MSAC Application 1804

Genetic testing to detect RET variants in patients with medullary thyroid cancer to determine eligibility for PBS subsidised selpercatinib treatment

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:

Disease overview

Medullary thyroid carcinoma (MTC) is a rare form of thyroid cancer, accounting for only 4% of all thyroid cancers (Cancer Australia 2024). It arises from parafollicular C cells within the thyroid, which are of neural crest origin, and hence MTC is considered a neuroendocrine tumour (Gild et al. 2023). MTC commonly presents with a thyroid nodule in the upper portion of the gland where C cells are primarily located, occurring in 75–95% of patients. Cervical lymphadenopathy is present in 70% of cases, and metastatic cervical lymphadenopathy occurring in 50% at initial presentation. Other symptoms include hoarseness, dysphagia, neck and throat pain. While 4–17% of cases have distant metastases affecting the brain, bones, lungs, or liver. Advanced MTC may cause diarrhoea and flushing as the tumour can secrete calcitonin and sometimes other hormonally active peptides (i.e., adrenocorticotropic hormone, calcitonin gene-related peptide) (Gild et al. 2023; Haddad et al. 2022).

REarranged during transfection (*RET*) mutations are genetic alterations found in patients with MTC and play a critical role in tumour development and progression. 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, central nervous system (CNS) and peripheral nervous system (PNS) neuron maintenance (Mulligan 2018). *RET* mutants are present in 70% of MTCs (Wirth et al. 2020). Patients harbouring more than 1 *RET*-mutant together with indels (insertion, deletion, or insertion and deletion of nucleotides in genomic DNA) or with indels alone present with more aggressive disease than those who do not (Gild et al. 2023).

MTCs are either sporadic (75-80% of presentations) or hereditary (20-25% of presentations) (Gild et al. 2023). *RET* mutations are pathognomonic in 98% of hereditary and 50-60% of sporadic MTCs (Gild et al. 2023; Parimi et al. 2023). Hereditary MTC is due to an inherited condition called multiple endocrine neoplasia 2 or 3 (MEN2, MEN3; formerly MEN2A, MEN2B), a condition that can cause tumours affecting the endocrine glands. MTC is usually the first tumour to develop (Haddad et al. 2022). In patients with a suspected clinical diagnosis of MEN2 or 3, either due to suspected MTC or another tumour type, detection of germline mutations in the *RET* gene is standard practice, as MEN2/3 results from germline mutations in the *RET* proto-oncogene. Patients with hereditary MTC typically present with bilateral tumours. Pheochromocytoma occurs in 40-50% of patients with MEN2A or MEN2B. Primary hyperparathyroidism is present is 10% to 25% of patients with MEN2A, but is absent in MEN2B. MEN2B is uniquely associated with marfanoid habitus, kyphoscoliosis/lordosis, joint laxity, mucosal neuromas typically at lips and tongue, and intestinal ganglioneuromas (Block et al. 1980; Eng C 1999; Yasir M et al. 2023).

Sporadic MTC is driven by somatic mutations, most commonly in *RET* (50-60% of cases) or *RAS* genes (Gild et al. 2023; Parimi et al. 2023). The most common somatic *RET* mutation is M918T (p.Met918Thr), which is associated with a more aggressive disease course and poor prognosis with increased risk of lymph node metastases, advanced tumour stage, and recurrence. Other *RET* mutations, include mutations in multiple other codons (883, 634) and deletions. In cases where *RET* mutations are absent, somatic *RAS* mutations (most commonly HRAS p.Gln61Arg) are often present, and these are generally associated with less aggressive tumour behaviour (Gild et al. 2023). Patients with sporadic MTC generally present with unilateral tumours and no other endocrine involvement (Block et al. 1980) (Somnay et al. 2013).

RET mutation status is required to determine eligibility for selpercatinib treatment. LIBRETTO-531 is a global, multicentre, randomised, open-label (sponsor blinded), controlled, phase III trial which provides evidence of the efficacy and safety of selpercatinib versus physician's choice of cabozantinib or vandetanib in treatment-naïve, advanced or metastatic, *RET* mutant MTC patients. Evidence from this trial demonstrated treatment with selpercatinib produced clinically meaningful improvement across multiple endpoints, including disease progression and survival.

In summary, the target population for this application is patients with a confirmed clinical diagnosis of *RET*-positive mutant MTC. This submission relates to the co-dependent technology, *RET* mutation testing to determine eligibility for PBS-subsidised treatment with selpercatinib.

Epidemiology

Current Australian epidemiological data on MTC is limited. The incidence rate of MTC varies by region, with reports estimating between 0.2–0.3 cases per 100,000 people (Milićević et al. 2021; Tao et al. 2024). In 2024, 4,335 patients (Australian Institute of Health and Welfare 2024) were projected to be diagnosed with thyroid cancer. A total of 4% of thyroid cancers (TC) will be attributable to the diagnosis of MTC (Cancer Australia 2024), totalling 173 patients in 2024. Although rare, MTC accounts for up to 13% of TC deaths (Gild et al. 2023). Patients with advanced progressive disease have a five-year survival of approximately 40% (Department of Health and Aged Care 2023). In patients with stage IV disease, 5 and 10-year relative survival rate has been reported to be as low as 28% and 21%, respectively (Haddad et al. 2022; Wells et al. 2015)).

An Australian retrospective study found the median age at diagnosis is 53 years old (Papachristos et al. 2023), consistent with overall TC trends, where the median age at diagnosis is 55 years for males and 49 years for females (Cancer Council Victoria 2024). However, hereditary MTC often presents at a younger age, occurring in early childhood in MEN2B, early adulthood in MEN2A, and middle age in FMTC (Eng C 1999). Regarding gender distribution, MTC also follows trends observed in overall thyroid cancers, which are more prevalent in females, with data from an Australian study reporting 57% of MTC patients were female (Papachristos et al. 2023) (Cancer Council Victoria 2024). A significant proportion of MTC cases are diagnosed at advanced stages. Over half (54%) present with advanced and metastatic disease (stage III 45% or stage IV 9%)(Papachristos et al. 2023).

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

Diagnosis

MTC is typically detected following a symptomatic presentation (e.g., thyroid nodule, cervical lymphadenopathy, unexplained diarrhoea) at a general practitioner (GP). Clinical examination of the thyroid gland and lymph nodes, along with blood tests including thyroid-stimulating hormone (TSH) and serum calcitonin levels. If MTC is suspected or diagnosed, referral to an endocrinologist or thyroid surgeon follows to confirm or further investigate the diagnosis (RACGP 2018).

Specialist diagnostic tests are then conducted to confirm stage, type, and histology. These tests may include additional imaging such as PET-CT scan, in particular ^{68}Ga-DOTATATE. Ultrasound and MRI, biopsy of tumour specimens using a variety of techniques including fine needle aspiration (FNA) and additional blood tests such as carcinoembryonic antigen (CEA) doubling times and serum calcitonin (if not conducted by GP). Elevated calcitonin level is an essential feature of this tumour, and a sensitive tumour marker used in the diagnosis (Master et al. 2024). Carcinoembryonic antigen (CEA) is another C cell marker used often in addition to calcitonin. Doubling times of calcitonin and CEA are recognised as reliable indicators of disease progression (Barbet et al. 2005). Preoperative calcitonin levels correlate with the degree of metastatic disease. Levels of <53 pg/mL reflect a low likelihood of lymph node metastases and if over 500 pg/mL, conversely, a high likelihood. At levels of >1000 pg/mL, distant metastatic disease is highly suggestive and preoperative staging should include extensive structural imaging (Danila et al. 2019).

All patients with a confirmed MTC diagnosis and suspected hereditary disease should undergo germline *RET* testing to determine whether their disease driven by a germline mutation. Germline *RET* testing of exons 8, 10, 11, and 13–16 is performed to exclude MEN2/3 and is funded under MBS item 73339. If a germline pathogenic *RET* variant is identified, first-degree relatives should be offered genetic counselling and testing under MBS item 73340 (Gild et al. 2023). Germline *RET* testing is an essential component of the standard diagnostic workup for MTC and is routinely conducted in clinical practice. However, germline *RET* testing only identifies hereditary MTC, which accounts for approximately 25% of cases. European Society for Medical Oncology (ESMO) guidelines state that somatic *RET* testing is not routinely required but is necessary for patients with advanced MTC being considered for selective RET inhibitors (Filetti et al. 2019). NCCN and Australian guidelines also support the use of somatic testing and state that selpercatinib is a preferred option for patients with *RET*-mutant positive disease (Gild et al. 2023; Haddad et al. 2022). Therefore, this application proposes MBS funding for *RET* mutation testing in patients with suspected somatic *RET* mutant MTC, in order to determine their eligibility for selpercatinib.

