Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1804 – RET variant testing for access to selpercatinib for the treatment of locally advanced or metastatic medullary thyroid cancer

Applicant: **Eli Lilly Australia Pty Ltd**

Date of MSAC consideration: **1 April 2026**

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

1. Purpose of the application

The integrated codependent application was received from Eli Lilly Australia Pty. Ltd. by the Department of Health, Disability and Ageing, which requested:

- Medicare Benefits Schedule (MBS) listing of testing of tumour tissue to detect *RET* proto-oncogene (*RET*) variants in patients with medullary thyroid cancer (MTC) for the determination of patient eligibility for treatment with selpercatinib; and
- Pharmaceutical Benefits Scheme (PBS) Section 85 General Schedule listing of selpercatinib for the treatment of locally advanced or metastatic MTC in patients who have evidence of a *RET* variant.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for genetic testing to detect *RET* variants in patients with medullary thyroid cancer to determine eligibility for PBS subsidised selpercatinib treatment. MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) at its March 2026 meeting was of a mind to recommend selpercatinib pending MSAC support for *RET* testing. MSAC acknowledged that there is a high clinical unmet need for effective treatments for the proposed condition. MSAC agreed that *RET* testing at diagnosis of medullary thyroid cancer would be appropriate to avoid delays in treatment. MSAC considered the proposed test is reliable and uses standard methods for genetic testing.

MSAC considered that the available evidence demonstrated improved clinical outcomes for patients with *RET*-positive medullary thyroid cancer treated with selpercatinib. MSAC considered that the overall financial impact of testing to the MBS would be low. However, MSAC noted the financial impact to the MBS would vary depending on the uptake of the test by prevalent patients living with medullary thyroid cancer. MSAC considered the new MBS item should not be restricted to once per lifetime to allow clinicians to order repeat *RET* testing as clinically necessary. MSAC advised that the MBS item descriptor should be pathologist determinable and considered a fee of $400 to be appropriate. MSAC further advised that the MBS item descriptor should restrict requesting of the test to specialist or consultant physicians.

Table 1 MSAC's supported MBS item descriptor

Category 6 – PATHOLOGY SERVICES	Group P7 – Genetics
MBS item AAAAA A test of tumour tissue from a patient with histologically confirmed medullary thyroid cancer requested by, or on behalf of, a specialist or consultant physician if the test is: a) to detect variants relating to at least the *RET* gene activating variant status, and b) to determine eligibility for a relevant treatment listed on the Pharmaceutical Benefits Scheme (PBS).	
Fee: $400.00 Benefit 75%: $300.00 85%: $340.00	

Consumer summary

This codependent application from Eli Lilly Australia Pty Ltd requested Medicare Benefits Schedule (MBS) listing of genetic testing to detect ret proto-oncogene (*RET*) alterations for treating people with locally advanced or metastatic medullary thyroid cancer so that they can access the medication, selpercatinib, on the Pharmaceutical Benefits Scheme (PBS). The Pharmaceutical Benefits Advisory Committee (PBAC) assessed selpercatinib for inclusion on the Pharmaceutical Benefits Scheme (PBS) as part of this codependent process.

Medullary thyroid cancer is rare, making up about 4% of all thyroid cancers. Some people develop it by chance. Others inherit it from a parent through genetic changes passed down in families who develop a condition called multiple endocrine neoplasia type 2 (MEN2). Around 70% of people with medullary thyroid cancer have changes in a gene called *RET*. Problems with the *RET* gene can cause the *RET* receptor (a protein) in cancer cells to stop working properly. The RET receptor is important because it controls cell growth by telling the cell when to grow. If the RET receptor is not working properly, the cell grows uncontrollably and can become cancerous. The medicine selpercatinib specifically targets the faulty *RET* receptor to help treat the cancer. Selpercatinib is used for people with advanced or metastatic medullary thyroid cancer, meaning cancer that has spread to other tissues and organs in the body.

Selpercatinib only works for people whose cancer has an abnormal *RET* gene. Because of this, people need genetic testing before they can receive the medicine. The test can be done using tissue that was already taken during the original biopsy to diagnose the cancer, so there are no safety concerns. In rare cases, a new biopsy may be required.

MSAC considered that *RET* testing accurately identifies people who would be suitable to receive selpercatinib. MSAC advised it is appropriate to test everyone who is newly diagnosed with medullary thyroid cancer, even if the cancer is not advanced or metastatic. This means that, if someone does progress from early-stage to late-stage cancer during their cancer journey, they can access selpercatinib right away and not have to wait for more test results.

This application was for somatic – not germline – *RET* testing, which means this test looks for *RET* gene changes in the tumour only. However, it is possible that an abnormal *RET* gene found in a tumour was an inherited variant in the *RET* gene. For those who may need testing to see if they have inherited a germline *RET* variant, there are MBS items already available for genetic testing for the patient and their first-degree family members.

MSAC noted that the PBAC at its March 2026 meeting deferred its decision but was of a mind to recommend selpercatinib to be listed on the PBS provided the MSAC supported adding *RET* testing to the MBS.

Consumer summary
MSAC considered *RET* testing to be good value for money. It would also have a modest impact on the MBS budget. MSAC therefore supported *RET* testing to be listed on the MBS. **MSAC's advice to the Commonwealth Minister for Health, Disability and Ageing** MSAC supported listing *RET* testing on the MBS for people with medullary thyroid cancer. MSAC considered *RET* testing is effective, safe, good value for money and will not have a large impact on the MBS budget. MSAC noted PBAC at its March 2026 meeting was of a mind to recommend the medicine selpercatinib for people with locally advanced or metastatic medullary thyroid cancer if MSAC supported the testing.

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

MSAC noted this codependent application from Eli Lilly Australia requested Medicare Benefits Schedule (MBS) listing of ret proto-oncogene (*RET*) variant testing for access to the tyrosine kinase inhibitor (TKI) selpercatinib to treat locally advanced or metastatic medullary thyroid cancer (MTC).

MSAC noted that at its March 2026 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) deferred its decision to list selpercatinib on the Pharmaceutical Benefits Scheme (PBS), with a mind to recommend pending MSAC's consideration of *RET* testing.

MSAC has not previously considered somatic *RET* testing in patients with MTC for MBS listing; however, MSAC recalled it had supported germline *RET* testing for suspected multiple endocrine neoplasia type 2 (MEN2; MBS items 73339 and 73340) in March 2018 (Application 1152). MSAC noted these patients would not require additional *RET* testing if they were diagnosed with germline *RET* variants because they would already be eligible for selpercatinib on the basis of their germline status. MSAC also recalled *RET* testing for non-small cell lung cancer (NSCLC), as part of a gene panel to access selpercatinib (MBS items 73437 and 73439) was considered and supported at its November 2022 meeting (Application 1721).

MSAC noted the consultation input from medical/health organisations and consumer groups indicated support for this application. MSAC noted feedback emphasised the importance of cascade testing and genetic counselling when a heritable variant is identified, but considered this not relevant to the application as it was for somatic testing of tumour tissue to enable access to treatment, rather than germline testing. However, MSAC acknowledged that the results from this testing may lead to additional germline testing for some patients and their families and this would be covered by existing MBS items for germline testing and cascade testing for first-degree relatives.

MSAC noted MTC is a rare form of thyroid cancer that accounts for approximately 4% of all thyroid cancers[1]. It can occur sporadically or as a hereditary condition due to germline genetic changes which may occur as part of conditions such as multiple endocrine neoplasia type 2 (MEN2). MSAC noted variants in the *RET* gene are present in approximately 70% of patients with MTC[2], occurring in about 98% of hereditary cases and around 50–60% of sporadic cases[3,4]. The

[1] Cancer Australia Types of thyroid cancer. https://www.canceraustralia.gov.au/cancer-types/thyroid-cancer/types-thyroid-cancer#references

[2] Wirth, et al 2020, 'Efficacy of Selpercatinib in RET-Altered Thyroid Cancers', *N Engl J Med*, vol. 383, no. 9, Aug 27, pp. 825-835 10.1056/NEJMoa2005651

[3] Gild, ML, et al. (2023). Medullary Thyroid Cancer: Updates and Challenges, *Endocrine Reviews*, Volume 44, Issue 5, October 2023, Pages 934–946, https://doi.org/10.1210/endrev/bnad013

[4] Parimi V, et al (2023). Genomic landscape of 891 RET fusions detected across diverse solid tumor types. *NPJ Precis Oncol* 7(1): 10.

RET gene encodes a transmembrane tyrosine kinase receptor. Clinically, MTC can range from slow-growing (indolent) to aggressive disease, and it is frequently metastatic, with around half of patients presenting with metastatic disease at diagnosis.

MSAC noted feedback from the Royal College of Pathologists of Australasia (RCPA) suggested that a fee of $682.35 for a small gene panel test, consistent with MBS item 73438, would be appropriate. MSAC further noted that the Neuroendocrine Cancer Australia supported a fee of $400, which aligned with the fee advice received from Genomics Australia (GA). MSAC agreed with GA that a fee of $400 was appropriate for the proposed single-gene method-agnostic test. MSAC acknowledged that *RET* testing methods are already well established in Australia and most laboratories will test using next-generation sequencing (NGS) based methods, as it is more sensitive and preferable compared to polymerase chain reaction (PCR) methods.

MSAC also agreed with ESC that using the wording '*RET* gene' in the MBS item descriptor was appropriate as the gene symbol is familiar terminology, so it was not necessary to also refer to the gene's full name 'ret-proto-oncogene' as suggested by the department. MSAC considered it appropriate to not specify testing frequency to allow clinicians to order repeat test if clinically necessary. MSAC noted that although it was unlikely that a patient would require additional testing, re-testing may be warranted in cases of tumour heterogeneity or treatment resistance. MSAC noted there were currently no second-generation *RET* inhibitors on the market, but considered this could change, so ensuring there were no restrictions on testing frequency would futureproof the MBS item. MSAC advised that the MBS item descriptor should be pathologist determinable and should restrict requesting of the test to specialist or consultant physicians. MSAC advised the department and the RCPA inform pathologists that the test is pathologist determinable.

MSAC noted that the testing could take place either at diagnosis (regardless of stage) or when patients have advanced or metastatic MTC. MSAC considered it appropriate to test at diagnosis to reduce treatment delays. MSAC considered this is particularly important for equity of access, as individuals in rural and remote areas often experience longer test turnaround times than those in metropolitan areas and if treatment is required, they may need to plan their travel to a metropolitan centre to receive treatment. MSAC acknowledged that, in some cases, patients diagnosed with early-stage disease may not require immediate access to selpercatinib, and that there may be a considerable period between genetic testing and initiation of treatment.

MSAC noted the absence of trial data evaluating test performance using standard Australian testing methods; however, it accepted the assumption that the test would have 100% sensitivity and specificity when performed successfully. MSAC noted that a quality assurance program (QAP) was available for *RET* testing in Australia and did not foresee additional implementation issues. MSAC considered the test to be safe as it is conducted on existing biopsy tissue obtained at diagnosis. However, MSAC noted in rare cases, if a new biopsy is required, it may carry some safety risks.

MSAC noted evidence supporting selpercatinib's effectiveness for patients with *RET* variants. MSAC acknowledged that there is a high unmet clinical need for effective treatments for the proposed condition. However, MSAC noted there was no evidence to support testing the drug's effectiveness in patients that are *RET* wildtype, raising uncertainty about codependency. However, MSAC noted that selpercatinib functions by binding to *RET* receptors that are activated due to *RET* gene variants. Therefore, MSAC agreed with ESC that based on its mechanism of action, the biologically plausibility that selpercatinib acts as a targeted treatment for patients with *RET* variant MTC was reasonable. Overall, MSAC considered that the clinical claim that selpercatinib is superior to placebo in terms of efficacy and has an inferior but clinically manageable safety profile in treatment naïve patients with *RET* positive advanced or metastatic medullary thyroid cancer was reasonable.

MSAC noted the stepped economic evaluation presented was a cost-utility analysis comparing selpercatinib to best supportive care (BSC). The incremental cost-effectiveness ratio (ICER) was analyses based on different numbers needed to treat (NNTs) and the ESC suggested $400 test

cost demonstrated that the ICER was not sensitive to the testing component of the application, with cost-effectiveness primarily driven by the high cost of selpercatinib.

MSAC noted that the financial impact to the MBS for testing all patients at diagnosis was $0 to < $10 million in Year 1 increasing to $0 to < $10 million in Year 6, based on estimated utilisation of approximately < 500 patients per year. Additional analyses in the commentary suggested that the financial impact to the MBS could be as high as $0 to < $10 million in Year 1 because of the prevalent patients requiring *RET* testing (approximately 500 to < 5,000 patients in total). MSAC considered this number to be highly uncertain because there were no reliable estimates of patients who were self-funding the test at the time, but MSAC noted that the commentary used an average number of patients accessing the test of about < 500 per year after Year 1, which aligned with the base case financial impact in Years 2 to 6. Overall, MSAC considered the financial impact to the MBS to be modest due to the rarity of MTC, although the financial impact to the PBS was substantial, driven by the high cost of selpercatinib.

4. Background

MSAC has not previously considered somatic *RET* variant testing in MTC and the PBAC has not considered selpercatinib for the treatment of locally advanced or metastatic MTC. The submission claimed somatic *RET* variant testing for determining eligibility for selpercatinib is routinely performed in clinical practice but is funded under state and territory hospital funding arrangements or privately. The commentary noted that PASC stated that the number of patients who have received selpercatinib thus far is very low, which suggested that it was likely only a small number of patients had been receiving somatic *RET* testing for predictive purposes (p14, Ratified PICO Confirmation 1804).

Germline *RET* variant testing has been previously considered by MSAC and supported for public funding for diagnostic purposes in patients suspected of Multiple Endocrine Neoplasia, type 2 (MEN2; MSAC Application 1152). Currently, there are two MBS funded items to (i) identify germline *RET* alterations in patients with a suspected clinical diagnosis of MEN2 (MBS item 73339) and (ii) facilitate familial cascade testing for detection of a known mutation in the *RET* gene in an asymptomatic relative of a patient with a documented pathogenic *RET* mutation (MBS item 73340).

Somatic nucleic acid based multigene panel testing of the fusion status of *RET*, among other genes, in a patient with a new diagnosis of non-small cell lung cancer (NSCLC) to determine eligibility for relevant treatments on the PBS are also publicly funded (MBS items 73437 and 73439).

5. Prerequisites to implementation of any funding advice

Laboratories conducting *RET* variant testing using in-house in vitro diagnostic (IVD) medical devices would be National Association of Testing Authorities (NATA) accredited to ensure validity and compliance with national quality standards, and commercial IVDs would be registered on the Australian Register of Therapeutic Goods (ARTG). In the application process, it was stated that testing would be performed by qualified molecular pathologists, who require expertise in next generation sequencing (NGS) or polymerase chain reaction (PCR) based assays used for *RET* testing.[5] Pathologist training and ongoing quality assurance programs are expected to support the standardisation and accuracy of *RET* testing, which is part of current standard practice in Australian laboratories.

