report, Table 47
(b) Contracted Assessment Report, Table 50
(c) Contracted Assessment Report, Table 52
(d) Contracted Assessment Report, Table 55

Taking into account this additional analysis, ESC reached the following conclusions regarding the cost-minimisation and cost-utility analyses:

- RET mutation testing in suspected index cases presenting with either MCT or in suspected index cases less than 50 years of age presenting with phaeochromocytoma is cost-saving compared with no RET mutation testing in the base case analyses and under a wide range of variations in the values of model parameters.
• RET mutation testing in suspected index cases coupled with familial testing, either with MCT or with phaeochromocytoma and age less than 50 years, is also cost-saving compared with no RET mutation testing in the base case analyses and under a wide range of variations in the values of model parameters. However, the models suggest that there is a positive net cost per QALY gained associated with adding RET mutation testing of family members to RET testing of suspected index cases.

On this basis the conclusion that RET mutation testing of suspected index cases presenting with either MCT or phaeochromocytoma cases alone is cost-saving appears to be robust. While, for each group, adding the testing of family members has a positive net cost per QALY gained, the cost per QALY appears to be relatively low. Therefore, the conclusion that RET mutation testing with subsequent targeted surveillance in family members is cost-effective is probably sound.

Main economic issues and areas of uncertainty
ESC accepted the advice that genetic counselling is funded through the public hospital system, within the public cancer clinics and is not expected to change. The benefit of including these RET mutation testing access items on the MBS is so a greater transparency and understanding about how state hospitals fund genetic testing is gained. It will also aid in balancing access to the test on a national level, against the present case of individual state and territory arrangements. Adding RET mutation testing to the MBS will have a relatively small impact on the MBS over 4 years, as described in the economic model.

The report excluded the cost of genetic counselling from the financial analysis, arguing that counselling will remain unchanged, as it is currently happening in public hospitals. However, ESC questioned if this was likely to be true, and if so, identified a likely under-estimate of costs of counselling if uptake of the MBS item was greater than expected.

ESC suggested that cost structures in public hospitals and private labs may differ, in contrast to the assumption in the report which made them equivalent in which case the conclusion in the contracted assessment report of MBS listing having no impact on costs of the overall healthcare system is questionable. ESC also noted that the stated expected increase in familial testing would also have cost implications.

ESC was not confident that the costs adequately reflect either side of the algorithm. On the one hand, there were insufficient details on the population needing support following prophylactic thyroidectomy, particularly the pharmacological support. On the other side, the cost of not identifying RET mutations and subsequently needing a thyroidectomy was unclear, particularly with regard to the flow-on effect of the invasive surgery and long-term follow through when needing to remove MCT once a tumour extended beyond the thyroid.

ESC questioned the stated populations in the economic evaluations, as they do not match exactly those used in the item descriptor. In particular, population (c) from the first item descriptor was not included in the cost minimisation analysis (CMA) and the CMA used a population less than 50 years of age for both (a) and (b) when the item descriptor only links (b) to age. The second evaluation, a CUA to assess screening of family members has included index cases when the item descriptor relates only to family members.

ESC was concerned whether the question addressed in the cost utility analyses (CUA) of familial screening is a match for the second proposed MBS item. The item relates specifically to the population of family members but an incremental cost-utility analysis of adding family members to RET mutation testing of suspected index cases was not performed. The analysis
that was performed compared RET mutation testing of a population comprising both index cases and family members with no RET testing for any of this group.

Any other important areas of uncertainty (e.g. budget impact, translation of clinical evidence into the economic evaluation, linkage between an investigative intervention and a subsequent therapeutic intervention and outcomes
ESC agreed that the quality of the contracted assessment would have been improved with the addition of data on the specificity and sensitivity of DNA testing and a greater explanation of the choices made to create the model and better alignment between the economic evaluations and the proposed item descriptors. ESC requested that the CUA economic model be provided to MSAC in its raw form for scrutiny.