Treatment pathway

It is well established that MTC cells do not respond to radioactive iodine, are resistant to conventional chemotherapy, and are not sensitive to the manipulation of TSH levels used for in treatment of differentiated thyroid cancers (Park et al. 2021). Local and international guidelines for the clinical management of MTC recommend surgery as the primary treatment, specifically total thyroidectomy upon diagnosis or early in life (Filetti et al. 2022; Gild et al. 2023; Haddad et al. 2022; Wells et al. 2015). However, the optimal approach to surgery can be nuanced and depend on multiple factors, including comorbidities and extent of disease. Surgery is only curative in approximately 40% of cases (Haddad et al. 2022; Maxwell et al. 2014).

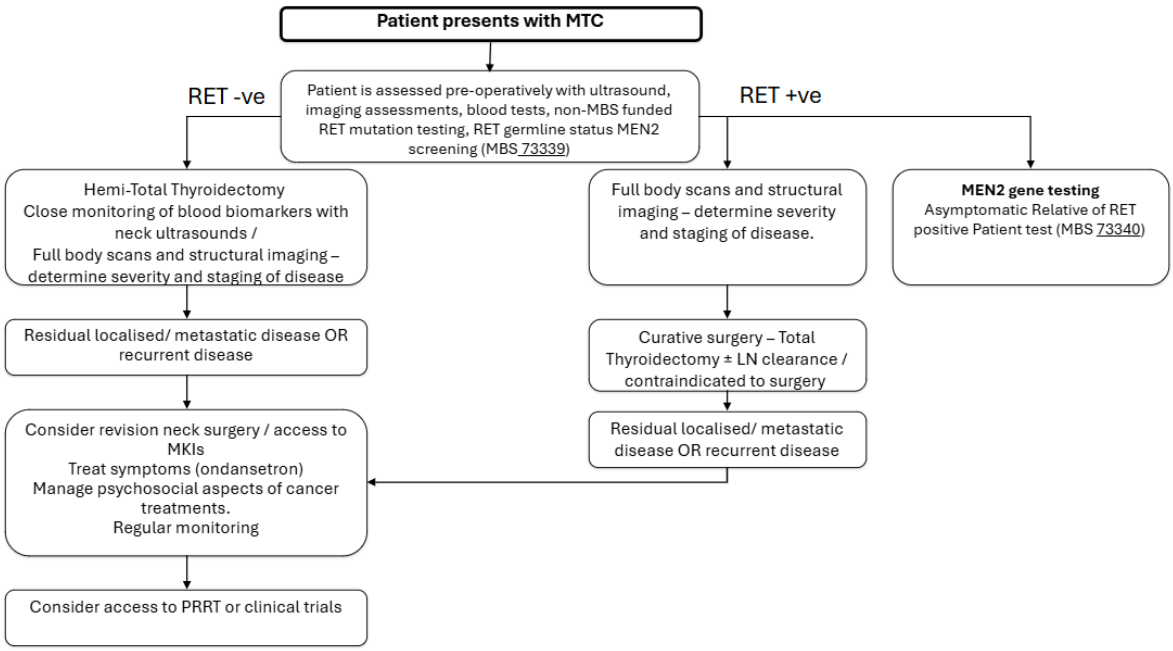
Rarely, MTC is identified in a hemithyroidectomy specimen; completion thyroidectomy is recommended for any patients with germline *RET* mutations, evidence of residual disease, or elevated postoperative calcitonin. Further, up to 50% of MTC will present with regional lymph node involvement. For locoregional MTC without distant metastasis, a comprehensive operation including total thyroidectomy and lymph node dissection is usually recommended.

In the absence of cervical nodal disease on ultrasound, and no evidence of distant metastases, American Thyroid Association guidelines recommend dissection of lateral lymph nodes (Wells et al. 2015) to be evaluated based on serum calcitonin levels. Lateral cervical nodal clearance is recommended when preoperative ultrasound of the ipsilateral neck is positive. Revision neck surgery may be appropriate for recurrent or metastatic MTC with either curative or palliative intent (Gild et al. 2023).

Many patients with advanced or metastatic MTC have already undergone surgery but experience disease progression, recurrence, or persistent residual disease. **REDACTED**

There are currently no PBS-listed therapies for patients with advanced or metastatic MTC. These patients receive therapies within standard of care that include treatments such as ondansetron, to treat symptoms of diarrhoea. In the absence of selpercatinib, the TGA has stated that the current standard of care in Australia for patients with advanced *RET* mutation positive MTC and advanced MTC regardless of *RET* mutation status is multikinase inhibitors (MKIs); specifically, vandetanib (TGA approved but not on the PBS) and cabozantinib (Not TGA approved for MTC) (Department of Health and Aged Care 2023). As MKIs are not on the PBS for MTC, it is anticipated patients access these treatments privately or through clinical trials. A summary of the current clinical management for patients diagnosed with MTC is presented in **Figure 1**.

Figure 1 Current clinical management of patients diagnosed with MTC



Abbreviations: LN, lymph node; MBS: Medicare Benefits Schedule; MEN2; Multiple Endocrine Neoplasia Type 2; MKI, multikinase inhibitor; MTC, medullary thyroid cancer; PRRT, Peptide receptor radionuclide therapy RET, rearranged in transfection

Provide a rationale for the specifics of the eligible population:

Selpercatinib is a highly selective, small molecule inhibitor of the *RET* receptor tyrosine kinase, designed to target oncogenic *RET* mutations and fusions. In enzyme assays, selpercatinib inhibits the kinase activity of *RET*, *RET*-V804L, *RET*-V804M, *RET*-A883F, *RET*-S904F, and *RET*-M918T. Given the specificity of selpercatinib for RET-driven oncogenesis, its clinical utility is restricted to patients with confirmed *RET* mutations.

LIBRETTO-531 is a phase III, randomised, open-label, multicentre study comparing selpercatinib to physicians' choice of cabozantinib or vandetanib in patients with advanced *RET*-mutant MTC, and provides the pivotal evidence for the co-dependent component of this application. Patients enrolled in the trial were required to have a confirmed *RET* gene alteration, identified in a tumour, germline DNA or blood sample. Additionally, two basket trials, LIBRETTO-001 and LIBRETTO-121, provide supplementary evidence for the submission. Both trials required evidence of an activating *RET* gene alteration, detected in the tumour tissue and/or blood. LIBRETTO-001 is an ongoing phase I/II, single arm, open-label study of selpercatinib in patients with *RET*-activated cancers including MTC. Importantly, the trial included both treatment-naïve and previously treated patients, with 53.8% treated with MKI. While LIBRETTO-001 is a phase I/II, single arm study of selpercatinib in paediatric and adolescent patients with advanced *RET*-activated cancers including MTC.

Germline *RET* mutation testing is standard practice and MBS-funded for patients diagnosed with MTC with suspected MEN2. Currently, two MBS items (73339 and 73340) provide funding for germline *RET* testing, allowing for the identification of hereditary MTC in patients with suspected MEN2 and asymptomatic family members. However, somatic *RET* mutation testing is not MBS-funded, despite 50–60% of sporadic MTC cases harbouring a somatic *RET* mutation.

A Sponsor-conducted interview with five treating clinicians confirmed that *RET* mutation testing is routine in Australian hospital settings for both germline and somatic mutations. A retrospective cohort study at Royal North Shore Hospital, Sydney, found that routine *RET* mutation testing using capillary (Sanger) sequencing was performed on 195 patients, of whom 80% had sporadic MTC and 20% had MEN2-positive MTC (Jayakody et al. 2018). *RET* mutation testing services are provided under state and territory hospital funding arrangements and patients are encouraged to have genetic testing through a public hospital. However, when patients are referred by a private facility, they are billed directly (Newton S et al. 2013). Expanding MBS funding for *RET* mutation testing would ensure equitable access to a funded test and appropriate patient selection for *RET*-targeted therapies.

RET mutation testing is commercially available in Australia through private pathology providers for a non-Medicare rebated fee. Australian Clinical Labs offers a comprehensive somatic mutation testing service, which includes testing for *RET* mutations, utilising next-generation sequencing (NGS) on formalin-fixed paraffin-embedded (FFPE) tumour samples. The out-of-pocket fee is approximately $750, with results available in 5–7 business days (Australian Clinical Labs 2023). Similarly, Sonic Genetics provides the ThyroSeq test, an extensive NGS panel that assesses 112 thyroid-related genes, including *RET*. This test is conducted in a USA-based laboratory, with results available within 14 business days. The cost is $2,100 for a single nodule and $1,164 for each additional nodule, when tested simultaneously (Sonic Genetics). The proposed MBS fee of $400 is consistent with other MBS listed pathology services for mutation testing in a single gene for a test of tumour tissue (e.g item 73338 for RAS mutation testing) and is consistent with the fee for MBS item 73339 for detection of germline mutation in the RET gene. RET mutation testing offered by Sonic Genetics and Australian Clinical Labs is priced higher than the proposed item, as these tests include broader mutation panels. The Department has previously assessed *RET* mutation testing for different applications, noting the existing MBS items for germline *RET* testing (73339 and 73340), and for *RET* testing in patients with a new diagnosis of non-small cell lung cancer (73437). As such, the Sponsor proposes a streamlined application.