[5] https://www.msac.gov.au/sites/default/files/2025-05/1804_-_pico_set.pdf

The commentary noted the submission did not state how many laboratories currently perform somatic or germline *RET* variant testing in Australia and this was not apparent during the evaluation. PASC noted that a quality assurance program (QAP) would be required to be assessed and established by the Royal College of Pathologists of Australasia Quality Assurance Programs (RCPA QAP) for use in laboratories in Australia. PASC considered that "a QAP should include training, standardisation and accuracy of *RET* variant testing, and the appropriate curation of activating *RET* variants (as in silico modelling is better validated for curation of loss of function variants)" (p16, Ratified PICO Confirmation 1804).

The commentary noted the submission did not provide information on any relevant IVDs on the ARTG. The commentary noted the NGS Oncomine Dx Target Test (ODxTT) is a gene panel test registered on the ARTG as a companion diagnostic test in patients with NSCLC and is indicated to detect sequence variations (SNVs, deletions, insertions, and fusions) in 26 cancer-related genes on DNA and RNA from formalin fixed paraffin embedded (FFPE) tissue samples.[6] In the LIBRETTO-531 trial, the LLT NGS assay was used but was not defined and details of the LLT assay were lacking. A concordance analysis was conducted in LIBRETTO-531 based on the enrolled MTC patients that compared the test results from using the LLT assay to the ODxTT test results (see Section 9 of the MSAC Executive Summary). During the application process, it was noted that somatic *RET* variant testing is offered privately as part of a comprehensive somatic mutation panel rather than a standalone test (offered by Sonic Genetics and Australian Clinical Labs); however, the details of these tests were not described.[7] It remained unclear what test would be used in clinical practice in Australia.

Selpercatinib was recommended by the Therapeutic Goods Administration (TGA) delegate on 1 September 2025 for the treatment of adult and adolescent (12 years of age and older) patients with advanced or metastatic *RET* variant MTC who require systemic therapy.

6. Proposal for public funding

The submission's proposed MBS item descriptor for somatic *RET* variant testing is presented in Table 2

Table 2 Submission proposed MBS item

Category 6 – Pathology Services Group P7 – Genetics
MBS item *YYYY Detection of mutations in the *RET* gene in patients with a clinical diagnosis of medullary thyroid cancer requested by a specialist or consultant physician who manages the treatment of the patient to determine access to specific therapies relevant to these mutations listed on the Pharmaceutical Benefits Scheme (PBS).
Fee: $400.00 Benefit 75% $300.00 85% $340.00

Source: Table 1-6, p46 of the submission

The applicant proposed MBS fee was $400 per test, which was the same as MBS item 73339 for the detection of germline *RET* variants and is consistent with other MBS items for single gene panel tests (e.g. MBS item 73338 fee $362.60). In the application process, it was noted that somatic *RET* variant testing is offered by Sonic Genetics at a non-Medicare rebatable fee of $2,100 for a single nodule and $1,164 for each additional nodule, and by Australian Clinical Labs at a non-Medicare rebatable fee of $750. These fees were noted to be higher than the proposed item as these tests include broader variant gene panels.

[6] https://www.tga.gov.au/resources/artg/426895

[7] https://www.msac.gov.au/sites/default/files/2025-05/1804_-_application_summary_*RET*_testing.pdf

The commentary noted that PASC considered the applicant proposed fee to be reasonable and comparable to other single gene tests listed on the MBS. Feedback from the Royal College of Pathologists of Australasia (RCPA) indicated that the RCPA considered the fee was too low and was concerned that some laboratories would not be able to provide the testing at the proposed fee. The RCPA instead suggested that a fee of $682.35 was more appropriate, citing MBS item 73438, which is for a multi-gene panel test. SA pathology confirmed that $400 would be sufficient to cover costs for *RET* testing by adapting an existing small solid tumour NGS panel to detect *RET* alterations for thyroid tumours.

PASC noted that testing of a single gene should not cost the same as a small gene panel. MSAC has previously supported single gene testing using NGS methods for a fee of $340 (Application 1750)[8], noting (p3) that 'most contemporary *IDH1* tumour testing is performed as part of a gene panel test (using next generation sequencing) rather than as a single gene test'. PASC additionally noted that not all laboratories need to be able to provide *RET* testing due to the small number of patients expected to be tested.

The proposed MBS item descriptor was test assay agnostic as was the current MBS item for germline *RET* variant testing. The submission noted that conventional DNA-based methods such as NGS and PCR were expected to be used in practice. The RCPA noted NGS offered significantly higher sensitivity for detecting *RET* variants and was more efficient and scalable, allowing laboratories to test for multiple tumour and gene types on a single platform. The commentary noted NGS was predominantly performed in the LIBRETTO-531 (263/291 [90.7%]) and the LIBRETTO-001 trials (86%) for detecting *RET* variants.

As discussed in Section 3 of the MSAC Executive Summary, the test expected to be used in Australian clinical practice, either a single gene or multi-gene panel test, was unclear. In MSAC Application 1766, MSAC considered that the proposed fee for *AKT* pathway testing ($2,200) was high given it assumed comprehensive genomic profiling (CGP) testing was required; however, MSAC considered that the need for CGP testing was not clearly justified, as the testing would be performed for 3 genes only and more targeted options for testing were available, which could reduce both costs and failure rates (p6, MSAC Application 1766 Public Summary Document [PSD] November 2024).[9]

The proposed MBS item descriptor allowed testing in patients with a clinical diagnosis of MTC. However, the commentary considered that patients with an already known germline *RET* variant would not require somatic testing since these patients would already be eligible for selpercatinib. It might be appropriate to include in the item descriptor that patients with "no known germline *RET* variant" would be eligible as per the test population described in the Ratified PICO Confirmation 1804.

PASC also noted that patients with a histological (rather than clinical) diagnosis of MTC would be eligible for testing, and advised that the proposed descriptor should permit more than one test per lifetime, because resistant variants may be identified in future that would be worthwhile identifying after treatment.

The key components addressed by the submission are presented in Table 3.

[8] 1750_final_psd_-_november_2024_-_redacted.pdf

[9] https://www.msac.gov.au/sites/default/files/2025-03/1766_final_psd_-_nov2024_-_redacted.pdf

Table 3 Key components of the clinical issue addressed by the submission

Component	Description
Population	Test: Medullary thyroid cancer (MTC) patients without germline variants Drug: Patients with histologically and cytologically confirmed advanced or metastatic MTC with a *RET* alteration (somatic or germline) and (WHO) ECOG PS ≤2
Intervention	Test: Testing of somatic tumour tissue using commercially available platforms or laboratory accredited in house tests. Drug: Selpercatinib orally administered in *RET* alteration MTC patients until disease progression. In patients with bodyweight ≥50 kg, the recommended dose of selpercatinib is 160 mg twice daily. In patients with bodyweight <50 kg, the recommended dose of selpercatinib is 120 mg twice daily
Comparator	Test: No testing for somatic *RET* alteration Primary: Best supportive care Secondary: Standard of care (cabozantinib 140 mg/day or vandetanib 300 mg/day)
Outcomes	Progression free survival, treatment failure free survival, overall survival, overall response, duration of response, safety, and health related quality of life
Clinical claim	In treatment naïve patients with *RET* alteration advanced or metastatic MTC, selpercatinib is superior to placebo in terms of efficacy and has an inferior, but clinically manageable, safety profile.

Source: Table 1-1, p29 of the submission
ECOG = Eastern Cooperative Oncology Group; MTC = medullary thyroid cancer; PS = performance status; *RET* = *RET proto-oncogene*; WHO = World Health Organisation

The commentary noted that the proposed populations for both testing and treatment with selpercatinib were inconsistently applied throughout the submission; in particular, the submission's requested MBS test and PBS treatment populations did not align with the populations in the Ratified PICO Confirmation, proposed change in clinical management, the clinical evidence, economic model, and the financial estimates (see Attachment to the MSAC ESC Report). As the intended testing and treatment populations were unclear in the submission, the generalisability of the evidence presented to the proposed testing and treatment populations in clinical practice is uncertain.

The commentary considered it appropriate that:

- The population eligible for testing was patients "with a confirmed histological diagnosis of MTC, who have not already undergone testing of tumour tissue for clinically significant *RET* variants and do not have a known germline *RET* variant" as per the (p4) Ratified PICO Confirmation 1804.

The population eligible for treatment with selpercatinib was *RET* variant locally advanced or metastatic MTC patients with unresectable disease and documented disease progression as per the LIBRETTO-531 trial.

7. Population

MTC is considered a neuroendocrine tumour that arises from parafollicular C cells within the thyroid and contributes to 4% of thyroid cancers.[10] There are two subtypes of MTC, (i) sporadic and (ii) hereditary. The submission stated clinically significant *RET* variants were present in 70% of all MTC patients (98% of hereditary and 50-60% of sporadic MTC). Sporadic MTC represents 75-80% of MTC cases and predominantly affects patients in their fifth or sixth decade of life. Hereditary MTC is primarily due to germline variants in the *RET* gene, and is present in 20-25% of cases with onset typically within a patient's third decade of life. Hereditary MTC is the primary component leading to the inherited condition MEN2, which consists of 3 related disorders: MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC). MEN2A is the cause of an estimated 23% of MTC cases and is characterised by MTC, pheochromocytoma, and primary

[10] Cancer Australia. Thyroid cancer in Australia statistics. URL: https://www.canceraustralia.gov.au/cancer-types/thyroid-cancer/thyroid-cancer-australia-statistics

parathyroid hyperplasia, where onset typically occurs in the third decade of life. MEN2B is responsible for <2% of MTC cases, is more aggressive than MEN2A, is characterised by MTC and pheochromocytoma (~50% of patients) but not hyperparathyroidism, and typically occurs within the first decade of life. FMTC accounts for <1% of MTC cases and is characterised by MTC without pheochromocytoma or parathyroid hyperplasia, and onset occurs during the fifth to sixth decade of life (Raue 1994; Wells 2015; Haddad 2022).[11,12,13]

RET is a transmembrane tyrosine kinase receptor encoded by the *RET* gene, which plays an important role in the development and maintenance of the enteric nervous and genitourinary systems in neonates such as kidney induction, spermatogonial stem cell maintenance, neural crest cell migration, and central and peripheral nervous system neuron maintenance (Walker & Mulligan 2025).[14] Pathogenic *RET* variants in MTC are usually point mutations at exons 10, 11, 13, 14, 15, 16, and rarely in exons 5 and 8, that lead to constitutive activation of *RET* and uncontrolled cell proliferation, tumour development, and progression (Gild 2023). The most common clinically significant *RET* variant causing sporadic MTC is *M918T* (in exon 16), which was noted to be associated with more aggressive disease, characterised by larger tumours, nodal and distant metastases, advanced stage at diagnosis, recurrence, and reduced survival. The commentary noted the prognosis of *RET M918T* variants may be similar in sporadic and hereditary MTC (Machens 2020).[15] Multiple *RET* variants or variants concurrent with *RET* may also exist and are associated with more aggressive disease (Romei 2016).[16]

The submission stated clinically significant *RET* variants were present in 70% of all MTC patients (98% of hereditary and 50-60% of sporadic MTC), which the commentary considered was consistent with the literature (Elisei 2019 reported 115/117 [98.3%] hereditary MTC had a germline *RET* variant; Ciampi 2019 reported 101/181 [55.8%] sporadic MTC had a *RET* variant; Shirali 2024 reported 139/191 [72.8%] of sporadic MTC had a *RET* variant).[17, 18, 19] The commentary noted the prevalence of *RET* variants may be higher in patients with advanced or metastatic disease where Romei 2016 reported approximately 94% of advanced tumours were *RET* variant. In some apparently sporadic MTC cases, following germline testing these patients may actually have the hereditary form (6% of cases; Gild 2023). In *RET* wildtype patients, variants

[11] Raue, F, et al. (1994). Multiple endocrine neoplasia type 2. Clinical features and screening. Endocrinol Metab Clin North Am. 1994;23(1):137.

[12] Wells SA Jr, et al. (2015). American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma Thyroid. 2015;25(6):567.

[13] Haddad, RI, et al. (2022). Thyroid Carcinoma, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network, 20(8), 925-951. https://doi.org/10.6004/jnccn.2022.0040

[14] Walker, TJ & Mulligan, LM (2025). Cellular mechanisms of *RET* receptor dysfunction in multiple endocrine neoplasia 2, *Endocr Relat Cancer*, vol. 32, no. 1, Jan 1, 10.1530/erc-24-0187.

[15] Machens, A, et al. Dissection of *RET* p.M918T-driven progression of hereditary vs. sporadic medullary thyroid cancer. *European Journal of Surgical Oncology*, Volume 51, Issue 3, 109549

[16] Romei, C, et al. (2016). New insights in the molecular signature of advanced medullary thyroid cancer: evidence of a bad outcome of cases with double *RET* mutations. *J Med Genet*. 2016 Nov;53(11):729-734. doi: 10.1136/jmedgenet-2016-103833. Epub 2016 Jul 28. PMID: 27468888.

[17] Elisei, R, et al. (2019). Twenty-Five Years Experience on *RET* Genetic Screening on Hereditary MTC: An Update on The Prevalence of Germline *RET* Mutations. *Genes (Basel)*. 2019 Sep 10;10(9):698. doi: 10.3390/genes10090698. PMID: 31510104; PMCID: PMC6771015.

[18] Ciampi R, et al. (2019). Genetic Landscape of Somatic Mutations in a Large Cohort of Sporadic Medullary Thyroid Carcinomas Studied by Next-Generation Targeted Sequencing. *iScience*. 2019 Oct 25;20:324-336. doi: 10.1016/j.isci.2019.09.030. Epub 2019 Sep 26. PMID: 31605946; PMCID: PMC6817656.

[19] Shirali, AS, et al. (2024). Next-Generation Sequencing in Sporadic Medullary Thyroid Cancer Patients: Mutation Profile and Disease Aggressiveness, *Journal of the Endocrine Society*, Volume 8, Issue 6, June 2024, bvae048, https://doi.org/10.1210/jendso/bvae048

at the *rat sarcoma oncogene* (*RAS*) contributed to approximately 70% of wildtype cases (Zhang 2024).[20]

The submission did not discuss the stability of the biomarker (i.e. the likelihood that the biomarker would change over time such as in the primary tumour and in metastases). The commentary noted that MSAC considered germline *RET* variants were stable (p150, MSAC Application 1152).[21] In comparison, the commentary noted the stability of somatic *RET* variants was uncertain, where in a study in 56 patients with metastatic MTC, Romei 2018 reported 20% (11/56) discordance in *RET* variant profiles reported between primary MTC tumour and subsequent metastatic tumour tissue.[22] Of these cases, the authors noted that in 3 patients (5%) the primary MTC tumour was *RET* wildtype compared to its metastatic tumour being positive for a *RET* variant. While conclusions were uncertain, this might warrant secondary testing for some patients who initially tested negative for a *RET* variant but later experience distant recurrence.