ESC noted that there was no evidence provided for the reported assumption of equal costs of providing the test in a public hospital compared to a private lab. However, ESC accepted that since there are only four labs performing the test at present, this may be of limited impact.

14. Other significant factors
ESC suggested that details with regard to the number of tests that were being performed by the laboratories for existing MBS genetic tests compared with state and territory requests might give an indication as to the likely proportional effect on the MBS item if a RET mutation testing option was added.

15. Summary of consideration and rationale for MSAC’s advice
MSAC noted that RET mutation testing, and the associated genetic counselling, of patients suspected of having multiple endocrine neoplasia type II (MEN2) and their close family members is currently standard clinical practice offered in state and territory hospitals and private facilities. Patients tested in public hospitals currently have the cost of the genetic test covered by the state health system whereas private patients are billed directly for the test. MSAC noted that currently RET mutation testing is provided by 3-4 laboratories nationally, but the rate of testing is higher in those jurisdictions which have a laboratory providing the test.

MSAC considered that in Australian practice there is no true comparator, as RET testing has replaced surveillance (including biochemical screening and imaging) in patients suspected of having MEN2 and their close relatives. The comparator in theory is no test with surveillance (including biochemical screening and imaging) offered to index patients and relatives.

MSAC accepted that the comparative evidence for clinical effectiveness of RET mutation testing seemed to show superiority even though it was based on historical controlled cohort studies. Results from these studies demonstrated that those patients diagnosed and treated since introduction of RET mutation testing had almost half the risk of medullary thyroid cancer (MTC) at the time of surgery, compared with those patients whose treatment decisions were based on biochemical screening pre-RET mutation testing (RR=0.53, 95% CI 0.32, 0.90). Results from five historical controlled studies suggested that the addition of RET mutation testing allows identification of patients at risk of MEN2 at a younger age, therefore prophylactic thyroid surgery can occur earlier and at a less advanced stage of MTC disease. MSAC noted, from Schreinemakers et al. 2010, that both age at time of total thyroidectomy and severity of MTC are significant predictors of the risk of residual or recurrent disease.

Although there were no studies available which specifically reported on the safety of RET mutation testing, MSAC agreed that the blood test for RET mutation testing is a safe procedure for patients. MSAC noted that the risk of adverse effects occurs in those patients
who are found to be RET mutation carriers where the recommended treatment is prophylactic thyroidectomy to avoid the risk of developing an MTC. Based on the available evidence, the rate of surgical complications is likely to be higher in those patients who undergo surgery at a later stage of disease. No studies were available which compared the safety of prophylactic thyroid surgery with therapeutic thyroid surgery.

MSAC accepted that clinical management with the addition of RET mutation testing appears to have superior effectiveness and at least non-inferior safety, compared with diagnosis and treatment of MEN2 without knowledge of RET mutation status (biochemical screening and imaging).

Despite the lack of long-term clinical follow-up data to use as a reference standard for MEN2 diagnosis, MSAC considered that the limited evidence available suggests that diagnoses made with the addition of RET mutation testing are likely to be more accurate than those made on the basis of biochemical screening. Particularly as RET mutation testing is associated with low rates of false positive and false negative results compared with biochemical screening which is associated with higher rates of late detection (false negatives) and false positives.

MSAC noted that RET mutation testing allows the targeted use of lifelong surveillance in patients and family members who have a definitive diagnosis of MEN2 or RET mutation and the avoidance of this requirement in those patients and family members without a RET mutation. It also allows appropriate treatment with prophylactic total thyroidectomy in family members with a confirmed RET mutation, and in index cases where the initial presentation was with phaeochromocytoma or hyperparathyroidism.