Are there any prerequisite tests? (please highlight your response)

Yes

Are the prerequisite tests MBS funded? (please highlight your response)

Yes

Please provide details to fund the prerequisite tests:

There currently exists MBS funding for the prerequisite diagnostic tests required to confirm MTC as part of current standard of care in Australia. Histological confirmation of MTC through biopsy and immunohistochemistry for calcitonin/CEA is required, with funding available under relevant MBS pathology items. FNA biopsy (MBS item 73051) is commonly performed to obtain tumour specimens for cytological examination of MTC. If necessary, a tissue sample obtained during surgical resection can be processed as a FFPE specimen for histopathological analysis. Laboratory tests, including serum calcitonin (MBS item 66695) and carcinoembryonic antigen (CEA) (MBS item 66650) which are essential for diagnosis. Funding for imaging including ultrasound of the neck (MBS item 55032), and PET-CT scan (MBS item 61598), which provide further assessment of tumour burden, lymph node involvement, and metastatic status. Currently, patients who receive a clinical diagnosis of MTC, with a suspected clinical diagnosis of MEN2 undergo germline *RET* mutation testing (MBS item 73339), performed on blood or buccal swab. This test identifies if patients have a germline *RET* mutation associated with MEN2, expected to be identified in 25% of MTC cases (Margraf et al. 2009). MEN2 is a group of disorders, associated with tumours of the endocrine system and in patients where a diagnosis of MEN2 is made, familial genetic testing is required (Margraf et al. 2009), this testing is reimbursed per MBS item 73340. Patients with suspected hereditary disease who will access germline *RET* mutation testing under MBS item 73339 will present with distinct clinical characteristics. Hereditary MTC often presents bilaterally. Pheochromocytoma is common in MEN2A and MEN2B, while primary hyperparathyroidism occurs only in MEN2A. MEN2B is distinguished by marfanoid habitus, spinal issues, joint laxity, mucosal neuromas, and intestinal ganglioneuromas (Block et al. 1980; Eng C 1999; Yasir M et al. 2023). Patients with MTC who do not have suspected MEN2 currently access testing under state and territory hospital funding arrangements, or privately.

RET mutation testing will determine if patients who are negative for a germline *RET* mutation are eligible for selpercatinib, however, germline *RET* mutation testing (MBS item 73339) is not considered a prerequisite for the proposed MBS item. Patients with suspected MEN2 have distinct clinical characteristics which are identifiable to treating clinicians, making negative results uncommon. The sponsor proposes the new MBS is not specific for somatic *RET* mutations. As *RET* mutation testing for access to selpercatinib will be conducted on tissue, it can identify germline mutations that may have been missed or be replacement for MBS item 73339 in a patient who otherwise meets eligibility criteria for selpercatinib. Utilisation of MBS item 73339 is low, in total, 18 claims were made for MBS item 73339 from January–December 2024. Consistent with MBS precedent, MSAC has already considered flow on consequences for germline/cascade testing of patients with germline RET mutations, would not need to be reassessed.

Intervention

Name of the proposed health technology:

RET mutation testing in patients with a confirmed diagnosis of MTC, to determine eligibility for PBS-subsidised selpercatinib.

Describe the key components and clinical steps involved in delivering the proposed health technology:

Proposed testing

Patients with a confirmed diagnosis of MTC require *RET* mutation testing to determine eligibility for PBS-subsidised selpercatinib. *RET* mutation testing is a molecular diagnostic procedure used to identify pathogenic *RET* mutations in patients with sporadic MTC. Sporadic MTC is primarily driven by point mutations or small insertions/deletions in the *RET* gene, which can be detected using conventional DNA-based methods such as Polymerase Chain Reaction (PCR) and targeted NGS (Belli et al. 2021; Wells et al. 2015). In contrast, *RET* fusions which result from chromosomal rearrangements observed in non-small cell lung cancer (NSCLC) and require DNA/RNA-based detection methods such as NGS or fluorescence in situ hybridisation (FISH) (Stinchcombe 2020) (Belli et al. 2021).

A tumour tissue biopsy is required for *RET* mutation analysis, which can be obtained through one of the following methods:

- FNA biopsy – Commonly used for initial cytological diagnosis of MTC, particularly in thyroid nodules or metastatic lymph nodes.
- Surgical resection – If the tumour has been removed, FFPE tissue sample from the resected specimen is preferred when available, as it provides a larger and more reliable tissue sample for analysis.

Genomic DNA is extracted from the tumour sample. Several approaches are available for the detection of *RET* alterations, and molecular analysis can be performed using NGS testing or PCR-based testing.

Next-Generation Sequencing (NGS)

NGS is a high-throughput sequencing technology that allows for a comprehensive analysis of multiple genes or entire genomes/exome. DNA is fragmented, sequenced, and analysed using advanced bioinformatics tools to identify both known and novel mutations, insertions, deletions, and complex rearrangements. It is the preferred method as it has high sensitivity of mutation detection allowing the identification of somatic mutations with low-variant allele frequencies (>3%-5%) or in tissue specimens with a low percentage of tumour cells. ESMO recommends NGS for patients with advanced cancers including thyroid cancer, in countries where tumour-agnostic targeted therapies are accessible (Mosele et al. 2024). In the LIBRETTO-001 trial, NGS testing was used to identify driver *RET* mutations in 86% of patients.

PCR-Based Testing

DNA Sanger sequencing is a reliable method for identifying single-nucleotide variations such as the missense mutations associated with MEN2A or familial MTC. However, it has lower sensitivity for detecting low-frequency mutations if they are present in less than 15%-20% of the tumour DNA (Belli et al. 2021).

PCR-based assays (qPCR and Digital PCR) are commonly used assays for detecting specific, known pathogenic *RET* mutations in MTC. This technique amplifies specific regions of the *RET* gene, and detects mutations in predefined hotspots (e.g., exons 10, 11, 13, 14, 15, and 16). However, PCR-based assay has limitations as it is restricted to known mutations and cannot detect novel or rare alterations compared to NGS (Belli et al. 2021). In the LIBRETTO-531 trial, patients *RET* alteration status was confirmed with the use of PCR, or NGS (LIBRETTO-531 CSR, page 47).

Both NGS and PCR-based testing have previously been recognised by the MSAC as acceptable methods for testing somatic mutations. Notably, MSAC Application 1554 supported the use of NGS-based somatic BRCA1/2 mutation testing, demonstrating high diagnostic accuracy and concordance with traditional PCR and Sanger sequencing methods (MSAC 2020). It is acknowledged that routine RET testing using the capillary (Sanger) sequencing method is commonly conducted as cited in local literature {Jayakody, 2018 #61}. Nonetheless, both methods are equally applicable and should be considered valid and reliable for *RET* mutation detection. As such, in keeping with MSAC preference, the proposed item descriptor does not specify a test method.

Identify how the proposed technology achieves the intended patient outcomes:

The mechanism of action of selpercatinib is to inhibit the *RET* receptor tyrosine kinase activity, specifically targeting oncogenic *RET* mutations, including *RET*, *RET*-V804L, *RET*-V804M, *RET*-A883F, *RET*-S904F, and *RET*-M918T. *RET* mutation testing will confirm eligibility for selpercatinib by identifying patients with a positive *RET* mutation. This will ensure only patients with the relevant *RET* alterations receive treatment.

Patients with *RET*-mutant MTC may experience significant clinical benefit with selpercatinib, including progression-free survival (PFS) and overall survival (OS) compared to standard of care, as demonstrated in the clinical trials presented in the co-dependent submission.

LIBRETTO-531 was a phase III randomised, open-label, multicentre study comparing selpercatinib (160 mg twice daily) to the treating physician's choice of cabozantinib (140 mg once daily) or vandetanib (300 mg once daily) in patients with advanced *RET*-mutant MTC who have not received previous treatment with a kinase inhibitor. Results of the LIBRETTO-531 trial demonstrate the key benefit of selpercatinib treatment for patients with advanced *RET*-mutant MTC is statistically significant and clinically meaningful improvement across multiple endpoints compared to MKIs cabozantinib or vandetanib (control arm). Patients receiving selpercatinib had a clinically meaningful and statistically significant reduction by 80% in the hazard of disease progression or death, along with a superior PFS rate compared to the control arm. The PFS rate at

36 months was 64.1% in selpercatinib arm versus 21.7% in the control arm. In addition, patients receiving selpercatinib reported less AEs requiring permanent discontinuation, reflecting in a longer time to TFFS in comparison to the control arm (63.8% vs. 19.2%, respectively). In Australia there are no therapies reimbursed on the PBS for the treatment of patients with *RET* mutant MTC, and as such standard of care includes no active therapies. The co-dependent submission will present results from a formal, pairwise indirect (Bucher) treatment comparison to inform the efficacy of selpercatinib, compared to placebo. Evidence from two single arm basket trials, LIBRETTO-001 and LIBRETTO-121 also provides evidence supporting the efficacy of patients with *RET* mutant MTC who have had prior MKI therapy, and in a pediatric population, respectively (LIBRETTO-001 CSR) (Morgenstern et al. 2024; Morgenstern et al. 2021).