The commentary also noted the Ratified PICO Confirmation 1804 stated that acquired resistance to targeted *RET* treatments can occur prior to initiation of treatment (i.e. primary resistance) due to on target variants or during treatment due to off target variants that bypass the inhibited *RET* pathway. The commentary noted that in patients treated with *RET* inhibitors (selpercatinib or pralsetinib) acquired resistance via the bypass mechanism was reported in 9/12 patients and the remainder were due to on target resistance (Hadoux 2023);[23] though the frequency of acquired resistance in practice was unclear.

Clinical presentations of MTC commonly include thyroid nodule in the upper portion of the gland where C cells are primarily located and cervical lymphadenopathy (i.e. swelling of lymph nodes). Approximately half of MTC patients present with stage III/IV MTC, of whom 10-20% may present with distant metastases in the brain, bones, lungs and liver. Clinical presentations of MTC are broadly similar between sporadic and hereditary MTC noting that onset of disease in hereditary MTC is earlier and typically involves bilateral tumours (i.e. both sides of the thyroid are involved) or multiple tumours compared to sporadic MTC in which onset is typically later and present with unilateral tumours.

MTC may be suspected following clinical examination, imaging and blood tests, while confirmation of MTC diagnosis occurs only after histopathological assessment of surgical or biopsy specimen (using fine needle aspirate [FNA]). Calcitonin and carcinoembryonic antigen (CEA) levels and doubling times are key features of MTC where shorter doubling times confer higher risk of recurrence and worse survival. High histological grade and advanced/metastatic stage of disease at diagnosis are also predictors of worse outcomes.

The commentary noted disease behaviour of MTC can range from indolent to aggressive. Santillan 2025 considered MTC to be a relatively slow growing tumour with favourable long term outcomes, including in patients with known metastatic disease.[24] In comparison, for patients with radiographic evidence of disease progression, their tumour may be considered more aggressive with greater disease burden and worse survival outcomes where rapid calcitonin or CEA doubling

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[20] Zhang, Y, et al. (2024). Molecular genetics, therapeutics and *RET* inhibitor resistance for medullary thyroid carcinoma and future perspectives. *Cell Commun Signal* 22, 460 (2024). https://doi.org/10.1186/s12964-024-01837-x

[21] Newton S, et al. (2013). Genetic testing for hereditary mutations in the *RET* gene. MSAC Application 1152, Assessment Report. Commonwealth of Australia, Canberra, ACT.

[22] Romei, C, et al. (2018). *RET* mutation heterogeneity in primary advanced medullary thyroid cancers and their metastases. *Oncotarget*. Jan 4;9(11):9875-9884. doi: 10.18632/oncotarget.23986. PMID: 29515777; PMCID: PMC5839408.

[23] Hadoux, J, et al. (2023). Patterns of Treatment Failure After Selective Rearranged During Transfection (*RET*) Inhibitors in Patients With Metastatic Medullary Thyroid Carcinoma, *JCO Precis Oncol,* vol. 7, Sep, p. e2300053 10.1200/po.23.00053.

[24] Santillan, MR, et al. (2025). Systemic Therapies for Advanced Medullary Thyroid Carcinoma. In: Raue, F., Frank-Raue, K. (eds) *Medullary Thyroid Carcinoma*. Recent Results in Cancer Research, vol 223. Springer, Cham. https://doi.org/10.1007/978-3-031-80396-3_12

times and high grade pathological grade were considered features of aggressive tumour behaviour (Santillan 2025). Ten year survival ranged between 76-92% in patients with locally advanced MTC and 38-53% in patients with metastatic MTC. In an Australian study centre (Royal North Shore Hospital in Sydney, Australia, between 1986 and 2020), Kesby 2022 (N=154) reported a median overall survival (OS) of 18.8 to 19.3 years in locally advanced or metastatic MTC patients and 11.8 years in the subset of patients with metastatic MTC. Notably, these survival estimates were likely representative of patients with indolent or non-progressive disease.

Test population

The submission considered two potential test scenarios as per the Ratified PICO Confirmation (pp19-20):

- Option 1: tumour tissue testing at diagnosis of or progression to (i.e. progression or recurrence) locally advanced or metastatic MTC (i.e. stage III/IV MTC).
- Option 2: tumour tissue testing at the point of diagnosis, irrespective of stage.

The submission proposed testing at the point of MTC diagnosis (i.e. Option 2) as the base case and noted this would avoid the need for tissue block and previous germline molecular report retrieval, allowing clinicians and patients to determine selpercatinib eligibility before disease progression. The commentary noted this was consistent with PASC advice that it would not be unreasonable to test all patients with MTC, regardless of stage. PASC also noted advice from the applicant's clinical experts that confirmation of a histological diagnosis of MTC would only occur after surgical resection when tumour tissue could be obtained for histology and that *RET* testing (either somatic or germline) would occur after this (p12, Ratified PICO Confirmation 1804). If surgery is not indicated, the tumour tissue sample would be obtained via biopsy. The commentary considered that previous germline molecular report retrieval would still be required irrespective of stage of testing in order to confirm variant status.

Alternatively, the commentary considered that testing at locally advanced or metastatic stages (Option 1) would also require tissue block retrieval and/or biopsy if the surgical resection sample was no longer viable, or if the tumour was unresectable (noting the increased likelihood of tumours being unresectable following progression to advanced/metastatic stages). The testing scenario in the pivotal trial LIBRETTO-531 was more aligned with Option 1 where *RET* variant testing was conducted at enrolment in patients with unresectable locally advanced or metastatic MTC and documented disease progression.

The commentary noted that PASC considered patients would undergo testing for germline *RET* variants for diagnostic purposes of determining familial risk of MEN2 or testing for somatic *RET* variants for predictive purposes of determining eligibility for selpercatinib treatment. PASC also stated that it may be appropriate to perform germline testing first for patients with a family history of MTC or MEN2, otherwise performing somatic testing first would be more appropriate (pp12-13, Ratified PICO Confirmation 1804).

PASC considered that while patients would be interested in testing for both purposes, the time from test to result of germline *RET* variant testing was expected to be 8 to 12 weeks due to the requirement for genetic counselling (where PASC noted there is a shortage of counsellors). In comparison, somatic testing of tumour tissue was likely to influence a patient's treatment faster given genetic counselling is not required. The turnaround time of *RET* variant testing itself (somatic or germline) was expected to be a few weeks according to clinical experts noted in the submission. PASC also considered somatic testing would be beneficial at reducing the number of patients who would require genetic counsellors (as those with wildtype *RET* genes in tumour tissue would not require genetic counselling or germline testing); this may therefore help triage the use of genetic counsellors to those most likely to need this service.

If a clinically significant *RET* variant was identified in tumour tissue, based on the tumour tissue test result alone, it would be unknown whether the variant was somatic or germline in origin. This could only be confirmed through germline *RET* testing, with a positive germline *RET* test indicative of a germline variant (which then has implications for cascade testing of family members) and a negative germline test indicative of a somatic *RET* variant. Patients with either a somatic or germline *RET* variant would be eligible for selpercatinib. Therefore, if a patient presents with a newly diagnosed MTC and has previously received germline testing, for the purposes of accessing selpercatinib, they would only require testing of tumour tissue if their previous test was unavailable or there was uncertainty about eligibility due to a wildtype, benign or negative finding. Alternatively, if a clinically diagnosed MEN2 patient with a newly diagnosed MTC has not previously received *RET* testing, then they will require tumour tissue testing. They may also require germline *RET* variant testing if the tumour test is positive for the *RET* variant.

As noted by the commentary in Section 1 of the MSAC Executive Summary, the proposed test population in the submission was not clear, though the test population as per the Ratified PICO Confirmation 1804 may be appropriate:

Patients with a confirmed histological diagnosis of MTC, who have not already undergone testing of tumour tissue for clinically significant *RET* variants and do not have a known germline *RET* variant (p4, Option 2 in Ratified PICO Confirmation 1804).

8. Comparator

Test comparator

The comparator test used in the submission was no testing for somatic *RET* variants; the commentary considered this may be reasonable.

The commentary noted the nominated comparator differed to the comparator test proposed in the Ratified PICO Confirmation 1804 which was 'germline *RET* variant testing (as suspected in patients with MTC) with no *RET* variant testing of tumour tissue'.

The commentary noted that germline *RET* variant testing may not be commonly conducted in practice due to limited access to genetic counsellors. Further, as noted by PASC, data from the Victorian Cancer Registry suggested only 66% of patients with MTC have been receiving germline testing, and based on the services processed for MBS item 73339, a total of 156 services were claimed between July 2020 and June 2025 in private clinical practice.[25] While germline testing may be funded by states and territories (i.e. in public hospitals), the nature and magnitude of this testing was unknown. Additionally, the commentary considered that somatic *RET* testing would not replace all germline *RET* testing. Those undergoing somatic *RET* testing with the test detecting a *RET* variant may still (and likely should) undergo germline *RET* testing for the diagnosis of MEN2.

[25] https://medicarestatistics.humanservices.gov.au/SASStoredProcess/guest?_PROGRAM=SBIP%3A%2F%2FMETASERVER%2FShared+Data%2Fsasdata%2Fprod%2FVEA0032%2FSAS.StoredProcess%2Fstatistics%2Fmbs_item_standard_report&DRILL=ag&group=73339&VAR=services&STAT=count&RPT_FMT=by+time+period+and+state&PTYPE=finyear&START_DT=202007&END_DT=202506

Treatment comparator

Best supportive care (BSC) was nominated as the main treatment comparator for selpercatinib, which the submission stated includes symptom control (e.g. diarrhoea) or palliative care (e.g. pain management). Cabozantinib and vandetanib were nominated as secondary comparators.

The commentary considered these nominations were reasonable noting that access to multikinase inhibitor (MKI) therapies in Australia for the treatment of MTC was limited, as cabozantinib is not TGA approved and vandetanib, while TGA approved for MTC, is not PBS-listed for MTC. As such, most patients would receive BSC. According to the Australian sample from Papachristos 2023, treatment with kinase inhibitors was only reported in 30/235 (12.8%) MTC patients, of which 20/235 (8.5%) had cabozantinib or vandetanib.

The commentary noted that while the submission considered cabozantinib and vandetanib as the current standard of care (SOC), the NCCN and ESMO guidelines noted preference for selective *RET* inhibitors in *RET* variant MTC (e.g. selpercatinib or pralsetinib). However, cabozantinib and vandetanib may be the preferred option in MTC irrespective of *RET* variant status in jurisdictions where selective *RET* inhibitors are not available.

The commentary also noted that the proposed population eligible for treatment with selpercatinib did not specify that a patient required prior surgery or has unresectable disease, which was not consistent with the LIBRETTO-531 trial or clinical guideline recommendations. For the submission's proposed population eligible for treatment, surgery may be considered the appropriate comparator; however, if the proposed treatment population was aligned with the LIBRETTO-531 trial, then BSC would be the appropriate comparator.

9. Summary of public consultation input

Consultation input was welcomed from:

1804 – Genetic testing to detect *RET* variants in patients with medullary thyroid cancer to determine eligibility for PBS subsidised selpercatinib treatment	No. of Inputs Received
Organisations (9)	
I am providing input on behalf of a consumer group or organisation. Consumer organisations are not-for-profit organisations representing the interests of healthcare consumers, their families and carers.	4
I am providing input on behalf of a medical, health, or other (non-consumer) organisation. For example, input on behalf of a group of clinicians, research organisation, professional college, or from an organisation that produces a similar service or technology.	5
Grand Total	**9**

MSAC received consultation input from the following organisations:

- Omico
- Public Pathology Australia (PPA)
- Rare Cancers Australia (RCA) (2 inputs)
- Royal College of Pathologists of Australasia (2 inputs) (RCPA)
- NeuroEndocrine Cancer Australia (NECA)
- Therapeutic Goods Administration (TGA)
- Australian Thyroid Foundation (ATF)

Level of support for public funding

Consultation input was supportive of public funding for testing options to detect *RET* variants in patients with medullary thyroid cancer (MTC) to determine eligibility for pharmaceutical benefits scheme (PBS) subsidised selpercatinib treatment. NECA asserted that the proposed targeted testing and treatment combination 'addresses a clear and urgent clinical need within a small but high risk population.'

Respondents, particularly consumer groups, viewed broader and more equitable access to *RET* genetic testing as important for improving clinical outcomes and ensuring appropriate access to targeted therapies.

Comments on PICO

The consultation input agreed with the proposed population and comparator, noting that individuals with rare cancers such as MTC are an underserved population with limited treatment options.

The input from consumer groups included information on individual experiences with MTC and *RET* testing. Input stated that treatment options for MTC remain limited and include radiation therapy, theranostics, non-targeted therapies, and extensive surgeries, which can have significant side effects and uncertain outcomes.

Perceived Advantages

Benefits of public funding reported in the consultation input included refining the diagnosis of MTC, guiding treatment decisions, and providing access to more timely, targeted, and better-tolerated treatment.

The RCPA and NECA both noted that clinical trials have shown that patients with *RET*-variant MTC treated with selpercatinib have better outcomes compared to standard therapies, including longer progression-free and overall survival. The RCPA stated that public funding for *RET* testing would align MTC management in Australia with current clinical practice guidelines.

Input from consumer groups stated that much of the current testing and treatment for MTC was self-funded and was a financial burden in addition to the physical and emotional burden of having cancer. Public funding of testing and associated targeted therapies would help to alleviate some of this burden.

RCA input included a patient's experience of accessing *RET*-targeted therapy, which led to a significantly improved quality of life compared to conventional therapies.

Consumer groups also emphasised the importance of genetic testing to families, stating that *RET* testing plays a crucial role in gene-informed cancer risk assessment, genetic counselling, and predictive testing for family members.

Perceived Disadvantages

The only disadvantage of public funding reported in the consultation input was the stress associated with the chance of identifying a heritable variant.

Support for Implementation and Issues

Consultation input supported the proposed approach to implementation, with no major problems foreseen 'assuming there is clear communication around where testing can be accessed and

that pathology laboratories are adequately equipped to perform somatic *RET* variant analysis' (NECA).

NECA and RCA both identified the need for counselling services for individuals with a heritable variant identified.

The consultation input partially agreed with the proposed service descriptor. RCPA recommended the wording refer to "pathological diagnosis" of MTC rather than "clinical diagnosis" and that the service descriptor specify somatic testing. The RCPA also supported the item being pathologist determinable.