MSAC considered it reasonable that a cost-minimisation analysis (CMA) was presented for diagnostic RET testing, as there is no evidence to suggest that health outcomes for MTC index cases will be affected by genetic testing. The CMA results indicated incremental cost savings may occur within 5 years of testing a patient. MSAC also considered it reasonable that a cost-utility analysis (CUA) was presented for diagnostic RET mutation testing in potential index cases and predictive RET mutation testing in their family members, as the ability to identify RET-mutation-positive family members via testing allows prophylactic thyroidectomy treatment and therefore both health costs and outcomes in family members are affected. The CUA results indicated RET mutation testing was dominant (i.e. is cheaper with more efficient surveillance and improved MTC outcomes). MSAC noted that sensitivity analyses suggested the base case results of both economic evaluations for diagnostic and combined diagnostic and predictive testing were relatively robust.

MSAC noted that an MBS fee of $400 for the diagnostic test had been used for the financial analyses, and a reduced fee of $200 for the predictive test (because the mutation being tested for in biological relatives would already be known from the index case).

MSAC noted that diagnostic RET mutation testing is estimated to occur in 130–260 patients in 2013, increasing to 147–294 in 2015. For predictive testing, the likely number of eligible family members who elect to have RET screening tests is estimated to be 150–359 in 2013, increasing to 169–406 in 2015. The total estimated cost to the MBS of diagnostic and predictive RET mutation testing in 2013 is $109,654, increasing to $123,906 in 2015. MSAC agreed that if the test is funded on the MBS, a cost saving would be observed in the state and territory systems due to transfer of testing services to the MBS; however, the costs of genetic counselling services provided in hospitals should continue as per current arrangements.
For the diagnostic testing descriptor, MSAC determined the following changes should be included:

- A broader generic description of ‘suspected clinical diagnosis of MEN2’ to encompass all the patient sub-groups, MEN2A and B, medullary thyroid cancer and phaeochromocytoma or paraganglioma; and
- Requesting the diagnostic test should be restricted to specialist treating practitioners and specialised genetic services to avoid general practitioners requesting the test without supportive genetic counselling.

For the predictive testing descriptor, MSAC determined the following change should be included:

- Requesting the predictive genetic test should be limited to specialised genetic services that can provide accredited genetic counselling.

MSAC considered it unnecessary to confine testing to central reference laboratories as laboratories offering the test are required to demonstrate compliance with the National Pathology Accreditation Advisory Council (NPAAC) regulatory and quality framework for molecular testing.

16. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of diagnostic genetic testing for hereditary mutations in the RET gene, MSAC supports public funding via a new MBS item, with an item descriptor of:

<table>
<thead>
<tr>
<th>Category 6 – Pathology services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of germline mutations in the RET gene in patients with a suspected clinical diagnosis of multiple endocrine neoplasia type 2 (MEN2).</td>
</tr>
<tr>
<td>1 test. Adequate for lifetime test.</td>
</tr>
<tr>
<td>Fee: $400</td>
</tr>
</tbody>
</table>

Explanatory Note: Prior to ordering these tests the ordering practitioner must ensure that the patient (or an appropriate proxy) has given informed consent. Testing can only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of predictive genetic testing for hereditary mutations in the RET gene, MSAC supports public funding via a new MBS item, with an item descriptor of:

<table>
<thead>
<tr>
<th>Category 6 – Pathology services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of a known mutation in the RET gene in an asymptomatic relative of a patient with a documented pathogenic germline RET mutation.</td>
</tr>
<tr>
<td>1 test. Adequate for lifetime test.</td>
</tr>
<tr>
<td>Fee: $200</td>
</tr>
</tbody>
</table>

Explanatory Note: Prior to ordering these tests the ordering practitioner must ensure that the patient (or an appropriate proxy) has given informed consent. Testing can only be performed
after genetic counselling provided by a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.

17. **Applicant’s comments on MSAC’s Public Summary Document**
No comment.

18. **Context for decision**
This advice was made under the MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers’ Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

19. **Linkages to other documents**
MSAC’s processes are detailed on the MSAC Website at: [www.msac.gov.au](http://www.msac.gov.au).