If no *RET* mutation is detected in patients with a diagnosis of MTC, the results may suggest alternative molecular drivers, such as *RAS* mutations, which are found in a subset of sporadic MTC cases. This will help guide personalised treatment plans, enabling clinicians to select the most appropriate therapy or consider clinical trial options.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

There is no registered trademark component associated with *RET* mutation testing. Multiple validated testing options are available, including NGS and PCR-based assays. These methods are widely used across different laboratory platforms and are not restricted to a single proprietary technology. Testing can be performed in accredited public and private molecular pathology laboratories. Therefore, there is no requirement for a trademarked test component for the proposed health technology.

This application requests an assay-agnostic MBS item for somatic *RET* mutation testing, as testing can be performed using a variety of validated sequencing methodologies in National Association of Testing Authorities (NATA)-accredited laboratories. Given that available sequencing technologies in Australia align with established clinical utility standards, it is not necessary to specify a particular assay for *RET* mutation testing.

The NGS and PCR testing modalities used in the Australian setting are consistent with those used the LIBRETTO-531, LIBRETTO-001, and LIBRETTO-121, which assessed the efficacy and safety of selpercatinib in patients with *RET* mutant MTC. As such, these trials provide direct evidence supporting both the accuracy and performance of *RET* mutation testing. Since these trials have already demonstrated the clinical validity of *RET* mutation detection, an additional assessment of the performance and accuracy of *RET* mutation testing using NGS and PCR is not presented in this submission.

The co-dependent treatment selpercatinib registered brand name is Retevmo®.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency): (please highlight your response)

Yes

Provide details and explain:

Frequency
Patients with a confirmed clinical diagnosis of MTC will be referred for a single *RET* mutation test to determine their eligibility for selpercatinib treatment. Patients only require one diagnostic *RET* mutation test per lifetime, consistent with the germline *RET* mutation testing (Newton S et al. 2013).

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Somatic *RET* mutation testing requires a tumour tissue biopsy (FNA or FFPE), which should be collected by a suitably qualified and trained professional, such as a medical specialist, endocrinologist or surgeon. The biopsy sample is then processed and analysed in a NATA-accredited laboratory, where PCR or NGS is performed by molecular pathologists. Based on genetic test results, selpercatinib will be prescribed by oncologists or endocrinologists for eligible patients.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

Not applicable.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

Patients eligible for the proposed health technologies to determine *RET* mutation status and determine eligibility for treatment with PBS-subsidised selpercatinib must have a confirmed clinical diagnosis of MTC. This diagnosis must be made by a qualified specialist, such as oncologists and endocrinologists.

In addition, the proposed PBS restriction for selpercatinib will include a clinical criteria specifying that patients must have advanced, or metastatic disease, and a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of no higher than 2 at treatment initiation. These criteria are consistent with the characteristics of patients enrolled in the LIBRETTO-531 trial (Hadoux et al. 2016), which provides the pivotal evidence for the efficacy and safety of selpercatinib in patients with *RET* mutant MTC.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology? (please highlight your response)

Yes

Provide details and explain:

Any *RET* mutation testing to inform access to selpercatinib will occur at NATA-accredited laboratories to ensure validity and compliance with national quality standards. Testing is performed by qualified molecular pathologists, who require expertise in NGS or PCR-based assays used for *RET* mutation detection. Pathologist training and ongoing quality assurance programs are expected to support the standardisation and accuracy of *RET* mutation testing, which is part of current standard practice in Australian laboratories.

Indicate the proposed setting(s) in which the proposed health technology will be delivered: (select all relevant settings)

☐ **Consulting rooms**
☐ Day surgery centre
☐ Emergency Department
☐ **Inpatient private hospital**
☐ **Inpatient public hospital**
☐ **Laboratory**
☐ **Outpatient clinic**
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

RET mutation testing would be undertaken in a laboratory setting, but specimen collection and some pre-analytical handling of the specimen could take place in multiple admitted and non-admitted patient settings.

Is the proposed health technology intended to be entirely rendered inside Australia? (please highlight your response)

Yes

Please provide additional details on the proposed health technology to be rendered outside of Australia:

Not applicable.

Comparator

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

This application is requesting an MBS item for *RET* mutation testing in patients with a clinical diagnosis of MTC to inform PBS-subsidised access to selpercatinib.

The appropriate comparator for *RET* mutation testing is 'no MBS-funded *RET* mutation testing'.

Surgical intervention is the primary treatment for patients with a clinical diagnosis of MTC. In cases of advanced or metastatic disease following surgery, patients are treated with pharmacological interventions to treat symptoms and systemic therapies such as MKIs. Currently, there are no PBS reimbursed therapies for the treatment of *RET* mutant MTC, any treatment of these patients with MKIs is expected to be a result of private, or off-label use. As such, the appropriate comparator for selpercatinib is standard of care.

List any existing MBS item numbers that are relevant for the nominated comparators:

Not applicable.

Please provide a rationale for why this is a comparator:

The comparator, 'no MBS-funded *RET* mutation testing' reflects current standard of care in Australia for patients with sporadic MTC who may harbour somatic *RET* alterations.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator? (please select your response)

☐ None – used with the comparator
☐ Displaced – comparator will likely be used following the proposed technology in some patients
☐ Partial – in some cases, the proposed technology will replace the use of the comparator, but not in all cases
☐ **Full – subjects who receive the proposed intervention will not receive the comparator**

Please outline and explain the extent to which the current comparator is expected to be substituted:

Currently, patients who receive a clinical diagnosis of MTC, with a suspected clinical diagnosis of MEN2 undergo germline *RET* mutation testing (MBS item 73339). In some cases, patients who have a germline *RET* mutation identified may not need to access somatic *RET* mutation testing. However, it is likely in most cases germline testing per MBS item 73339, and *RET* mutation testing per the new MBS item, will either be conducted concurrently, or the new item will supersede MBS item 73339. This application proposes the use of somatic *RET* mutation testing in patients with a clinical diagnosis MTC to determine eligibility for treatment with PBS-subsidised selpercatinib. Patients with a confirmed *RET* mutation must also meet the PBS eligibility criteria for selpercatinib treatment. With the implementation of somatic *RET* mutation testing, it is anticipated that this

testing will entirely replace the comparator, 'no MBS-funded *RET* mutation testing' for patients with sporadic MTC who may harbour somatic *RET* alterations. This ensures that all eligible patients have equitable access to a funded tests and appropriate patient selection to targeted therapy based on their mutation status.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator): (please select your response)

☐ **Health benefits**
☐ Health harms
☐ Resources
☐ Value of knowing

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

There are currently no PBS-listed targeted therapies available in Australia for the treatment of *RET*-mutant, advanced or metastatic MTC. *RET* mutation testing is essential to identify patients with *RET*-positive MTC who may be eligible for selpercatinib. This targeted therapy directly inhibits the *RET*-driven tumour growth, replacing the current reliance on MKIs, which are less selective, associated with higher toxicity and not PBS-funded for MTC.

The clinical benefit of *RET* mutation testing is well established and has been the standard practice in Australian hospitals for over a decade to inform prognosis. Given that *RET* mutation testing is already performed in hospital settings, the introduction of an MBS item for this test is unlikely to significantly increase overall testing volume. However, the cost-effectiveness of *RET* mutation testing under a Commonwealth-funded MBS item will be considered, alongside the cost-effectiveness of selpercatinib.

Outcomes related to the therapeutic component

Health benefits

Clinical evidence from the pivotal trial LIBRETTO-531 showed that patients with RET-mutant MTC who receive selpercatinib experience a more favourable prognosis compared to those treated with MKIs, such as cabozantinib and vandetanib.

The LIBRETTO-531, LIBRETTO-001 and LIBRETTO-121 trials demonstrated that treatment with selpercatinib led to a clinically meaningful reduction in disease progression and survival benefits in treatment-naïve, pre-treated, adolescent, and paediatric patients with advanced *RET*-mutant MTC. Additionally, the LIBRETTO-531 trial showed that selpercatinib had better tolerability compared to current standard of care with MKIs, an important factor in prolonging treatment duration and delaying progression of the disease.

Clinical effectiveness outcomes

- Progression free survival (PFS)
- Overall survival (OS)
- Overall response rate (ORR)
- Comparative tolerability

Safety

The LIBRETTO-531 trial demonstrated an acceptable safety profile of selpercatinib. The overall incidence of any at least 1 treatment emergent adverse events (TEAEs) were comparable between the selpercatinib group and the control group of cabozantinib or vandetanib (99.5% vs 99.0%). The rate of Grade ≥3 TEAs, any serious adverse events (SAEs), and AEs or SAEs leading to treatment discontinuation were lower in the selpercatinib arm compared to the control arm.