The consultation input ranged from agreeing to disagreeing with the proposed service fee. PPA stated that at least one laboratory could adapt an existing small solid tumour next generation sequencing (NGS) panel to detect *RET* mutations for thyroid tumours and that the proposed fee of $400 was adequate. NECA stated the fee was appropriate and in line with comparable genetic tests. The RCPA stated that the true cost of testing via NGS was more closely aligned with MBS item 73438, which is priced at $682.35 for a small gene panel, and strongly recommended aligning the *RET* testing fee with the small panel fee. The RCPA asserted that if the fee is set too low, laboratories may be unable to offer the test, leading to limited access, long turnaround times and delayed treatment for patients who may benefit from targeted therapies.

10. Characteristics of the evidence base

The submission presented a linked evidence approach, and the components are presented in Table 4.

Table 4 Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in clinical trials	Used in economic model
Accuracy and performance of the test (cross sectional accuracy)	The submission did not present test validity evidence.	☒ k=0 n=NA	NA	No
Prognostic evidence (longitudinal accuracy)	Elisei 2008 was a 10 year retrospective study that investigated the prognostic impact of somatic *RET* variants compared to *RET* wildtype in patients with MTC (N=100).	☒ k=1 n=100	Low to moderate risk	No
Change in patient management	Local and international clinical management guidelines (Gild 2023; ESMO [Filetti 2022] and NCCN [Haddad 2022]).	☒ k=3 n=NA	NA	NA
Treatment effect (enriched)	A single pairwise Bucher ITC of selpercatinib from LIBRETTO-531 and placebo from EXAM informed the primary clinical claim of selpercatinib vs BSC in the *RET* variant population. LIBRETTO-531 was a phase III open label randomised controlled trial of selpercatinib (n=193) vs physician's choice of cabozantinib or vandetanib (n=98) in patients with advanced or metastatic MTC who had a *RET* variant (determined by NGS or PCR), with unresectable disease, documented disease progression per RECIST v1.1, and were treatment naïve to kinase inhibitors. EXAM was a phase III double blinded, randomised control trial of cabozantinib (n=219) vs placebo (n=111) in advanced or metastatic MTC patients irrespective of *RET* variant status (determined by PCR), with unresectable disease, documented disease progression per mRECIST, and were treatment exposed to kinase inhibitors. The *RET* variant subgroup informed the ITC.	☒ k=2 n=621	LIBRETTO-531 low to moderate risk EXAM moderate risk	Yes

Source: Sections 2A to 2D of the submission

BSC = best supportive care; ESMO = European Society for Medical Oncology; k=number of studies; ITC = indirect treatment comparison; mRECIST = modified Response Evaluation Criteria in Solid Tumours; MTC = medullary thyroid cancer; n=number of patients; NA = not applicable; NATA = National Association of Testing Authorities; NCCN = National Comprehensive Cancer Network; NGS = next generation sequencing; PCR = polymerase chain reaction; RECIST = Response Evaluation Criteria in Solid Tumours

Notes:

ZETA was included as a sensitivity analysis that informed the BSC arm in the indirect comparison, however, this was not relevant to the MSAC Executive Summary and will not be presented here.

11. Comparative safety

Adverse events from testing

No test safety data was presented in the submission.

The submission considered that *RET* variant testing of tumour tissue was not expected to introduce new safety concerns, primarily because testing would occur following diagnosis of MTC on tumour tissue samples obtained from surgical resection, which reduces the need to biopsy (unless unresectable). The risk of a biopsy or rebiopsy was noted in the circumstance where the initial resected specimen was no longer viable, available or sufficient.

- The commentary considered that while testing at diagnosis was proposed to avoid the need for molecular report retrieval, in practice, for a patient who had a previous *RET* variant test and experienced progression or recurrence to stage III/IV, molecular report retrieval would still be required and thus potentially delay time to treatment. In circumstances where insufficient tissue samples were obtained or the sample is no longer viable or available (e.g. in archival tumour tissue), the commentary considered a rebiopsy may be performed. PCR based Sanger Sequencing performed in EXAM resulted in approximately one third of test results being unknown and was predominantly due to insufficient tissue sample potentially attributed to the use of archival tissue samples to determine *RET* variant status.
- Furthermore, for some patients there may be an extended period of time from when surgical resection was performed (and MTC diagnosed) and when the patient progresses to locally advanced or metastatic MTC. In these cases, rebiopsy may be considered to discern whether the tumour is metastatic disease or a different primary tumour. Even if metastatic disease is confirmed, retrieval of previous specimens/reports may not be available due to the progression of time. The commentary also noted the submission did not consider the possibility of developing resistance to treatment, for example, following disease recurrence or progression on treatment. In this circumstance, a second test may be considered (as is permitted under the proposed MBS item descriptor) and rebiopsy may be required; however, the likelihood or frequency of this was uncertain.

Adverse events from changes in management

The adverse events (AEs) in LIBRETTO-531 (selpercatinib vs cabozantinib or vandetanib) in *RET* variant patients and EXAM (cabozantinib vs placebo) in patients irrespective of *RET* variant status are presented in Table 5 1. The placebo arm from EXAM represented BSC in the submission, which the commentary considered reasonable.

Table 5 1Summary of safety results LIBRETTO-531 and EXAM (SAS)

	LIBRETTO-531		EXAM		RD % (95% CI)
AE	SELP (N=193)	CABO/VAND (N=97)	CABO (N=214)	PBO (N=109)	SELP vs PBO
Any TEAE	192 (99.5)	96 (99.0)	214 (100)	104 (95)	**5.1 (0.6, 9.6)**
Treatment related	178 (92.2)	95 (97.9)	NR	NR	NE
Grade ≥3 TEAE	119 (61.7)	79 (81.4)	167 (78)	36 (33)	**25.2 (10.6, 39.9)**
Treatment related	84 (43.5)	71 (73.2)	NR	NR	NE
Any SAE	59 (30.6)	33 (34.0)	113 (53)	26 (24)	**25.5 (10, 41)**
Treatment related	18 (9.3)	17 (17.5)	NR	NR	NE
AE leading to treatment discontinuation	11 (5.7)	30 (30.9)	49 (23)	10 (9)	-11.5 (-24, 1)
Treatment related	5 (2.6)	25 (25.8)	NR	NR	NE
SAE leading to treatment discontinuation	7 (3.6)	10 (10.3)	NR	NR	NE
Treatment related	2 (1.0)	6 (6.3)	NR	NR	NE
Deaths	10 (5.2)	16 (16.5)	141 (65.8)	77 (70.6)	-16.1 (-29.4, -2.7)
Deaths due to AE on treatment	5 (2.6)[a]	3 (3.1)[b]	NR[c]	NR[c]	NE
Death due to study disease	1 (0.5)	3 (3.1)	NR	NR	NE

Source: Table 2-24, p92 of the submission (LIBRETTO-531); Table 16, p58, Table 18, p51, Table 19, p51, Table 20, p63, NICE TA516 Assessment Report (EXAM); RD analyses conducted during the evaluation

AE = adverse event; CABO = cabozantinib; CI = confidence interval; n = number of participants reporting data; N = total participants in group; NE = not evaluable; NR = not reported; PBO = placebo; RD = risk difference; SAE = serious adverse event; SAS = safety analysis set; SELP = selpercatinib; TEAE = treatment emergent adverse event; VAND = vandetanib

[a] 5 deaths in selpercatinib arm due to diabetic ketoacidosis (1), COVID 19 (1), multiple organ dysfunction syndrome (1), pneumonia (1) and sudden death (1). One death was related to treatment (not reported which one).

[b] 3 deaths in cabozantinib/vandetanib arm due to cholangitis (1), haemorrhage (1), sudden death (1).

[c] values not reported but the NICE TA516 Assessment Reported stated that “treatment related remaining at 4 5% for cabozantinib and 1%

for placebo at both the interim and final analysis"
Note:
Bold text indicates a RD value that did not include 0.
Grey shaded cells indicates the treatment arms used in the ITC of AEs
The AE for EXAM were from NICE TA516 as these were not reported in the publications. The NICE TA516 Assessment Report noted these were from the respective CSRs at the latest DCOs
The ITC of selpercatinib and placebo was based on the RD from LIBRETTO-531 (selpercatinib vs cabozantinib/vandetanib) compared to the RD from EXAM (placebo vs cabozantinib). A RD <0 favoured selpercatinib.
Data cutoff dates and median follow up duration

- LIBRETTO-531 DCO March 2024, median follow up for safety NR (median follow up for PFS was 17.4-22.1 months and for OS was 25 months)
- EXAM DCO August 2014, minimum follow up 42 months

An indirect comparison of AEs conducted by the commentary suggested an inferior safety profile for selpercatinib compared to placebo which was expected given the comparison was between an active vs non active treatment arm. Though, comparisons between LIBRETTO-531 and EXAM were limited due to the differences in follow up time (median of 25 months vs minimum of 42 months), the use of subsequent anticancer therapies and potential bias in the reporting of AEs in the placebo arm from EXAM due to functional unblinding. Nonetheless, the commentary considered it may be reasonable to expect active treatment with selpercatinib to have an inferior safety profile compared to placebo with AEs manageable through dose reductions and omissions.

Based on the direct evidence from LIBRETTO-531, selpercatinib appeared to have a more favourable safety profile compared to cabozantinib and vandetanib. Higher rates of AEs in the cabozantinib and vandetanib arm may be expected due to the non-selective mechanism of action of these MKIs relative to the highly selective mechanism of action of selpercatinib. However, there was potential reporting bias in AEs particularly in the cabozantinib or vandetanib arm due to the open label trial design and crossover.

The submission did not present the consequences of false positive results (i.e. resulting in *RET* wildtype patients receiving selpercatinib) or false negative results (i.e. resulting in *RET* variant patients not receiving selpercatinib). The commentary considered the implications of false positive results could not be informed by the evidence given the lack of selpercatinib efficacy data in *RET* wildtype patients, although it would be reasonable to expect increased risk of AEs relative to BSC. The commentary also noted that NGS was stated to have greater sensitivity than PCR and there might be implications of false positive results if laboratories in practice opt for PCR based assays. The commentary considered the implications of false negative results would be associated with forgone treatment benefit with selpercatinib in *RET* variant MTC patients. Nonetheless, the commentary acknowledges that PASC stated test validity evidence was not required for this submission. In addition, the commentary considered that testing conducted under NATA accredited laboratories in practice may minimise these risks.

12. Comparative effectiveness

The available evidence is presented in Table 6.

Table 6 Data availability to inform comparisons

Proposed test vs no test	Not available/presented	
Proposed test vs alternative test	Not available/presented	
	Selpercatinib	**Best supportive care[a,b]**
Biomarker test positive	LIBRETTO-531	EXAM
Biomarker test wildtype	Not available/presented	EXAM

Source: Section 2A to 2D of the submission
[a] ZETA was used as a sensitivity analysis in the indirect comparison for best supportive care but is not presented in the MSAC Executive Summary.
[b] Placebo was used as a proxy for best supportive care which the commentary considered was reasonable

The commentary noted that PASC advised that analytical validity was not required to be assessed and a reference standard was not required as the clinical utility standard was the same as what is currently used in Australia for testing of activating *RET* variants (NGS or Sanger sequencing, which are well established methods; p16, Ratified PICO confirmation 1804).

The commentary noted the submission only presented evidence for selpercatinib treatment in the *RET* variant population (LIBRETTO-531) and did not present evidence of selpercatinib treatment in the *RET* wildtype population, although the commentary acknowledged that this evidence was limited.

Comparative accuracy/test performance – Diagnostic yield

The submission did not present test performance evidence as per PASC's advice that NGS and PCR were the clinical utility standard in Australia.

The submission presented the diagnostic yield calculated as the inverse of the number of patients who need to be tested using NGS/PCR of tumour tissue to identify one patient with a *RET* variant alteration (i.e. the number needed to test [NNT]). The submission's NNT was estimated based on:

- The assumption that test sensitivity was 100%.
- The proportion of patients diagnosed at or progressed to locally advanced or metastatic MTC (85%), which was estimated as the proportion of the eligible test population who were diagnosed at or progressed to stage III/IV MTC calculated from the submission's financial estimates (see Section 11 of the MSAC Executive Summary). The commentary cautions against relying on this estimate, since the submission substantially underestimated the population who would be eligible for testing due to inappropriate accounting of prevalent patients prior to 2026. Based on revised estimates by the commentary, the total proportion of stage III/IV MTC patients in the total eligible test cohort was 66.3% (1,373/2,070). Regardless, applying this proportion was inconsistent with proposed testing in patients at the point of MTC diagnosis (the base case assumption in the submission).
- The proportion of patients with progressive and symptomatic MTC (57.2%) based on a post hoc analysis from the ZETA trial (Kreissl 2020).[26] ZETA was a phase III, randomised, double blinded trial that compared vandetanib (n=231) to placebo (n=100) in patients with locally advanced or metastatic MTC with unresectable disease, and who had been exposed to kinase inhibitors. The submission stated the proportion of patients who had progressed and were symptomatic was 107/187; however, the commentary noted this proportion reflected the proportion of progressive and symptomatic MTC patients with a *RET* variant in ZETA. The actual proportion of stage III/IV MTC patients with progressive and symptomatic disease was 55.6% (184/331; Table 1; Kreissl 2020). Regardless, the proposed test population was irrespective of whether a patient had progressive disease and the commentary considered this proportion should not be applied.
- The proportion of patients with a *RET* variant (70%). The commentary considered this was potentially higher in patients with advanced or metastatic MTC.

An NNT of 2.97 was reported in the submission. However, the commentary noted that based on the submission's inputs, the calculation would result in an NNT of 2.92. Nonetheless, this had almost no impact on the economic model and financial estimations (Section 10 and 11 of the

[26] Kreissl MC, et al. (2020). Efficacy and Safety of Vandetanib in Progressive and Symptomatic Medullary Thyroid Cancer: Post Hoc Analysis From the ZETA Trial. *J Clin Oncol*. 2020 Aug 20;38(24):2773-2781. doi: 10.1200/JCO.19.02790. Epub 2020 Jun 25. PMID: 32584630; PMCID: PMC7430220.

MSAC Executive Summary) and the submission's base case inputs were considered not applicable to the proposed test population as discussed above.

The commentary considered the NNT estimated by the submission limited testing in stage III/IV MTC patients with progressive and symptomatic disease which did not align with the MBS item descriptor or testing Options 1 or 2. Alternative NNT estimates calculated by the commentary are shown in Table 7; these assumed different test populations and used more appropriate inputs. In addition, NNT assuming a higher *RET* variant prevalence in locally advanced or metastatic MTC patients estimated by the commentary is also presented.

Table 7 NNT estimates by the commentary, assuming different testing populations and biomarker prevalence

Testing population	Assumption	NNT	
		RET **prevalence in MTC = 70%**	***RET*** **prevalence in locally advanced or metastatic MTC = 94%**
Submission estimate	Stage III/IV MTC (85%) with progressive and symptomatic disease (57.2%)	$\frac{1}{0.85 \times 0.572 \times 0.70}$=2.92	$\frac{1}{0.85 \times 0.572 \times 0.94}$=2.18
PICO Option 1: stage III/IV MTC patients	Stage III/IV MTC only (66.3%)[a]	$\frac{1}{0.663 \times 0.70}$=2.15	$\frac{1}{0.663 \times 0.94}$=1.60
PICO Option 2: all patients diagnosed with MTC	All patients diagnosed with MTC (100%)	$\frac{1}{0.70}$=1.43	Not applicable since this prevalence was in advanced/metastatic MTC
Testing as per LIBRETTO-531 population	Locally advanced or metastatic MTC (66.3%) with progressive (55.6%)[b] and unresectable (NR) disease[c]	$\frac{1}{0.663 \times 0.556 \times 0.70}$=3.87	$\frac{1}{0.663 \times 0.556 \times 0.94}$=2.89

Source: Table 4-18, p164 of the submission; Table 1, Kreissl 2020; p2, Romei 2016 [27]
MTC = medullary thyroid cancer; NNT = number needed to test; NR = not reported
[a] Proportion of the eligible test population who were stage III/IV using revised estimates
[b] Proportion with progressive and symptomatic disease in Kreissl 2020
[c] The proportion of patients with unresectable MTC was not apparent in the submission or the literature

Estimates by the commentary indicated the NNT for testing at stage III/IV MTC (Option 1) was 2.15 and for testing at diagnosis (Option 2) was 1.43, both notably lower than the submission's estimate of 2.92. The NNT estimated by the commentary as per the testing population from LIBRETTO-531 was 3.87, but this may be overestimated since the proportion of patients with unresectable MTC was not apparent in the literature.

The commentary noted that in LIBRETTO-531 the concordance of the LLTs was evaluated against the Oncomine Dx Target Test (ODxTT). LLTs was not defined but was presumably the NGS assay used in the trial. Based on samples from 254 patients that were submitted for testing, positive ODxTT results were obtained for 199 of 207 evaluable samples, resulting in a 96.1 percent positive agreement in *RET* variant status between LLT and ODxTT results. Negative percent agreement was not reported. As noted in Section 3 of the MSAC Executive Summary, it was not clear what test, either single gene test or gene panel, would be used in Australian clinical practice.

Prognostic evidence

The submission presented evidence from Elisei 2008 who evaluated the prognostic impact of somatic *RET* variants in 100 patients with sporadic MTC who underwent thyroid surgery. Prior

[27] Romei, C, et al. (2016). New insights in the molecular signature of advanced medullary thyroid cancer: evidence of a bad outcome of cases with double *RET* mutations. *J Med Genet*. 2016 Nov;53(11):729-734. doi: 10.1136/jmedgenet-2016-103833. Epub 2016 Jul 28. PMID: 27468888

therapies were not reported in this study, although given this study was conducted prior to the approval of systemic therapies such as cabozantinib and vandetanib, it might be reasonable to expect prior therapy use was low. *RET* variants were identified in 43/100 (43%) patients (M918T was the most common *RET* variant [34/43; 79%]] the remainder were *RET* wildtype [57/100; 57%]).The *RET* variant group had a higher proportion of stage III/IV disease (68% [30/43] vs 33% [19/57], respectively) and distant metastases (30% [13/43] vs 23% [13/57], respectively) compared to the *RET* wildtype. The presence of *RET* variants was significantly associated with larger tumour size, lymph node involvement, distant metastases, and advanced TNM stage at diagnosis. Patients with *RET* variant MTC had higher rates of persistent disease and lower survival than those who were *RET* wildtype. Patients with *RET* variant(s) demonstrated significantly lower OS compared to those with *RET* wildtype (log rank p=0.006), with approximately 75% survival at 10 years compared to nearly 100% in the *RET* wildtype patients.

The commentary noted similar observations were made in Ciampi 2019 who reported a significant correlation between the presence of *RET* alterations and advanced stage of disease, higher tumour category, and the presence of both lymph node and distant metastases. More deaths occurred in patients with a *RET* variant compared to patients with a *RAS* variant (~14% vs 0%, respectively, over median follow up of 65 months).[28] Prior therapies were also not reported in this study. In comparison, the commentary noted Shirali 2024 did not report a difference in survival between patients with *RET M918T*, *RET* other, and *RET* wildtype. The 5 year disease specific survival and OS rates were 85.3% and 83.8% for *RET M918T*, 89.2% and 89.2% for *RET* other, and 85.5% and 85.5% for *RET* wildtype. This was potentially attributed to the relatively high rates of systemic therapies used in the *RET* variant groups (78/122 [63.9%]) including selective *RET* inhibitors (51/122 [41.8%]) and non-selective MKIs (47/122 [38.5%]), reflecting the more contemporary treatment landscape in Shirali 2024 as compared to Elisei 2008.

The commentary considered the evidence suggests that, among patients with MTC, those with a *RET* variant were correlated with more advanced disease at diagnosis and with more distant metastases. The commentary also considered the evidence suggesting that *RET* variant was associated with lower OS may also be related to the fact that *RET* variants were correlated with more advanced disease at diagnosis rather than poorer prognosis from baseline, and there may be insufficient evidence to suggest that patients with *RET* variants may have worse prognosis than *RET* wildtype. With selective *RET* inhibitors and MKIs available in the current treatment landscape, the commentary considered any potential differences in survival between *RET* variants and its complement may be less apparent than in the past based on Shirali 2024.

Predictive evidence

An overview of the PFS and OS results from LIBRETTO-531 and EXAM and the base case ITC of selpercatinib vs placebo in the *RET* variant population are presented in Table 8.

[28] As noted in Section 5 of the advice to MSAC, *RAS* variants are the most commonly reported variant in *RET* wildtype patients

Table 8 Overview of PFS and OS in LIBRETTO-531 and EXAM and the base case ITC

	Intervention		Comparator		
	Events n/N	**Median, months (95% CI)a**	**Events n/N**	**Median, months (95% CI)a**	**HR (95% CI); p value[b]**
PFS: LIBRETTO-531 selpercatinib vs cabozantinib or vandetanib					
ITT (*RET* variant)	34/193	Not reached (35.8, NE)	47/98	13.9 (12.2, 19.5)	**0.202 (0.128, 0.320); <0.0001**
PFS: EXAM cabozantinib vs placebo					
ITT (any *RET* status)	79/219	11.2 (NR, NR)	60/111	4.0 (NR, NR)	**0.28 (0.19, 0.40); <0.0001**
RET variant	NR/107	*13.8 (NE, NE)*	NR/62	*4.6 (NE, NE)*	0.23 (0.14, 0.38); <0.0001
RET wildtype	NR/35	*5.8 (NE, NE)*	NR/11	*5.3 (NE, NE)*	0.53 (0.19, 1.50); 0.2142[c]
RET unknown[d]	NR/77	*11 (NE, NE)*	NR/38	*3 (NE, NE)*	0.30 (0.16, 0.57); 0.0001
OS: LIBRETTO-531 selpercatinib vs cabozantinib/vandetanib					
ITT (*RET* variant)	10/193	Not reached	16/98	Not reached	0.275 (0.124, 0.608); 0.0007
OS: EXAM cabozantinib vs placebo					
ITT (any *RET* status)	141/219	26.6 (NR, NR)	71/111	21.1 (NR, NR)	0.85 (0.64, 1.12); 0.24
RET variant	NR/107	NR (NR, NR)	NR/62	NR (NR, NR)	0.79 (0.54, 1.17); NR
RET wildtype	NR/35	NR (NR, NR)	NR/11	NR (NR, NR)	0.68 (0.33, 1.38); NR
RET unknown[d]	NR/77	NR (NR, NR)	NR/38	NR (NR, NR)	0.91 (0.56, 1.48); NR
Base case Bucher ITC: selpercatinib LIBRETTO-531 (ITT [*RET* variant]) vs placebo EXAM (*RET* variant subgroup)					
Bucher ITC PFS HR					0.05 (0.02, 0.09)
Bucher ITC OS HR					0.22 (0.09, 0.53)

Source: Table 2-18, p85 of the submission (LIBRETTO-531); Table 14.2.2.1.2 Attachment 2.5 LIBRETTO-531 data tables May 2024; Table 1, Scherman 2016 (EXAM); Figure 1A and 2 pp4 5, Schlumberger 2017 (EXAM); Table 2 34, p105 of the submission (ITC)
BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; ITT = intention to treat; n/N = number of events; NE = not evaluable; NR = not reported; OS = overall survival; PFS = progression free survival
[a] EXAM reported median PFS in weeks (as per Table 1, Sherman 2016), thus for comparability with the other trials, these values were converted to months by dividing by 4.345
[b] LIBRETTO-531 and EXAM reported stratified HRs based on the respective randomisation strata.
[c] Hazard ratio not proportional
[d] In EXAM most patients in the unknown category either had no tumour sample available at the time of analysis or had a tumour DNA sample that failed PCR amplification.
Notes:
Bold text indicates statistically significant threshold met in LIBRETTO-531 or EXAM. Only applied to outcomes included in statistical analysis hierarchy.
Grey shaded cells indicate patients that informed the indirect comparison.
PFS in LIBRETTO-531 were according to the RECIST v1.1 and in EXAM was according to the mRECIST
Data cutoff dates and median follow up duration

- LIBRETTO-531 DCO March 2024, median follow up 17.4 22.1 months for PFS, median follow up 25 months for OS
- EXAM DCO June 2011, median follow up of 13.9 months for PFS, minimum 42 months follow up for OS

The inverse HR of the comparator trial (EXAM) was used to calculate the ITC of selpercatinib vs placebo

The commentary noted that in LIBRETTO-531, selpercatinib demonstrated a significant PFS benefit over cabozantinib or vandetanib in the ITT (*RET* variant) population (HR = 0.202, 95% CI 0.128, 0.320, p<0.0001); and in EXAM, cabozantinib demonstrated a significant PFS benefit over placebo in the ITT population (HR = 0.28, 95% CI 0.19, 0.40, p<0.0001) with a consistent trend observed in the *RET* variant subgroup (HR = 0.23, 95% CI 0.14, 0.38). The commentary noted LIBRETTO-531 was not powered to detect a statistically significant difference in OS (HR = 0.275, 95% CI 0.124, 0.608) and no significant OS difference was observed in EXAM (ITT HR = 0.85, 95% CI 0.64, 1.12; *RET* variant subgroup: HR = 0.79, 95% CI 0.54, 1.17) but there was a trend in favour of the intervention arms. In the Bucher ITC using cabozantinib or vandetanib as

the common reference, selpercatinib demonstrated improved PFS (HR = 0.05, 95% CI 0.02, 0.09) and OS (HR = 0.22, 95% CI 0.09, 0.53) compared to BSC.

The commentary noted that predictive evidence presented for selpercatinib pertained to only patients with a confirmed *RET* variant. The commentary also noted there was no evidence presented in the submission (nor apparent during the evaluation) of selpercatinib efficacy in *RET* wildtype patients to conclude that *RET* variant was a treatment effect modifier. Therefore, the commentary considered the codependency claim was not supported by the LIB*RET*TO-531 trial.

However, the submission considered the high selectivity of selpercatinib for *RET* receptors was biologically plausible and potentially supported codependency. The commentary noted that claims of codependency based on biological plausibility have previously been considered by MSAC, such as in MSAC applications 1669 and 1617. For application 1669 on *KRAS G12C* variant testing for determining eligibility for sotorasib in locally advanced or metastatic NSCLC, MSAC considered that the claim of codependency based on biological plausibility "…was acceptable as sotorasib is a first in class medicine targeting the *KRAS G12C* variant, and thus designing a trial that treated people without the pathogenic variant would have been difficult to justify ethically" (p3 and 19, MSAC Application 1669 PSD April 2022).[29] MSAC deferred its decision for Application 1669. For application 1617 on *BRAF V600* testing to determine eligibility for encorafenib in patients with metastatic colorectal cancer, MSAC noted that the "trial only enrolled patients with the *V600E* variant, and so could not assess the effect for patients who are *V600* negative or had another *V600* variant. Therefore, MSAC considered that the rationale for codependency was based on biological plausibility and on preclinical studies, which have not shown that encorafenib is effective against *BRAF V600* wildtype tumours" (p3, MSAC Application 1617 PSD April 2021).[30] MSAC supported application 1617.

Change in management in practice

The submission did not provide formal evidence to support a change in clinical management, and instead a descriptive summary of the change in clinical management following *RET* variant testing was presented based on local and international clinical management guidelines (Gild 2023, Filetti 2022, Haddad 2022) as well as the LIBRETTO-531 trial.[31, 32]

The submission did not expect that if somatic *RET* variant testing were to be publicly funded that the pattern of testing would change, as the submission assumed that the test is already routinely performed in clinical practice. This claim was considered questionable by the commentary given that PASC noted the patients currently receiving somatic *RET* variant testing was likely low given limited access to selpercatinib in practice. Furthermore, if MBS funding of somatic testing was supported, the commentary considered it possible that the number of MBS funded germline *RET* variant tests (MBS 73339 and 73340) may also increase due to increases in cascade testing (i.e. a patient with a positive test result from somatic testing may be interested in subsequent germline testing).

The commentary also considered there may be potential test safety concerns from rebiopsy in the circumstance of insufficient tumour tissue samples, or in the prevalent patient cohort whose archived tumour samples are no longer viable or available, but the frequency of occurrence is unclear. Additionally, given the uncertainty of test accuracy evidence, the commentary

[29]https://www.msac.gov.au/sites/default/files/documents/1669%2520-%2520Final%2520PSD_Mar-Apr2022_Redacted.pdf
[30]https://www.msac.gov.au/sites/default/files/documents/1617%2520Final%2520PSD%2520-%2520Mar-Apr%25202021_redacted.pdf
[31] Filetti, S, et al. (2022). ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer. *Ann Oncol*. 2022 Jul;33(7):674-684. doi: 10.1016/j.annonc.2022.04.009. Epub 2022 Apr 28. PMID: 35491008.
[32] Haddad, RI, et al. (2022). Thyroid Carcinoma, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*, 20(8), 925-951. https://doi.org/10.6004/jnccn.2022.0040

considered there remained the possibility of implications from false positive results (unknown efficacy and increase risk of AEs in *RET* wildtype) and false negative results (foregone treatment benefit in *RET* variant), but that these might be mitigated in practice where testing is conducted at NATA accredited laboratories.