Clinical utility of test

Treatment effect modification of selpercatinib in MTC patients with a *RET* mutation status (predictive validity).

Longitudinal accuracy outcomes

Other test-related considerations:

- Test turn-around time
- Estimated number of patients being tested
- Number needed to test
- Cost of testing per patient

These test-related considerations align with the ratified PICO frameworks for other codependent submissions where the clinical utility standard is the same as what would be used in Australian clinical practice (e.g. MSAC Application 1750).

Healthcare system

- Cost-effectiveness analysis of selpercatinib
- Overall cost impact to MBS and PBS

Proposed MBS items

How is the technology/service funded at present? (for example: research funding; State-based funding; self-funded by patients; no funding or payments):

Costs associated with somatic RET mutation testing

Currently, germline *RET* mutation testing is standard practice in Australia and is MBS-funded for patients with a suspected clinical diagnosis of MEN2. There is no MBS funding for somatic *RET* mutation testing, however, *RET* mutation testing services are provided in public hospitals funded under state and territory hospital funding arrangements.

Somatic *RET* mutation testing is also commercially available in Australia through private pathology providers, however, it is only offered as part of a comprehensive somatic mutation panel rather than a standalone test. Australian Clinical Labs provides this service for a non-Medicare rebatable fee of $750. Alternatively, Sonic Genetics offers a more extensive thyroid-related gene panel, including *RET*, at a non-Medicare rebatable fee of $2,100 for a single nodule and $1,164 for each additional nodule (Australian Clinical Labs 2023) (Sonic Genetics).

Costs associated with selpercatinib

Selpercatinib is not currently PBS reimbursed for the treatment of *RET* mutant MTC.

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention: (please copy the below questions and complete for each proposed item)

Proposed item details

MBS item number (where used as a template for the proposed item)	MBS item 73339 and 73437 used as a template for the proposed item descriptor
Category number	6
Category description	Pathology Services
Proposed item descriptor	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).
Proposed MBS fee	$400
Indicate the overall cost per patient of providing the proposed health technology	$400
Please specify any anticipated out of pocket expenses	No additional out-of-pocket costs are expected
Provide any further details and explain	The proposed MBS fee of $400 is consistent with other MBS listed pathology services for mutation testing in a single gene for a test of tumour tissue (e.g item 73338 for RAS mutation testing) and is consistent with the fee for MBS item 73339 for detection of germline mutation in the RET gene. RET mutation testing offered by Sonic Genetics and Australian Clinical Labs is priced higher than the proposed item, as these tests include broader mutation panels.

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

As previously described, patients with suspected MTC typically present to a GP or endocrinologist with a thyroid nodule or cervical lymphadenopathy. Initial diagnosis involves cytological assessment (for FNA biopsy samples) or histopathological assessment (surgical biopsy samples FFPE tumour tissue), along with immunohistochemical analysis of calcitonin and CEA levels to confirm diagnosis.

If MTC is confirmed and the patient has suspected MEN2, they are referred for germline *RET* mutation testing (MBS item 73339). If a pathogenic germline *RET* variant is identified, the patient is diagnosed with hereditary MTC, and first-degree relatives should be offered genetic testing (MBS item 73340).

Patients with suspected sporadic MTC may have somatic *RET* mutation testing at a public hospital or private facility for an out-of-pocket cost. All MTC patients are then managed by an endocrinologist, endocrine surgeon, or oncologist, depending on disease stage, and treatment decisions are based on tumour burden, metastatic status, and surgical eligibility. This application proposes that patients with a confirmed diagnosis of MTC will be tested under MBS item 73339 where appropriate and/or will be eligible for *RET* mutation testing to inform PBS-subsidised access to selpercatinib.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology? (please highlight your response)

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

To access *RET* mutation testing to inform access to PBS-subsidised selpercatinib, patients must have an existing diagnosis of MTC. The proposed technology is not intended to be used for the initial diagnosis of MTC but rather for molecular characterisation of the tumour in patients with sporadic MTC. As such, no differences are expected in the clinical management algorithm prior to the usage of the proposed tests versus the comparator, which is 'no MBS-funded *RET* mutation testing'.

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

RET mutation testing will be conducted using a tumour tissue sample, which can be obtained via either FNA biopsy (MBS item 73051) or FFPE tissue sample obtained in surgical resection. It is important to note that these procedures are already routinely performed as part of the clinical diagnosis and management of MTC.

Explain what other healthcare resources are used in conjunction with the comparator health technology:

The same healthcare resources (tumour tissue sampling via FNA biopsy (MBS item 73051) or FFPE tissue sample obtained during surgical resection) are required in conjunction with the comparator. However, *RET* mutation testing is currently funded under state and territory hospital arrangements.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

Currently patients with a clinical diagnosis of MTC, hereditary or sporadic, are treated with standard of care, which includes surgery as the primary treatment. In cases of advanced or metastatic disease, following surgery patients are treated with pharmacological interventions such as systemic therapies to manage symptoms and tumour progression.

Patients accessing the proposed health technology, *RET* mutation testing, will continue to be treated with standard of care and therefore the overall clinical management pathway remains largely unchanged. *RET* mutation testing will enable identification of eligible patients for PBS-subsidised selpercatinib. Healthcare resources used in conjunction with the proposed health technology (e.g., tumour biopsy, surgical resection, pathology assessment, specialist consultations) are already part of routine MTC management.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:

This co-dependent application requests MBS listing for *RET* mutation testing in patients with a clinical diagnosis of MTC, to inform access to PBS-subsidised selpercatinib. It is anticipated that patients who access this diagnostic service will have met the PBS eligibility criteria for treatment with selpercatinib. Eligibility criteria for selpercatinib includes advanced or metastatic MTC with evidence of *RET*-mutant tumour material. Patients who meet the eligibility criteria will be able to initiate selpercatinib irrespective of line of therapy.

Selpercatinib is administered orally, twice daily and is available in hard capsules of two strengths: 40 mg and 80 mg. The recommended dose of selpercatinib is based on body weight as follows:

- 50 kg or greater: 160 mg twice daily
- Less than 50 kg: 120 mg twice daily

In Australian clinical practice, it is expected that treatment with selpercatinib will continue until disease recurrence and/or progression or if unacceptable toxicity occurs that cannot be managed with dose adjustment. Following the initiation of selpercatinib, patients require ongoing assessment to monitor treatment response, disease progression, and adverse events. Clinical evaluation by an oncologist or endocrinologist to monitor treatment tolerability and symptom management, analysis of calcitonin and CEA serum levels and ultrasound to assess tumour response, which is part of current patient management for MTC treated with current standard of care.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

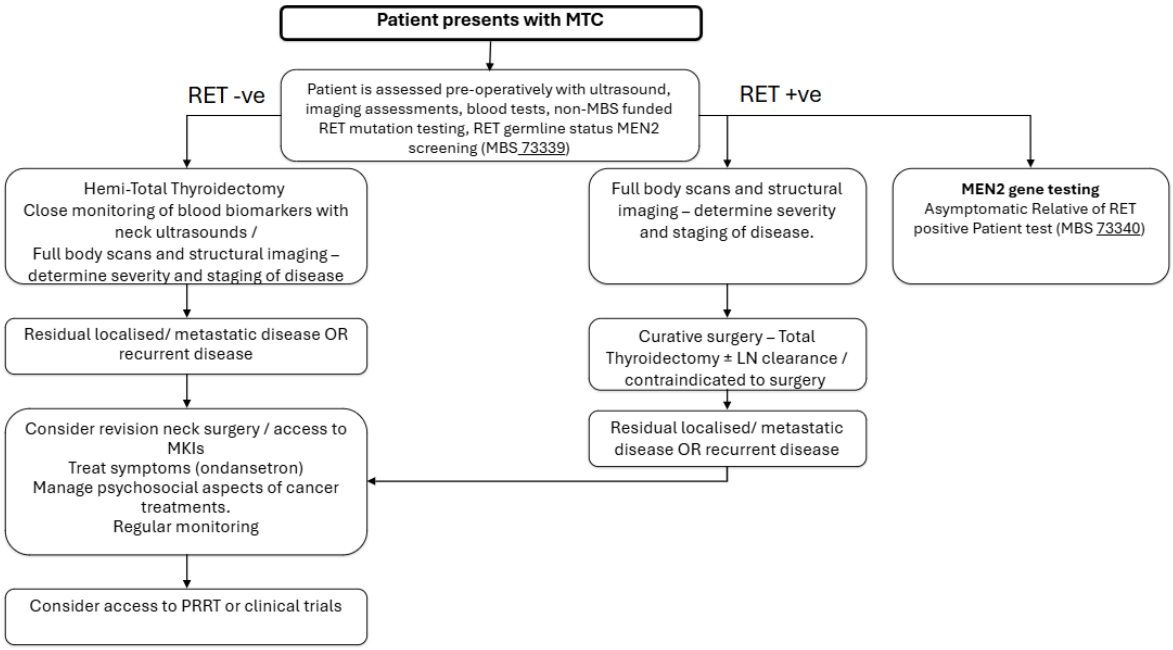
The proposed health technology and co-dependent access to selpercatinib are intended to be delivered in conjunction with current standard of care. MBS-funded *RET* mutation testing will be integrated into the existing patient management algorithm to identify patients eligible for selpercatinib treatment.