The submission stated that "patients with advanced, metastatic, or progressive *RET* variant MTC will be eligible for selpercatinib, including patients with residual, recurrent, or metastatic disease following surgery, irrespective of prior systemic therapy". The commentary considered this was not consistent with the requested PBS restriction. The commentary noted that as the proposed PBS restriction stands, all patients with *RET* variant locally advanced or metastatic MTC would be treated with selpercatinib irrespective of eligibility for surgery, progressive disease status, and prior therapies. The commentary noted clinical management guidelines recommended systemic therapies in patients with recurrent or persistent MTC that is unresectable (which was not specified by the submission), and this was similar in LIBRETTO-531. For alignment with clinical management guidelines and LIBRETTO-531, the commentary considered treatment with selpercatinib should be limited to patients with locally advanced or metastatic MTC who test positive for a *RET* variant and whose disease was progressive and unresectable.

The submission considered most patients would receive selpercatinib as a first line therapy. It also proposed use in patients who have had prior kinase inhibitor therapies; however, the commentary noted the requested restriction made no indication as to whether a patient must have progressed on this therapy to be eligible for selpercatinib. In LIBRETTO-001, pretreated patients were those who had progressed on or were intolerant to first line therapy and efficacy was potentially supported, albeit the commentary acknowledges this was a phase I/II study that did not investigate comparative efficacy.

For patients who are *RET* wildtype, they will most likely receive BSC which involves palliative care and symptomatic management of MTC since in Australia there is limited access to non-selective MKIs such as cabozantinib (not TGA approved) and vandetanib (not PBS listed).

The submission noted that given the high selectivity of selpercatinib to *RET* kinase receptor, the biological rationale for selecting treatment in *RET* wildtype patients was not justified. The commentary reiterates the biological rationale was plausible; however, there is as yet no evidence to inform efficacy in patients who are *RET* wildtype, and the claim of codependency should be considered incompletely supported.

Generally, the commentary considered the change in clinical management following *RET* variant testing and subsequent treatment with selpercatinib as presented by the submission was inconsistent with the requested PBS restriction, clinical management guidelines, and LIBRETTO-531. The commentary reiterates that aligning the population eligible for treatment to locally advanced or metastatic MTC patients with progressive and unresectable disease would be supported in the clinical management guidelines and LIBRETTO-531. However, the commentary maintains there was no clear evidence to support the exclusion of *RET* wildtype patients from treatment, noting the nominated comparator was BSC and these patients have no other PBS listed treatment options available.

13. Economic evaluation

The submission presented a modelled economic evaluation (cost utility analysis), based on an indirect comparison of selpercatinib and BSC in patients with advanced or metastatic MTC who have a confirmed *RET* variant.

Table 9 summarises the key component of the economic evaluation.

Table 9 Key components of the economic evaluation

Component	Description	Comments from commentary
Comparison modelled	*RET* variant testing and treatment with selpercatinib compared to no *RET* variant testing and treatment with BSC in stage III/IV MTC patients with a *RET* variant.	This approach was presented in absence of test sensitivity/specificity parameters.
Outcomes	LYG, QALYs gained	Reasonable.
Time horizon	25 years vs trial period of 45 months in LIBRETTO-531.	Potentially not applicable to the trial population of patients with unresectable and documented disease progression. Extrapolating from 45 months to 25 years was uncertain. The time horizon was not a key driver of the model.
Methods used to generate results	Partitioned survival model (PF, PD, and death) using Excel.	Reasonable.
Cycle length	Weekly cycle length	Disease progression, treatment discontinuation, and disease management costs were potentially overestimated relative to clinical practice where these events likely occurred at longer intervals.
Test parameters	No test accuracy parameters were included in the base case. A once off cost of $1,189 per *RET* variant identified was applied in the selpercatinib arm based on the NNT (2.97) and proposed MBS fee ($400). NNT was estimated based on the proportion of MTC patients diagnosed or progressed to stage III/IV disease (85%), the proportion with progressive and symptomatic disease (57.22%) and the proportion of MTC with a *RET* variant (70%).	Based on the submission's inputs an NNT of 2.92 was correctly calculated and the cost was $1,169 per *RET* variant identified, although this had almost no impact on the ICER. For consistency with the test population (i.e., patients diagnosed with MTC irrespective of stage of disease or progression status), the NNT would be estimated from the proportion of MTC expected to have a *RET* variant (i.e., 1/70% = 1.43). NNT was not a key driver in the model.
Implications of false positive and false wildtype results	Assumed 100% sensitivity and 100% specificity.	Test parameters were not considered in the model. The model was built to vary test sensitivity and specificity, but inferences were limited in absence of efficacy data of selpercatinib treatment in *RET* wildtype patients.
Allocation to health states	LIBRETTO-531 informed the transitions in the selpercatinib arm. A HR approach was adopted to inform the transitions in the BSC arm based on the ITC of LIBRETTO-531 (ITT; *RET* variant) and EXAM (*RET* variant subgroup).	The ITC OS HR was not appropriate as no significant OS difference was observed between cabozantinib and placebo in the EXAM trial. The OS HR from LIBRETTO-531 was more appropriate but was also associated with uncertainties. In addition, LIBRETTO-531 and the model population had reduced applicability to the requested population (implications noted in the row below).

Component	Description	Comments from commentary
Extrapolation method	No KM was used in the model. Parametric models were fitted to the selpercatinib arm to extrapolate PFS and OS based on visual fit, statistical fit, and clinical plausibility. OS extrapolation was selected based on an arbitrary decision that if survival at 25 years was >32% the extrapolation was not clinically plausible.[a] PFS was extrapolated using the Weibull function and OS was extrapolated using the Spline knot 3 function. ToT in the selpercatinib arm was assumed to equal PFS. BSC was modelled by applying the inverse of the PFS HR (0.05) and OS HR (0.22) derived from the ITC to the selpercatinib arm. No convergence was assumed. Based on a trial follow up period of 45 months and a 25 year time horizon, the cost and benefits that occurred over the extrapolated period were: 74%, 73%, and 43% of LYG, QALYs gained, and costs in the selpercatinib arm, respectively. 43%, 43%, and 56% of LYG, QALYs gained and costs in the BSC arm, respectively.	The trials represented patients who were expected to progress and die faster in comparison to the requested population. The incremental benefit of selpercatinib vs BSC was potentially overestimated relative to clinical practice. Consequently, the ToT with selpercatinib and therefore treatment costs were potentially underestimated. OS, ToT, and PFS modelling were key drivers of the model.
Health related quality of life	Utility values were informed from LIBRETTO-531 EQ 5D 5L index score using Australian tariffs (Norman 2023). PF = 0.8839 and PD = 0.8672.	PD utility (0.8672) was informed by 61/291 patients from LIBRETTO-531 and was potentially biased. Utilities were a moderate driver of the model.
Selpercatinib costs	The submission assumed the following dose reductions for selpercatinib based on 141 patients: Tx cycle 1 = 98.45% 160 mg BID, 0.52% 120 mg BID, and 1.04% 80 mg BID Tx cycle 2 onwards = 4% 160 mg BID, 49.33% 120 mg BID, 41.33% 80 mg BID, and 5.33% 40 mg BID*	Over 90% of patients had dose reductions after treatment cycle 2 in the model which was considerably greater than reported in LIBRETTO-531 (46%) and could not be independently verified. Dose re escalations were also not considered. Selpercatinib treatment costs were potentially underestimated, but this may be partially offset given the absence of dose omissions.

Source: Sections 3.2 to 3.5 of the submission
BID = twice daily; BSC = best supportive care; EQ 5D 5L = EuroQoL 5 Dimension 5 level; HR = hazard ratio; ICER = incremental cost effectiveness ratio; ITT = intention to treat; KM = Kaplan-Meier; LYG = life year gained; MTC = medullary thyroid cancer; OS = overall survival; PD = progressed disease; PF = progression free; PFS = progression free survival; QALY = quality adjusted life year gained; ToT = time on treatment; Tx = treatment
[a] 32% was half of the general population survival after 25 years in patients aged 54 years
* The applicant's pre-subcommittee response (PSCR) acknowledged that there was an error in the dose adjustment data provided for Tx cycle 2 onwards, and provided corrected data.

The submission adopted a partition survival model consisting of the 3 health states: progression free (PF), progressed disease (PD), and death. Patients entered the model in the PF health state and received either selpercatinib or BSC. After each weekly cycle, patients either remained in the PF health state, transitioned to the PD health state (as per RECIST v1.1 defined disease progression), or died based on the background all-cause mortality rate (absorbing health state). Patients in the PD health state either remained or died. Patients in the PF health state were assumed to have stable disease or were not actively progressing, experienced PF utilities, and incurred costs associated with treatment and disease management. Patients in the PD health state experienced PD utilities and incurred disease management costs. Terminal care costs were incurred upon death. AE management (grade ≥3) costs and disutilities were incurred in both treatment arms as informed by the LIBRETTO-531 and EXAM trials.

The submission did not incorporate test variables (i.e. costs and outcomes for false positive and false negative cohorts were not modelled) and instead the submission captured *RET* variant testing using NNT (2.97) (see Section 9 of the MSAC Executive Summary) and the proposed cost of *RET* variant testing ($400). The submission's estimated cost per *RET* variant patient identified

was $1,189 and was applied to the selpercatinib arm. As noted in Section 9 of the MSAC Executive Summary, the NNT of 2.92 was the correct estimate and resulted in a cost of $1,169; regardless, the inputs informing this estimate were not applicable to the proposed test population.

The commentary considered the application of testing to only the selpercatinib arm implied that the patients in the BSC arm had an unknown *RET* variant status; however, it was acknowledged that the submission's approach was taken to capture *RET* variant testing in the absence of test sensitivity/specificity inputs. The commentary considered this approach may be reasonable given that PASC considered NGS and PCR to be the clinical utility standard for *RET* variant testing in Australia and that test analytical performance was not required to be assessed in this submission (p16, Ratified PICO Confirmation 1804). However, the commentary noted there may be a preference for NGS in practice, and the RCPA noted greater sensitivity with NGS compared PCR. Therefore, if laboratories in clinical practice opt for PCR there may be implications from false positive results (e.g., uncertain efficacy, increased AEs in *RET* wildtype), false negative results (e.g., foregone benefit in *RET* variant), and unknown test results (e.g., rebiopsy and/or retesting).

As discussed in Section 9 of the MSAC Executive Summary, the commentary noted that testing as captured by the NNT only considered testing in stage III/IV MTC patients with progressive and symptomatic disease, which did not capture the entire proposed test population (i.e., all patients diagnosed with MTC), nor was it consistent with the proposed population eligible for treatment (i.e. not restricted to patients with progressive disease). However, the commentary acknowledged that the claim of codependency was made on *RET* variant locally advanced or metastatic MTC.

The commentary's analysis of the test scenario under different assumptions (see Table 7) led to the following implications for the estimated NNT and cost per patient:

- PICO Option 2: assuming that all patients with MTC were tested at diagnosis and irrespective of disease progression status led to an NNT of 1.43 and the cost per *RET* variant patient estimated was $571.43.
- PICO Option 1: assuming that patients at stage III/IV were tested, irrespective of disease progression status led to an NNT of *2.15* and the cost was $*861.88*.
- LIBRETTO-531 test population: assuming the test population was the same as LIBRETTO-531 led to an NNT of 3.87 and the cost was $1,550.15.

The commentary noted that while somatic *RET* variant testing was expected once per lifetime, there may be circumstances where a second test would be conducted which was not considered in the model. For example:

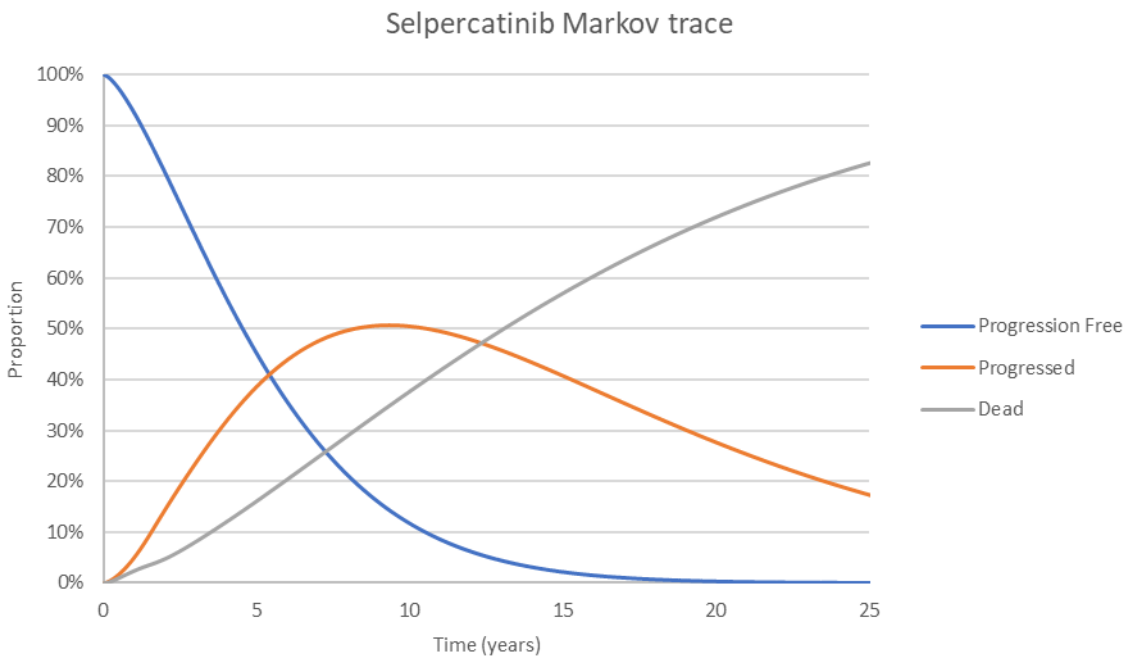
- If a patient developed treatment resistance, this may warrant a second test (p24, Ratified PICO Confirmation 1804).
- Additional testing costs may be incurred if a patient was referred for germline testing.
- For patients whose test result was unknown (e.g., due to failed test sample or insufficient tissue sample) they may require rebiopsy and retesting.
- As discussed in Section 8 of the MSAC Executive Summary, given the indolent nature of MTC, for patients diagnosed many years prior to a distant metastasis, rebiopsy may be required to discern whether the tumour is metastatic disease or a different primary. In the case of metastatic disease, a secondary test may be performed to confirm *RET* variant status if the patient initially tested as *RET* wildtype in the primary tumour, but given the extended time between diagnosis and metastatic disease for some patients, retrieval of specimens/reports may no longer be possible, which would warrant a second test.

Regardless, the commentary noted *RET* variant testing cost to detect one patient with *RET* variant MTC as captured by NNT was not a key driver of the model (varying or omitting NNT led to <1% changes in the ICER; see Table 12.).

The commentary noted the model was built to incorporate sensitivity and specificity parameters. However, implications of varying test parameters in the model were not considered reliable by the commentary since this only impacted costs and lacked inputs for selpercatinib treatment effect in patients with *RET* wildtype MTC, and did not include implications from false results (e.g. utility decrement due to incorrect treatment received) or unknown test results (e.g. rebiopsy).

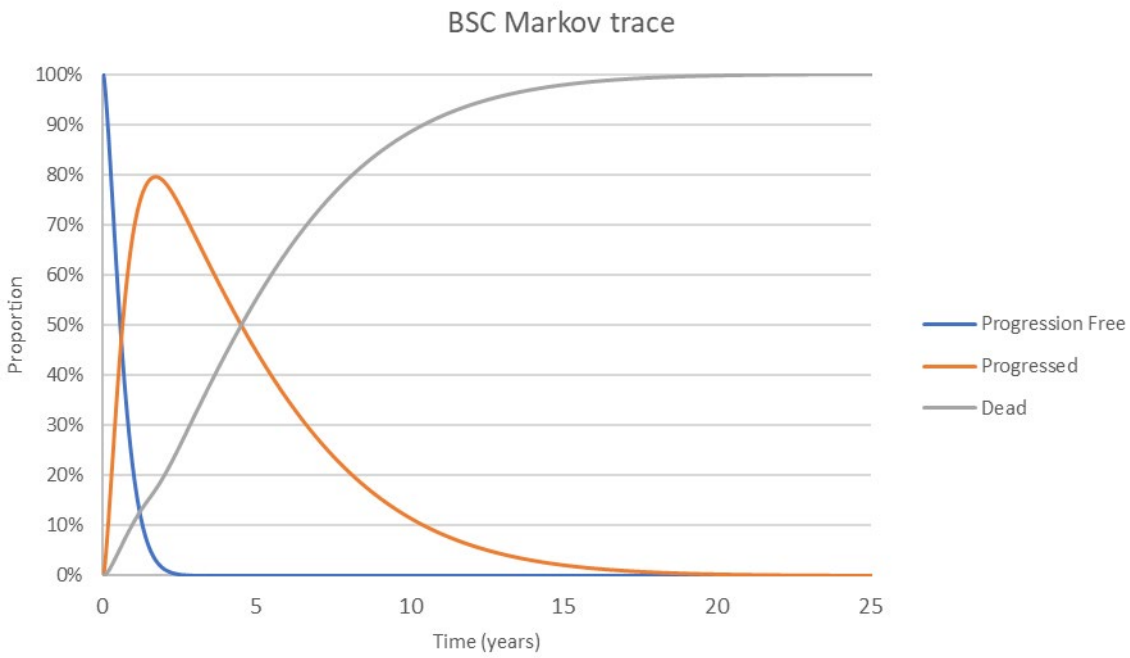
The Markov traces for the selpercatinib and BSC arms are shown in Figure 1 and Figure 2.

Figure 1 Markov trace - selpercatinib



Source: 'Markov trace' worksheet from the economic model

Figure 2 Markov trace - BSC



Source: 'Markov trace' worksheet from the economic model
BSC = best supportive care

An overview of the base case incremental cost effectiveness ratio (ICER) is shown in Table 10. and disaggregated results in Table 11 .

Table 10 Results of the stepped economic evaluation

Step and component	Selpercatinib	BSC	Increment
Step 1: quasi trial based analysis per LY gained over 45 month time horizon			
Costs	**$Redacted**	$21,191	**$Redacted**
LYG	3.259	2.771	0.488
Incremental cost/extra LYG gained			**$Redacted**[1]/LYG
Step 2: cost per LY gained over 25 year time horizon			
Costs	**$Redacted**	$41,744	**$Redacted**
LYG	9.260	4.385	4.875
Incremental cost/extra LY gained			**$Redacted**[2]/LYG
Step 3: cost per QALY gained over 25 year time horizon			
Costs	**$Redacted**	$41,744	**$Redacted**
QALYs gained	7.845	3.757	4.088
Incremental cost/extra QALY gained			**$Redacted**[2]**/QALY gained**

Source: Table 3-22, p144 of the submission; 'Deterministic Results' worksheet from the economic model
BSC = best supportive care; LYG = life years gained; QALYs = quality adjusted life years
Notes:
Results are discounted
The redacted values correspond to the following ranges:
[1] *$355,000 to < $455,000*
[2] *$55,000 to < $75,000*

Table 11 Disaggregated results (discounted)

Resource item	Selpercatinib	BSC	Increment	% of total incremental
Costs				
Drug acquisition	$**Redacted**	$0	$**Redacted**	**Redacted**%
RET variant testing	$1,189	$0	$1,189	0%
Disease management[a]	$11,836	$5,686	$6,150	**Redacted**%
AE management	$3,210	$1,035	$2,175	**Redacted**%
Terminal care	$22,142	$35,022	$12,881	**Redacted**%
Total	$**Redacted**	$41,744	$**Redacted**	100%
LYG				
PF	4.433	0.644	3.789	78%
PD	4.827	3.742	1.085	22%
Total	9.260	4.385	4.875	100%
QALYs gained				
PF	3.857	0.566	3.290	80%
PD	3.988	3.191	0.798	20%
Total	7.845	3.757	4.088	100%

Source: 'Deterministic Results' worksheet from the economic model
AE = adverse event; BSC = best supportive care; LYG = life year gained; PD = progressed disease; PF = progression free; QALY = quality adjusted life year
[a] Included ECG monitoring costs ($1,213)

For the comparison of selpercatinib vs BSC in patients with locally advanced or metastatic MTC, the ICER was $55,000 to < $75,000 per QALY gained over a 25 year time horizon ($**Redacted** incremental costs, 4.875 incremental life year gained (LYG), and 4.088 incremental QALYs gained).

The commentary noted the incremental benefits were driven by OS modelling that was favourable to the selpercatinib arm, where benefits were driven by extended occupation of both the PF (4.433 LYG, 3.857 QALYs gained) and PD states (4.827 LYG, 3.988 QALYs gained) over the 25 year time horizon. In comparison, most patients in the BSC arm experienced progression by year two and were modelled to die thereafter (PD state: 3.742 LYG, 3.191 QALYs gained; PF: 0.644 LYG, 0.566 QALYs gained).

The commentary noted the incremental costs were driven by selpercatinib drug acquisition costs ($**Redacted**), but were potentially overestimated due to the submission's assumption that >90% of patients had dose reductions after 28 days of treatment and was constant for the 25 year time horizon. *RET* variant testing as captured by the once off cost per *RET* variant identified ($1,189) was not a driver in the model. Implications of *RET* variant testing and treatment with selpercatinib or BSC was limited as the submission did not consider the relevant parameters to explore false positive and false negative test scenarios (e.g. no test sensitivity or specificity data, and lack of efficacy data of selpercatinib in the *RET* wildtype MTC).

The sensitivity analysis in the submission and conducted by the commentary that pertain to testing are shown in Table 12.

Table 12 Sensitivity analyses in the submission and additional analyses conducted during the evaluation

	Analyses	Inc LYG	Inc QALY	Inc cost ($)	ICER ($/QALY)	%Δ[a]
	Base case	**4.875**	**4.088**	**$Redacted**	**$Redacted[1]**	
	***RET* variant testing (base case: NNT = 2.97, MBS fee = $400)**					
1	NNT = 2.2	4.875	4.088	**$Redacted**	**$Redacted[1]**	- **Redacted** %
2	*RET* variant test costs = excluded	4.875	4.088	**$Redacted**	**$Redacted[1]**	- **Redacted** %
Additional analysis conducted by the commentary						
A1	NNT assume testing at diagnosis = 1.43	4.875	4.088	**$Redacted**	**$Redacted[1]**	- **Redacted** %
A2	NNT assume testing at stage III/IV irrespective of progression = 2.15	4.875	4.088	**$Redacted**	**$Redacted[1]**	- **Redacted** %
A3	NNT assume testing as per LIBRETTO-531 = 3.87	4.875	4.088	**$Redacted**	**$Redacted[1]**	+ **Redacted** %
A4	*RET* variant testing MBS fee = $682.35	4.875	4.088	**$Redacted**	**$Redacted[1]**	+ **Redacted** %

Source: Table 3-26, pp146 7 of the submission; additional analysis conducted during the evaluation
ICER = incremental cost effectiveness ratio; Inc = incremental; MBS = Medicare Benefits Schedule; NNT = number needed to treat; QALY = quality adjusted life year
[a] %Δ = percentage change from base case ICER
The redacted values correspond to the following ranges:
[1] $55,000 to < $75,000

See Section 6 of the Economics Sub-Committee: Advice for PBAC for a detailed description of the economic evaluation.

14. Financial/budgetary impacts

The submission adopted an epidemiological approach to estimating the financial implications of *RET* variant testing. The submission's base case assumed that *RET* variant testing was performed at diagnosis of MTC irrespective of stage of disease (Option 2). The submission also presented a scenario analysis that assumed *RET* variant testing was performed at diagnosis or progression to stage III/IV MTC (Option 1).

The submission estimated incident MTC patients based on the prevalence of MTC in thyroid cancers being 4% and the incident thyroid cancer cases from the Australian Institute of Health and Welfare (AIHW). The submission assumed there would be a proportion of patients diagnosed at stage III/IV MTC (54%) and a proportion of stage I/II MTC patients who progressed to stage III (12%) or stage IV MTC (21%) each year, with these assumptions based on the Australian study Papachristos 2023. Progression to stage III was only assumed to occur in the first two years.

The test populations were comprised of:

- Option 2 (base case): incident MTC (any stage) patients between 2026 and 2031 and all prevalent stage I/II MTC patients diagnosed between 2021 and 2025 who later progressed to stage III/IV during 2026 to 2031 and had no known germline *RET* variant.
- Option 1: incident stage III/IV MTC patients between 2026 and 2031 and prevalent stage I/II MTC patients diagnosed in 2021 to 2025 who later progressed to stage III/IV MTC during 2026 and 2031.

The commentary considered the testing populations were underestimated as the submission did not include all prevalent patients who were diagnosed with MTC and alive prior to 2026. In addition, the commentary noted the submission assumed that prevalent patients had undergone germline *RET* variant testing and only those without a known germline variant would receive somatic testing (75%). The commentary noted that based on MBS service data, MBS item 73339 was claimed a total of 156 times between 2020/21 and 2024/25 at the time of the evaluation (out of 831 estimated incident MTC cases from 2021 to 2025 in the submission [18.8%, 156/831] although, as noted above, the denominator was considered underestimated). The commentary acknowledged that germline testing is also performed at state/territory funded clinics and hospitals, but the number of germline tests was not apparent.

The submission assumed that only patients with progressive and symptomatic stage III/IV MTC (as informed by Kreissl 2020 [57.2%]) were eligible for selpercatinib. The prevalence of *RET* variant was assumed to be 70%. The proportion of patients receiving each dosing regimen of selpercatinib was informed by the Sponsor's data on file. Treatment persistence was informed by the ToT curve in the model (based on PFS). Uptake rate of both test and treatment was assumed to be 100% of eligible patients.

The submission stated there were < 500 grandfathered patients from a compassionate access program and self-paying patients. Grandfathered patients were assumed to be part of the prevalent population, though it was considered not reasonable by the commentary to include these patients in the test population as they would have already been tested in order to be receiving selpercatinib treatment.

The commentary considered the population eligible for treatment was underestimated since the submission did not capture all prevalent MTC patients who progressed to stage III/IV and were alive in the years prior to 2026; the submission assumed only patients with progressive and symptomatic MTC were eligible despite the requested population not being exclusive to those with progressive disease; and the proportion of patients diagnosed with stage III/IV MTC from Papachristos 2023 excluded patients who were not indicated for surgery despite these patients forming part of the requested population.

In addition, the commentary considered the submission's estimation of patients who progressed to stage III/IV MTC may not be appropriate since the submission did not adjust the proportions reported in Papachristos 2023 to reflect yearly progression and overestimated progression each year. The proportion who experienced distant recurrence (21%) in Papachristos 2023 included patients with stage III disease, which the commentary considered could potentially double count patients who progressed to stage IV in the base case. Further, the submission inappropriately assumed no patients progressed to stage III MTC after Year 2 which underestimated progression after Year 2.

The commentary considered that treatment utilisation was also potentially underestimated, since the submission assumed over 90% of patients were treated at lower selpercatinib doses, compared to 46% of patients in LIBRETTO-531 who were reported to have a dose reduction. In addition, the proportion of patients on treatment based on the modelled ToT (as informed by LIBRETTO-531) was potentially underestimated compared to clinical practice since the requested treatment population potentially represented patients who had more favourable prognosis and hence longer treatment durations.

Alternative estimates were calculated by the commentary to address the issues above and attempt to better capture the population eligible for testing and treatment in practice. The following changes were made by the commentary while maintaining the assumption that testing occurred at diagnosis of MTC:

- Assumed that all incident MTC patients between 2021 and 2025 were still alive in 2026 and contributed to the total number of prevalent MTC patients eligible for testing.

- Assumed that all incident MTC patients diagnosed at or progressed to stage III/IV between 2021 and 2025 were still alive in 2026 and contributed to the total number of prevalent stage III/IV MTC patients eligible for treatment.
    - The commentary acknowledged that the true prevalent population could not be estimated with the information provided in the submission (i.e. all prevalent MTC patients alive up to 2026 not just between 2021 and 2025), and the populations eligible for testing and treatment remain underestimated. There might be an offset effect given these assumptions considered all patients were alive at 2026; however, given the indolent nature of MTC, this effect might be small.
- Assumed that the proportion of patients who had local or distant recurrence reflected a yearly proportion and applied in all years. In Papachristos 2023, 12% of patients experienced local recurrence over 48 months and 21% experienced distant recurrence over 72 months. The yearly proportion who experienced local recurrence and distant recurrence was crudely estimated to be 3% and 3.50%, respectively.
- Did not assume that prevalent patients received germline *RET* variant testing (based on low use of current MBS items). The commentary noted that germline testing is offered at state/territory funded services, however, this estimate was not apparent during the evaluation. Assuming no germline testing in prevalent patients presented a conservative estimate of patient numbers (if germline testing was assumed, patient numbers would decrease; the magnitude however is not clear).
- Did not assume the < 500 grandfathered patients were included in the prevalent test population as they would have received testing already (but were included in the treated prevalent population).
- Did not assume that treatment was exclusive to patients with progressive and symptomatic disease.
- Assumed that the proportion of patients at each respective selpercatinib dose (160 mg, 120 mg, 80 mg, and 40 mg BID) was informed by the LIBRETTO-531 trial

The estimated use and financial implications of somatic *RET* variant testing and selpercatinib treatment to the MBS in the submission and those estimated by the commentary under both testing scenarios (Option 1 and 2) are presented in Table 13.