As per the current clinical algorithm, curative surgery remains the primary treatment for patients with resectable disease. Patients with residual, recurrent, or metastatic disease following surgery (unless contraindicated) can initiate selpercatinib, irrespective of prior systemic therapy. REDACTED.

Algorithms

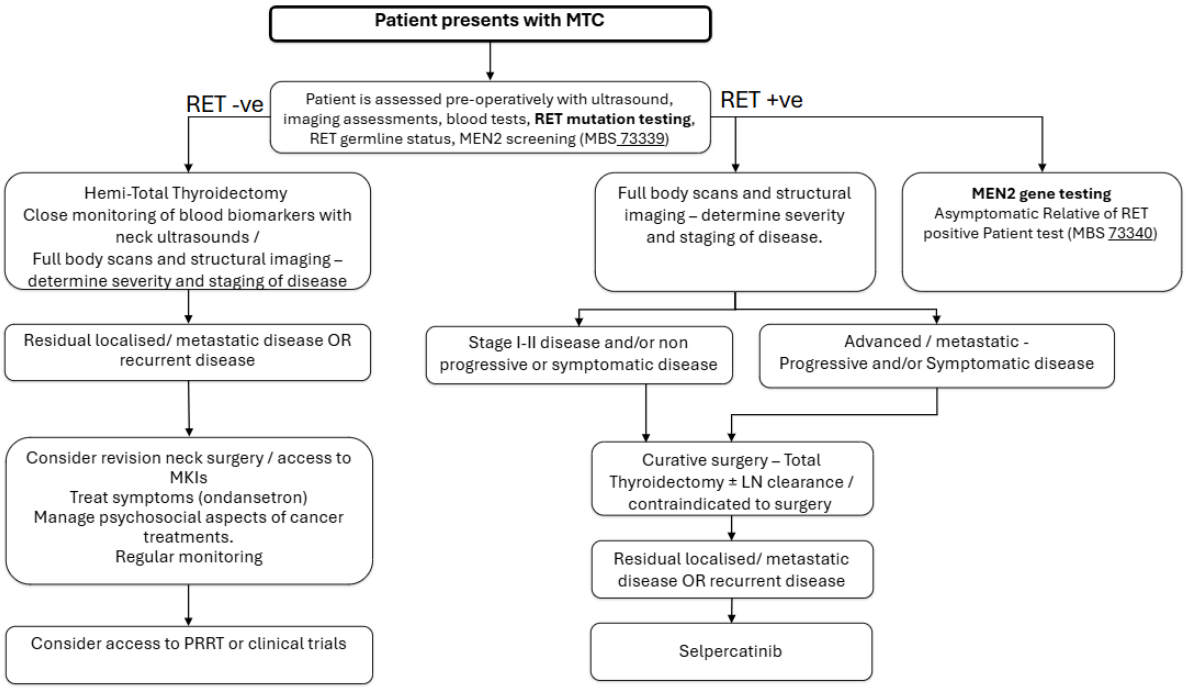
Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Figure 2 Current clinical management of patients diagnosed with MTC



Abbreviations: LN, lymph node; MBS: Medicare Benefits Schedule; MEN2; Multiple Endocrine Neoplasia Type 2; MKI, multikinase inhibitor; MTC, medullary thyroid cancer; PRRT, Peptide receptor radionuclide therapy RET, rearranged in transfection

Figure 3 Proposed clinical management of patients diagnosed with MTC



Abbreviations: LN, lymph node; MBS: Medicare Benefits Schedule; MEN2; Multiple Endocrine Neoplasia Type 2; MKI, multikinase inhibitor; MTC, medullary thyroid cancer; PRRT, Peptide receptor radionuclide therapy RET, rearranged in transfection

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)? (please select your response)

☐ **Superior**
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

RET mutation testing, followed by targeted treatment with selpercatinib is superior to no MBS-funded *RET* mutation testing and standard of care.

This application proposes that *RET* mutation testing, as a co-dependent technology, is necessary to determine treatment eligibility for selpercatinib in patients with confirmed diagnosis of MTC. The use of *RET* mutation testing, followed by treatment with selpercatinib in eligible patients, results in superior health outcomes and a manageable safety profile compared to 'no MBS-funded *RET* mutation testing' and treatment with the current standard of care.

This clinical claim is supported by the selpercatinib clinical trials presented in the PBAC submission. The pivotal trial LIBRETTO-531 demonstrated superior efficacy and an acceptable safety profile for selpercatinib compared to MKIs cabozantinib and vandetanib in advanced or metastatic *RET*-mutant MTC. The necessity of *RET* mutation testing is reinforced by the clinical utility of the test, as selpercatinib is a highly selective RET inhibitor and only effective in patients with a confirmed *RET* mutation. *RET* mutation testing ensures appropriate patient selection preventing the use of selpercatinib in patients unlikely to benefit, thereby optimising treatment outcomes and improving overall clinical management.

Overview of LIBRETTO-531

LIBRETTO-531 was a phase III randomised, open-label, multicentre study comparing selpercatinib to cabozantinib and vandetanib in patients with advanced *RET*-mutant MTC who have not received previous treatment with a kinase inhibitor. Patients were randomly assigned in a 2:1 ratio to receive selpercatinib (160 mg twice daily) (N=193) or the treating physician's choice of cabozantinib (140 mg once daily) or vandetanib (300 mg once daily) (control group, N=98). Patients were stratified according to *RET* mutation (M918T vs. other). Treatment continued until disease progression confirmed by blinded independent central review (BICR), unacceptable toxicity, or death. Patients who discontinued treatment for radiographic disease progression that was confirmed by BICR and were randomised to cabozantinib or vandetanib may have been eligible for crossover to selpercatinib if they met the eligibility criteria for crossover. The primary outcome evaluated was PFS. Treatment failure-free survival (TFFS) was a secondary, alpha-controlled endpoint that was to be tested only if PFS was significant. Other secondary endpoints included overall response, comparative tolerability and safety.

The results from the LIBRETTO-531 trial demonstrated treatment with selpercatinib in patients with advanced *RET*-mutant MTC showed statistically significant and clinically meaningful improvement across multiple endpoints compared to MKIs cabozantinib or vandetanib (control arm). A summary of key results is provided below:

Efficacy:

Patients treated with selpercatinib experienced a statistically significant reduction in the risk of disease progression or death compared to those in the control arm. The hazard ratio for PFS, stratified by *RET* mutation, was 0.20 (95% CI: 0.128–0.320; p<0.0001), indicating an 80% reduction in the risk of progression or death with selpercatinib.

After three years of treatment, median PFS was not reached in the selpercatinib group, meaning more than 50% of patients remained progression-free. In contrast, the control arm had a median PFS of 13.93 months (95% CI: 12.2–19.5 months). Long term benefit of selpercatinib is further supported by PFS rates over time. At 12 months, the PFS rate was 90.5% (95% CI: 85.1–94.0) for selpercatinib versus 63.9 (95%CI: 51.8–73.7) for the control group. By 36 months, the PFS rate declined to 64.1% (95% CI: 46.6–77.2) for selpercatinib and 21.7% (95% CI: 9.9–36.4) for the control group.

Selpercatinib patients reported superior treatment tolerability compared with the control arm, an important factor in prolonging treatment duration and delaying progression of the disease. Patients treated with selpercatinib had a statistically significantly lower proportion of time on treatment that patients reported as "high side effect bother" (8%) than the control arm (24%). The results of this analysis demonstrate that selpercatinib provides clinically important improvements compared to control, which extend beyond the benefits of PFS.

Safety:

The results of the LIBRETTO-531 trial also support the acceptable safety profile of selpercatinib. The overall incidence of any at least 1 TEAEs were comparable across both treatment groups (99.5% vs 99.0%). However, the rate of Grade ≥3 TEAEs, any SAEs, and AEs or SAEs leading to treatment discontinuation were lower in the selpercatinib arm compared to the control arm.