Table 13 Estimated use and financial implications of somatic *RET* testing and selpercatinib treatment to the MBS in the submission and by the commentary according to testing Options 1 (at stage III/IV) and Option 2 (at diagnosis)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of somatic *RET* variant testing						
Number of patients tested if tested at diagnosis of MTC (Option 2)	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]
Number of patients tested if tested at stage III/IV MTC (Option 1)	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]
Number of patients treated	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	$**Redacted**[1]	**Redacted**[1]	**Redacted**[1]
Financial implications to the MBS and PBS[a]						
Testing cost to MBS (Option 2)	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]
Testing cost to MBS (Option 1)	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]
Total ECG costs[b]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]
Net MBS costs (Option 2)	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]
Net cost to PBS/RPBS	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[3]	$**Redacted**[3]	$**Redacted**[3]	$**Redacted**[4]
Alternative estimates conducted by the commentary						
Estimated extent of use of somatic *RET* variant testing						
Number of patients tested if tested at diagnosis of MTC (Option 2)	**Redacted**[5]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]
Number of patients tested if tested at stage III/IV MTC (Option 1)	**Redacted**[5]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]
Number of patients treated	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]
Financial implications to the MBS and PBS[a]						
Testing cost to MBS (Option 2)	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]
Testing cost to MBS (Option 1)	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]
Total ECG costs	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]
Net MBS costs (Option 2)	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]	$**Redacted**[2]
Net cost to PBS/RPBS	$**Redacted**[6]	$**Redacted**[6]	$**Redacted**[6]	$**Redacted**[7]	$**Redacted**[7]	$**Redacted**[7]

Source: Table 4-3, p151; Table 4 14, p160; Table 4 15, p160 of the submission; calculated by the commentary using the financial workbook
ECG = electrocardiography; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
[a] assumed 80% MBS benefit for *RET* testing (proposed fee = $400 or $320 at 80% benefit)
[b] the submission assumed 80% MBS benefit for ECG testing (MBS item 11714 fee = $28.25 or $22.60 at 80% benefit)
[c] Accounted for GF patients in 2026 who already had testing
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *$0 to < $10 million*
[3] *$10 million to < $20 million*
[4] *$20 million to < $30 million*
[5] *500 to < 5,000*
[6] *$40 million to < $50 million*
[7] *$50 million to < $60 million*

Assuming somatic *RET* variant testing at diagnosis of MTC, the submission estimated the cost of testing to be $0 to < $10 million in 2026 increasing to $0 to < $10 million in 2031. Assuming testing only at stage III/IV MTC, the test costs were $0 to < $10 million in 2026 increasing to $0 to < $10 million in 2031. In addition, ECG costs associated with monitoring patients on treatment with selpercatinib was estimated to cost the MBS $0 to < $10 million in 2026 increasing to $0 to < $10 million in 2031. However, both ECG and testing costs to the MBS were calculated using an 80% benefit, which was not appropriate. As ECG testing is required for monitoring during use of selpercatinib, this is likely to be performed as an outpatient service and its financial impact therefore be calculated using an 85% benefit. However, *RET* testing may be performed as an in-hospital service, and in those cases would be eligible for a 75% benefit. As a result, the reliability of the financial estimates is uncertain.

Based on the alternative estimates by the commentary, assuming *RET* variant testing at diagnosis of MTC, the cost of testing was $0 to < $10 million in 2026 decreasing to $0 to < $10 million in 2031. Assuming testing at stage III/IV MTC, the test costs were $0 to < $10 million in 2026 decreasing to $0 to < $10 million in 2031.

The commentary considered the submission's eligible test population and costs were underestimated primarily due to the inadequate accounting for prevalent MTC patients. Noting MTC's relatively indolent nature, the commentary considered these patients may contribute a sizeable proportion to the test population in practice. The commentary also acknowledged that patients prior to 2021 were not accounted for and may suggest that the prevalent MTC population in practice is further underestimated.

Moreover, the commentary's estimates crudely assumed that all prevalent patients would undergo testing in 2026, whereas in practice uptake of testing in prevalent patients diagnosed at earlier stages may be gradual.

15. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- Alterations at the *RET* gene may be correlated with more advanced disease at diagnosis and subsequent distant metastases but the evidence to suggest patients with *RET* variant(s)s had a worse prognosis than *RET* wildtype at baseline was insufficient.

Economic issues:

- *RET* variant testing was captured as a once off cost per *RET* variant detected based on the NNT of 2.92 and the proposed Medicare Benefits Schedule (MBS) fee ($400). Due to the narrower population used to calculate the submission's NNT, the NNT was overestimated. The ESCs considered the commentary's calculation (using NNT = 1.43) to be more reliable, but acknowledged that *RET* variant testing was not found to be a driver for the economic model.

Financial issues:

- The submission inadequately accounted for prevalent MTC patients prior to 2026. Noting MTC's relatively indolent nature, these patients may contribute a sizeable proportion to the test population in practice. As such, the eligible test population and costs were underestimated.

Other issues:

- The ESCs raised concerns around the lack of a *RET*-specific quality assurance program (QAP) in Australia, and queried whether this would lead to delays or issues with implementation. To meet MBS requirements, regulatory and quality assurance processes for *RET* testing will need to be completed with the TGA.
- The ESCs considered that a restriction on the frequency of testing may not be necessary, noting that *RET* variant status may change over time. However, the ESCs also noted that *RET* activating variants are driver variants that typically develop early and tend to be conserved throughout the disease course. As such, the ESCs considered that there may be a rationale for limiting testing to once per lifetime. MSAC may wish to consider whether the MBS item descriptor should include a frequency restriction.

ESC's discussion

The joint MSAC Evaluation Subcommittee/PBAC Economics Sub-Committee (hereafter referred to as the ESCs) noted that this integrated codependent application sought:

- Medicare Benefits Schedule (MBS) listing of testing of tumour tissue to detect *RET* proto-oncogene (*RET*) variants in patients with medullary thyroid cancer (MTC) for the determination of patient eligibility for treatment with selpercatinib; and
- Pharmaceutical Benefits Scheme (PBS) Section 85 General Schedule listing of selpercatinib for the treatment of locally advanced or metastatic MTC in patients who have evidence of a *RET* variant.

The ESCs noted and welcomed consultation feedback submitted on behalf of 3 consumer organisations and 4 medical, health or other non-consumer organisations. The ESCs noted that the feedback was supportive of the proposed test. In particular, the feedback highlighted that testing was important to ensure timely, equitable access to relevant treatments, such as selpercatinib if it is PBS listed, noting patient experiences of delayed diagnoses, repeat surgeries, and exposure to therapies with limited benefit but significant side effects. The ESCs noted access to the test and treatment would reduce significant physical, psychological and financial burden, improve quality of care and increase confidence in care pathways for patients with MTC and their families and carers.

The ESCs noted that MTC consists of sporadic and hereditary subtypes, and that 70% of all patients with MTC have a clinically significant *RET* variant. The ESCs noted that roughly half of MTC patients present with stage III/IV MTC. The ESCs noted that current treatment options for patients with MTC in Australia are limited, with no drugs currently funded specifically for MTC.

The ESCs noted inconsistencies between the PASC-endorsed population in the PICO confirmation and the population proposed in the ADAR. The ESCs suggested that the appropriate test population should be defined as 'patients with a confirmed histological diagnosis of MTC who have not previously undergone tumour testing for clinically significant *RET* variants and who do not have a known germline *RET* variant', as per the 1804 Ratified PICO Confirmation. The ESCs noted that the applicant agreed in its pre-subcommittee response (PSCR) that this population definition was appropriate.

The ESCs considered the proposed clinical position of testing at diagnosis (rather than at diagnosis of or progression to stage III/IV MTC) to be appropriate, because it reduces the need for rebiopsy at disease progression (which may not always be possible) and provides value of knowing for patients. The ESCs also considered that testing at diagnosis minimises treatment delays, and that it is becoming standard practice for molecular oncology tests.

The ESCs noted that the NCCN guidelines recommend somatic *RET* testing in patients who are *RET* germline wildtype or unknown. The ESCs considered that it would be practical for somatic testing on tumour tissue to be performed prior to germline testing because the turnaround time is generally faster than germline testing, there is no requirement for genetic counselling before somatic testing, and it would reduce both downstream testing volume and the psychological burden of downstream germline testing as only those patients for whom *RET* activating variant is identified in their tumour may cascade to germline testing. The ESCs noted only patients with a positive *RET* variant on tumour tissue would require germline testing, for the purposes of informing cascade testing.

The ESCs noted that the proposed test was method agnostic, in line with the current MBS item (73339) for germline *RET* variant testing, but that next-generation sequencing (NGS) or polymerase chain reaction (PCR) were expected to be used in Australia. The ESCs noted that the submission had not presented test performance evidence and acknowledged the applicant's comments in the PSCR that this was in line with PASC advice that assessment of analytical validity was not required. The ESCs agreed with PASC's advice that both NGS and PCR are well established genetic testing methodologies in Australia, and considered that it was therefore acceptable to assume 100% sensitivity and 100% specificity. The ESCs considered that NGS has higher sensitivity than PCR. The ESCs suggested that MSAC could consider whether it is appropriate for an explanatory note to include that NGS is the preferred test method, when it is available.

The ESCs noted a QAP would be required to be implemented if *RET* testing is listed on the MBS and queried whether this would lead to delays or issues with implementation. The ESCs further noted that external quality assessment (EQA) schemes for molecular testing of *RET* alterations (including in MTC) are available, such as German EQAP [QuIP], and that in Australia there are QAPs for gene panels that include *RET* testing.

The ESCs noted the submission's proposed item descriptor, along with changes proposed by the department.

The ESCs considered that both the MBS item descriptor and the PBS restriction should only reference the gene's symbol, "*RET*", rather than also the full gene name, given the symbol is widely recognised among clinicians and that the gene may be known by multiple names. The ESCs considered that referring to the "*RET* gene" would provide greater consistency.

The ESCs considered whether the proposed MBS item should allow for *RET* testing, or if it should include a restriction on frequency of testing. While the submission itself did not provide evidence regarding the stability of *RET* variant status, the ESCs noted and agreed with the commentary

that, while *RET* status is typically stable, it can change over time due to tumour heterogeneity and with treatment. Therefore, the ESCs considered that testing should not necessarily be limited to once per lifetime. However, the ESCs also considered that there may be a rationale for limiting frequency of testing, given *RET* activating variants are driver variants that typically develop early and tend to be conserved throughout the disease course.

The ESCs considered it appropriate that the test be requested by specialists and be pathologist determinable, consistent with other similar items on the MBS. Additionally, the ESCs considered that an explanatory note should be included alongside the item, defining activating *RET* variants.

The ESCs considered that the applicant's proposed fee of $400 appeared reasonable for the proposed test, noting that it was the same as the fee for MBS item 73339 for the detection of germline testing.

The ESCs considered that the department should consider amending the existing MBS item for germline *RET* testing to include wording to support tumour testing before germline testing as the preferred sequence of testing for patients diagnosed with MTC.

The ESCs considered it appropriate that testing be limited to tumour tissue testing, and should exclude ctDNA testing.

The item descriptor suggested by the ESCs is outlined below:

Table 14 MBS item descriptor wording as considered appropriate by the joint ESCs

Category 6 - Pathology Services - Group P7 – Genetics
MBS item YYYY A test of tumour tissue from a patient with histologically confirmed medullary thyroid cancer requested by, or on behalf of, a specialist or consultant physician if the test is: (a) to detect variants relating to at least the RET gene activating variant status, and (b) to determine eligibility for a relevant treatment listed on the Pharmaceutical Benefits Scheme (PBS). Fee: $400.00 Benefit 75% $300.00 85% $340.00 (See para PN.1.2 of explanatory notes to this Category)

The ESCs noted the proposed test comparator was no *RET* variant testing of tumour tissue, and considered that this was appropriate.

The ESCs noted that the submission did not present any test safety data but stated that testing was not expected to introduce any safety concerns. The ESCs considered this reasonable given testing would typically be performed on tissue samples obtained via surgical resection, and biopsy for the purposes of *RET* testing would only be needed if a resection specimen was not available or could not be used.

The ESCs further noted that the submission did not present direct evidence of the efficacy of selpercatinib in patients with *RET* wildtype. The ESCs noted that evidence to support the claim of codependency had not been presented. However, the ESCs noted that based on its mechanism of action, it was biologically plausible that selpercatinib acts as a targeted treatment for patients with *RET* variant MTC.

The ESCs noted that the test population in the key trial presented in the submission, LIBRETTO-531, was patients with *RET* variant locally advanced or metastatic MTC with unresectable disease and documented disease progression at enrolment, who were treatment naïve to kinase inhibitors. The ESCs noted the assay used in the key trial tested for point mutations in the *RET* gene, rather than fusions, which is consistent with the most common type of *RET* variants found in MTC.

The ESCs noted the submission's clinical claim and considered it to be reasonable.

The ESCs noted that the submission presented a cost utility analysis (CUA) based on an indirect comparison of selpercatinib and best supportive care in patients with advanced or metastatic MTC who have a confirmed *RET* variant. The ESCs noted that the model used a number needed to test (NNT) approach, rather than considering false negative or false positive results. The ESCs noted that the base case incremental cost-effectiveness ratio (ICER) was $55,000 to < $75,000, but that this used a NNT of 2.97, which assumed testing only at diagnosis of or progression to stage III/IV. The ESCs noted an additional analysis conducted by the commentary, which corrected the NNT to 1.4 to assume testing at diagnosis of MTC. However, the ESCs noted that this had minimal impact (-Redacted%) on the ICER, given the comparatively small cost of testing versus the overall cost of selpercatinib treatment.

The ESCs noted that the submission's estimated net cost to the MBS included both *RET* testing at a cost of $400 and electrocardiogram (ECG) costs associated with monitoring patients on treatment with selpercatinib. However, the ESCs considered the submission had underestimated the net cost to the MBS, because it inadequately accounted for prevalent MTC patients prior to 2026. The ESCs concluded that, due to the indolent nature of MTC, these patients may contribute to a sizeable test cost in practice. The ESCs noted the commentary had presented alternative financial estimates accounting for the prevalent patients, which resulted in a net cost to the MBS in Year 1 approximately 4 times that of the original submission.

The ESCs also noted that the financial implications to the MBS were calculated using an 80% benefit, noting that ECG monitoring is likely to be eligible for an 85% benefit as an outpatient service, while *RET* testing may be performed in-hospital and would therefore be eligible for a 75% benefit. However, since the proportion of patients receiving in-hospital testing is uncertain, the impact of this on the financials was also uncertain. The ESCs considered the commentary's estimates (which corrected the NNT) to be informative, and more plausible than the submission's estimates, although noted that it did not account for the incorrectly applied 80% MBS benefit, and therefore that there remained some uncertainty in the overall costs to the MBS.

16. Applicant comments on MSAC's Public Summary Document

The applicant did not have any comments.

17. Further information on MSAC

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