Additionally, in the LIBRETTO-001 and LIBRETTO-121 trials, presented as supplementary evidence in the PBAC submission, further support the requirement for *RET* mutation testing as part of patient eligibility. Both trials required evidence of an activating *RET* gene alteration, detected in the tumour tissue and/or blood. LIBRETTO-001 is a phase I/II, single arm, open-label study of selpercatinib in patients with RET-activated cancers including MTC. While LIBRETTO-001 is a phase I/II, single arm study of selpercatinib in paediatric and adolescent patients with advanced RET-activated cancers including MTC. The results of the *RET*-mutant MTC population were consistent with the pivotal evidence from LIBRETTO-531. Across these trials, selpercatinib demonstrated strong efficacy, with improvements in PFS and OS. These findings support the efficacy and safety of selpercatinib across different patient populations including treatment-naïve, those previously treated with MKI and paediatric and adolescent patients.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

There are currently no PBS-subsided therapies available in Australia for the treatment of MTC. As previously discussed, surgery is the primary treatment but is curative in 40% of cases (Haddad et al. 2022) (Maxwell et al. 2014). Patients with MTC are often diagnosed at a more advanced stage (Papachristos et al. 2023) and *RET* mutations are present in 70% of MTCs (Wirth et al. 2020). Patients harbouring more than 1 *RET*-mutant present with more aggressive disease (Gild et al. 2023). Patients with advanced, recurrent or metastatic disease, pharmacological interventions are used to manage symptoms such as ondansetron for diarrhoea and systemic therapies, including MKIs.

MTC accounts for up to 13% of TC deaths (Gild et al. 2023). Patients with advanced progressive disease face poor survival outcomes, with a five-year survival rate of 40% (Department of Health and Aged Care 2023) and in patients with metastatic disease, a 5 and 10-year relative survival rate is as low as 28% and 21%, respectively (Haddad et al. 2022), (Wells et al. 2015)).

As such, there is a significant unmet need for an intervention that slow disease progression and improve survival outcomes. Selpercatinib is a highly selective RET inhibitor that has demonstrated a clinically meaningful reduction in disease progression and survival benefits in patients with *RET*-mutant MTC. Compared to the comparator, 'no MBS-funded *RET* mutation testing' and treatment with standard of care, *RET* mutation testing is essential for identifying patients eligible for selpercatinib, providing them with access to targeted therapy that can significantly reduce disease progression and improve survival outcomes.

Identify how the proposed technology achieves the intended patient outcomes:

This co-dependent application request MBS listing for *RET* mutation testing to inform access to treatment with PBS-subsidised selpercatinib.

Selpercatinib is a highly selective, small molecule inhibitor of the *RET* receptor tyrosine kinase, designed to target oncogenic *RET* mutations and fusions. Tumorigenesis in MTC is driven mainly by point mutations in the RET gene. In enzyme assays, selpercatinib inhibits the kinase activity of *RET*, *RET*-V804L, *RET*-V804M, *RET*-A883F, *RET*-S904F, and *RET*-M918T. Given the specificity of selpercatinib for RET-driven oncogenesis, its treatment with selpercatinib will require patients to have a confirmed *RET* mutation.

For some people, compared with the comparator(s), does the test information result in:
(please highlight your response)

A change in clinical management?	**Yes**
A change in health outcome?	**Yes**
Other benefits?	**No**

Please provide a rationale, and information on other benefits if relevant:

Not applicable.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator? (please select your response)

☐ **More costly**
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

The comparator for *RET* mutation testing proposed in this application is 'no MBS-funded *RET* mutation testing'. In Australia, there is currently no requirement for patients with MTC to undergo somatic *RET* mutation testing, as there is currently no PBS-listed targeted therapy for MTC. The introduction of the proposed technology will be associated with an increased cost to the MBS, compared to the comparator, 'no MBS-funded *RET* mutation testing'.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1	Phase III RCT: A Multicenter, Randomised, Open-label, Phase 3 Trial Comparing Selpercatinib to Physicians Choice of Cabozantinib or Vandetanib in Patients With Progressive, Advanced, Kinase Inhibitor-Naïve, *RET*-Mutant Medullary Thyroid Cancer (LIBRETTO-531)	Phase 3 Trial of Selpercatinib in Advanced RET-Mutant Medullary Thyroid Cancer LIBRETTO-531 ClinicalTrials.gov Identifier: NCT04211337	The primary objective was to compare the efficacy and safety of selpercatinib to cabozantinib and vandetanib in patients with advanced *RET*-mutant MTC who have not received previous treatment with a kinase inhibitor. Patients were randomly assigned in a 2:1 ratio to receive selpercatinib (160 mg twice daily) (N=193) or the treating physician's choice of cabozantinib (140 mg once daily) or vandetanib (300 mg once daily) (N=98) (control group).	https://pubmed.ncbi.nlm.nih.gov/37870969/	October 21, 2023
2	Phase 1/2 single arm RCT: patients with advanced solid tumours, including *RET*-mutant MTC, *RET*-fusion-positive solid tumours (e.g., NSCLC, thyroid, pancreas, colorectal) and other tumours with RET activation	LIBRETTO-001 ClinicalTrials.gov Identifier: NCT03157128	The primary objective to assess the efficacy and safety of selpercatinib in patients with advanced solid tumours. All patients (N=837; n=324 *RET*-mutant MTC) received selpercatinib in two phases: Phase 1 (dose escalation) and Phase 2 (dose expansion). Patients receive dose escalation, in 28-day continuous cycles at doses of 20 mg once daily to 240 mg twice daily. In phase 2, patients receive the recommended dose of 160mg twice daily.	Original: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02517518/full Long term follow-up: https://ascopubs.org/doi/10.1200/JCO.23.02503	February 28, 2023 August 02, 2024
3	Phase 1/2 single arm RCT: in paediatric and adolescent patients with advanced solid or primary central nervous system (CNS) tumour with *RET*-mutation, including RET-mutant MTC, *RET* fusion-positive papillary thyroid cancer (PTC) and other solid tumours.	Oral selpercatinib in paediatric patients (pts) with advanced *RET*-altered solid or primary CNS tumours LIBRETTO-121 ClinicalTrials.gov Identifier: NCT03899792	The primary objective is to assess the efficacy and safety of selpercatinib in adolescence and paediatric patients with advanced *RET*-altered solid tumours. All patients (N=27; n=14 *RET*-mutant MTC) received selpercatinib in two phases: Phase 1 (dose escalation/expansion) and Phase 2 (dose expansion). Dose escalation continued until maximum tolerated dose, or the recommended phase 2 dose (maximum 160 mg twice daily) was reached, or until the Sponsor determined an appropriate dose based on pharmacokinetic (PK) exposure and toxicity.	Abstract of preliminary: https://ascopubs.org/doi/10.1200/JCO.2021.39.15_suppl.10009 Abstract of follow-up: https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.10022	May 28, 2021 May 29, 2024

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
4	Clinical Practice Guidelines	Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	The aim of clinical practice guidelines is to provide physicians with the best available evidence on particular issues and recommendations for the best standards of care. These guidelines recommend *RET* testing for somatic mutations for treatment of advanced MTCs with selective RET inhibitors.	10.1093/annonc/mdz400	Dec 1 2019
5	Clinical Practice Guidelines	ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer	This article provides updated treatment recommendations on thyroid cancer. These guidelines recommend DNA quantitative PCR or NGS analysis are the preferred approaches for testing RET mutations.	https://www.annalsofoncology.org/article/S0923-7534(22)00694-9/fulltext	April 22 2022
6	Clinical Practice Guidelines	Consensus Statement: Recommendations on Actionable Biomarker Testing for Thyroid Cancer Management	A review of international guidelines to evaluate the evidence supporting the use of actionable biomarkers in patients diagnosed with thyroid cancer. These guidelines recommend next-generation sequencing (NGS) or polymerase chain reaction (PCR) testing methods for RET variants.	10.1007/s12022-024-09836-x.	Nov 23 2024
7	Clinical Practice Guidelines	Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group	The ESMO Precision Medicine Working Group update the recommendations for the use of tumour next-generation sequencing (NGS) for patients with advanced cancers in routine practice.	10.1016/j.annonc.2024.04.005	May 27 2024
8	Narrative review	Management of Advanced Thyroid Cancer: Overview, Advances, and Opportunities	This review article states that next-generation sequencing (NGS) is the preferred approach for somatic testing in contrast to single-gene tests	https://ascopubs.org/doi/full/10.1200/EDBK_389708	May 15 2023

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

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

**** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).*

References

Australian Clinical Labs (2023). Somatic Mutation Testing in Solid Tumours. Supporting treatment decisions and improving outcomes for cancer patients.

Australian Institute of Health and Welfare (2024). Cancer Data in Australia. Book 1a – Cancer incidence (age-standardised rates and 5-year age groups).

Barbet J, Lc Campion, F Kraeber-Bodéré, J-F Chatal and GS Group (2005). Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. *The Journal of Clinical Endocrinology & Metabolism* 90(11): 6077-6084.

Belli C, F Penault-Llorca, M Ladanyi, N Normanno, JY Scoazec, L Lacroix, JS Reis-Filho, V Subbiah, JF Gainor, V Endris, M Repetto, A Drilon, A Scarpa, F André, JY Douillard and G Curigliano (2021). ESMO recommendations on the standard methods to detect RET fusions and mutations in daily practice and clinical research. *Annals of Oncology* 32(3): 337-350.

Block MA, CE Jackson, KA Greenawald, JB Yott and AH Tashjian, Jr (1980). Clinical Characteristics Distinguishing Hereditary From Sporadic Medullary Thyroid Carcinoma: Treatment Implications. *Archives of Surgery* 115(2): 142-148.

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

Cancer Council Victoria Thyroid cancer statistics and trends. https://www.cancervic.org.au/cancer-information/statistics/thyroid-cancer.html#:~:text=Thyroid%20cancer%20five%2Dyear%20relative%20survival,-Figure%207%20shows&text=It%20demonstrates%20that%20five%2Dyear,from%2074%25%20to%2095%25.

Danila R, R Livadariu and D Branisteanu (2019). Calcitonin revisited in 2020. *Acta Endocrinol (Buchar)* 15(4): 544-548.

Department of Health and Aged Care (2023). Australian Public Assessment Report for Gavreto.

Eng C PG (1999). *Multiple Endocrine Neoplasia Type 2*. GeneReviews. eattle (WA): University of Washington, Seattle;.

Filetti S, C Durante, D Hartl, S Leboulleux, L Locati, K Newbold, M Papotti, A Berruti and EG Committee (2022). ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer. *Annals of Oncology* 33(7): 674-684.

Filetti S, C Durante, D Hartl, S Leboulleux, LD Locati, K Newbold, MG Papotti and A Berruti (2019). Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 30(12): 1856-1883.

Gild ML, RJ Clifton-Bligh, LJ Wirth and BG Robinson (2023). Medullary Thyroid Cancer: Updates and Challenges. *Endocrine Reviews* 44(5): 934-946.

Haddad RI, L Bischoff, D Ball, V Bernet, E Blomain, NL Busaidy, M Campbell, P Dickson, QY Duh, H Ehya, WS Goldner, T Guo, M Haymart, S Holt, JP Hunt, A Iagaru, F Kandeel, DM Lamonica, S Mandel, S Markovina, B McIver, CD Raeburn, R Rezaee, JA Ridge, MY Roth, RP Scheri, JP Shah, JA Sipos, R Sippel, C Sturgeon, TN Wang, LJ Wirth, RJ Wong, M Yeh, CJ Cassara and S Darlow (2022). Thyroid Carcinoma, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 20(8): 925-951.

Hadoux J, F Pacini, RM Tuttle and M Schlumberger (2016). Management of advanced medullary thyroid cancer. *The lancet Diabetes & endocrinology* 4(1): 64-71.

Jayakody S, J Reagh, M Bullock, A Aniss, R Clifton-Bligh, D Learoyd, B Robinson, L Delbridge, S Sidhu, AJ Gill and M Sywak (2018). Medullary Thyroid Carcinoma: Survival Analysis and Evaluation of Mutation-Specific Immunohistochemistry in Detection of Sporadic Disease. *World Journal of Surgery* 42(5): 1.

Margraf RL, DK Crockett, PM Krautscheid, R Seamons, FR Calderon, CT Wittwer and R Mao (2009). Multiple endocrine neoplasia type 2 RET protooncogene database: repository of MEN2-associated RET sequence variation and reference for genotype/phenotype correlations. *Hum Mutat* 30(4): 548-556.

Master SR, PM Mathias and B Burns (2024). Medullary Thyroid Cancer. *StatPearls*. Treasure Island (FL), StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.

Maxwell JE, SK Sherman, TM O'Dorisio and JR Howe (2014). Medical management of metastatic medullary thyroid cancer. *Cancer* 120(21): 3287-3301.

Milićević S, D Bergant, T Žagar and B Perić (2021). Crude annual incidence rate of medullary thyroid cancer and RET mutation frequency. *Croat Med J* 62(2): 110-119.

Morgenstern D, Casanova M, van Tilburg C., Ziegler D., Martin Campbell M., Watt T., Pappo A., Willis Laetsch T., Liu D., Kang S., Wright J. and Kang H. (2024). Safety and efficacy of selpercatinib in pediatric patients with RET-altered solid tumors: Updated results from LIBRETTO-121. *Journal of Clinical Oncology* 42(16_suppl): 10022-10022.

Morgenstern DA, L Mascarenhas, M Campbell, DS Ziegler, K Nysom, M Casanova, AS Pappo, CM Albert, M Xia, SS Barker, J Wright and TW Laetsch (2021). Oral selpercatinib in pediatric patients (pts) with advanced RET-altered solid or primary CNS tumors: Preliminary results from the phase 1/2 LIBRETTO-121 trial. *Journal of Clinical Oncology* 39(15_suppl): 10009-10009.

Mosele MF, CB Westphalen, A Stenzinger, F Barlesi, A Bayle, I Bièche, J Bonastre, E Castro, R Dienstmann, A Krämer, AM Czarnecka, F Meric-Bernstam, S Michiels, R Miller, N Normanno, J Reis-Filho, J Remon, M Robson, E Rouleau, A Scarpa, C Serrano, J Mateo and F André (2024). Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group. *Annals of Oncology* 35(7): 588-606.

MSAC (Medical Services Advisory Committee). Application No. 1554 – Amendment to MBS item 73295 to allow testing for somatic BRCA mutation to allow patient access to firstline maintenance treatment with olaparib. Public Summary Document https://www.msac.gov.au/sites/default/files/documents/1554%2520-%2520Final%2520PSD_Jul2020_redacted.pdf

Mulligan LM (2018). 65 years of the double helix: Exploiting insights on the RET receptor for personalized cancer medicine. *Endocr Relat Cancer* 25(8): T189-t200.

Newton S, Schubert C, Morona J, Fitzgerald P and M T. (2013). Genetic testing for hereditary mutations in the RET gene. MSAC Application 1152, Assessment Report., Commonwealth of Australia, Canberra, ACT.

Papachristos AJ, LE Nicholls, R Mechera, AM Aniss, B Robinson, R Clifton-Bligh, AJ Gill, D Learoyd, SB Sidhu, A Glover, L Delbridge and M Sywak (2023). Management of Medullary Thyroid Cancer: Patterns of Recurrence and Outcomes of Reoperative Surgery. *The Oncologist* 28(12): 1064-1071.

Parimi V, K Tolba, N Danziger, Z Kuang, D Sun, DI Lin, MC Hiemenz, AB Schrock, JS Ross, GR Oxnard and RSP Huang (2023). Genomic landscape of 891 RET fusions detected across diverse solid tumor types. *NPJ Precis Oncol* 7(1): 10.

Park H, H Yang, J Heo, TH Kim, SW Kim and JH Chung (2021). Long-Term Outcomes and Causes of Death among Medullary Thyroid Carcinoma Patients with Distant Metastases. *Cancers (Basel)* 13(18).

RACGP (Royal Australian College of General Practitioners) (2018). Differentiating between benign and malignant thyroid nodules *An evidence-based approach in general practice*. *AJGP* 47(November 2018).

Somnay YR, D Schneider and H Mazeh (2013). Thyroid: Medullary Carcinoma. *Atlas Genet Cytogenet Oncol Haematol* 17(4): 291-296.

Sonic Genetics ThyroSeq. Thyroid molecular testing, thyroid nodule molecular panel, ThyroSeq v3 Genomic Classifier, ThyroSeq Cancer Risk Classifier (CRC). https://www.sonicgenetics.com.au/our-tests/all-our-tests/thyroseq/

Stinchcombe TE (2020). Current management of RET rearranged non-small cell lung cancer. *Ther Adv Med Oncol* 12: 1758835920928634.

Tao Z, X Deng, B Guo, Z Ding and Y Fan (2024). Subgroup analysis of steadily increased trends in medullary thyroid carcinoma incidence and mortality in the USA, 2000–2020: a population-based retrospective cohort study. *Endocrine-Related Cancer* 31(5): e230319.

Wells SA, Jr., SL Asa, H Dralle, R Elisei, DB Evans, RF Gagel, N Lee, A Machens, JF Moley, F Pacini, F Raue, K Frank-Raue, B Robinson, MS Rosenthal, M Santoro, M Schlumberger, M Shah and SG Waguespack (2015). Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 25(6): 567-610.

Wirth LJ, E Sherman, B Robinson, B Solomon, H Kang, J Lorch, F Worden, M Brose, J Patel and S Leboulleux (2020). Efficacy of selpercatinib in RET-altered thyroid cancers. *New England Journal of Medicine* 383(9): 825-835.

Yasir M, Mulji NJ and K A. (2023). *Multiple Endocrine Neoplasias Type 2. [Updated 2023 Aug 14]*. StatPearls [Internet]. Treasure Island (FL).