

PPMSAC Application 1152:
Final Decision Analytic Protocol (DAP) to
guide the assessment of genetic testing
for hereditary mutations in the RET gene
January 2012

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a decision analytic protocol that will be used to guide the assessment of genetic testing for hereditary mutations in the RET gene for (i) patients with symptoms of multiple endocrine neoplasia type II (MEN2) and (ii) unaffected relatives of a patient with a documented RET mutation to determine the risk of disease. The protocol was finalised after inviting relevant stakeholders to provide input and will provide the basis for the evidence-based assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted “PICO” approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

- P**atients – specification of the characteristics of the population or patients in whom the intervention is intended to be used;
- I**ntervention – specification of the proposed intervention;
- C**omparator – specification of the therapy most likely to be replaced by, or added to, the proposed intervention; and
- O**utcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention.

Purpose of application

In October 2010, an application was received from the Pathology Services Table Committee (PSTC) by the Department of Health and Ageing requesting a Medicare Benefits Schedule (MBS) listing of genetic testing for mutations in the RET gene for (i) patients with symptoms of multiple endocrine neoplasia type II (MEN2), and (ii) unaffected relatives of a patient with a documented RET mutation to determine the risk of disease. The proposal is for two new MBS items to cover the use of diagnostic and predictive testing for mutations in the RET gene.

Adelaide Health Technology Assessment (AHTA), School of Population Health and Clinical Practice, University of Adelaide, as part of its contract with the Department of Health and Ageing, has drafted this decision analytic protocol to guide the assessment of the safety, effectiveness and cost-effectiveness of the diagnostic and predictive testing for mutations in the RET gene, in order to inform MSAC's decision-making regarding public funding of the intervention.

Background

Current arrangements for public reimbursement

Currently, there is no MBS listing for any test that detects mutations on the RET gene. Patients are therefore encouraged to have their blood sample collected through a public hospital, so that facility may be charged for the genetic testing. When patients are referred by a private facility, they are billed directly as private health insurance generally provides a subsidy for testing only if the MBS also provides a rebate for the test (ALRC 2003; PaLMS 2011).

The Australian Genetic Testing Survey in 2006 reported five accredited laboratories offering genetic testing of the RET gene (Suthers 2008). Currently, the Royal College of Pathologists of Australasia genetic testing website lists only two pathology laboratories that offer RET testing (RCPA 2009). The Cancer Genetics Diagnostic Laboratory, PaLMS-RNSH in NSW, offers PCR and sequencing of specific exons 10, 11, 13, 14, 15 and 16, with a 3 month turnaround. Similarly, the Molecular Pathology Division of the Institute of Medical and Veterinary Science (IMVS), offers a gene screen for all exons and associated splice junctions by direct sequencing, with a turnaround of 3 months (RCPA 2009). The IMVS charges \$1,150 for an RET gene screen for a South Australian patient, \$480 for a known mutation test.

Regulatory status

In vitro diagnostic medical devices (IVDs) are, in general, pathology tests and related instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or in making decisions concerning clinical management (Therapeutic Goods Administration 2009).

The Therapeutic Goods Administration (TGA) regulatory framework for IVDs changed in July 2010, such that in-house laboratory tests now receive the same level of regulatory scrutiny as commercial kits. As testing of the RET gene is currently only provided as an in-house IVD, it would be classified as a Class 3 in-house IVD (see Box 1). There will be a transition period of 4 years to allow currently supplied goods to be included under the new regulation (IVD Australia 2010).

Laboratories that manufacture in-house Class 3 IVDs are required to notify the TGA of the types of IVDs manufactured in each laboratory for inclusion on a register. These laboratories must have National Association of Testing Authorities (NATA) accreditation, with demonstrated compliance with the suite of standards on the validation of in-house IVDs, as published by the National Pathology Accreditation Advisory Committee (NPAAC), for each test manufactured. Manufacturers of Class 2, Class 3 and Class 4 IVDs must hold certification from a regulatory body to show compliance with a suitable conformity assessment procedure (Therapeutic Goods Administration 2009). NATA accreditation includes (but is not limited to) the use of direct sequencing on both DNA strands in all exons in which pathogenic mutations have been identified; and confirmation of the mutation on an independent PCR reaction¹.

¹ MESP member and endocrinologist, R Clifton-Bligh, email received on 20th June 2011

Box 1 Classification of Class 3 *in vitro* diagnostic medical devices

Therapeutic Goods (Medical Devices) Regulations 2002 –Schedule 2A

1.3 Detection of transmissible agents or biological characteristics posing a moderate public health risk or high personal risk

1. **An IVD is classified as Class 3 IVD medical devices or a Class 3 in-house IVD if it is intended for any of the following uses:**
 - a. detecting the presence of, or exposure to, a sexually transmitted agent;
 - b. detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation;
 - c. detecting the presence of an infectious agent where there is a significant risk that an erroneous result would cause death or severe disability to the individual or foetus being tested;
 - d. pre-natal screening of women in order to determine their immune status towards transmissible agents;
 - e. determining infective disease status or immune status where there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient;
 - f. the selection of patients for selective therapy and management, or for disease staging, or in the diagnosis of cancer;
 - g. **human genetic testing;**
 - h. to monitor levels of medicines, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient;
 - i. the management of patients suffering from a life-threatening infectious disease;
 - j. screening for congenital disorders in the foetus.

Note: For paragraph (f) An IVD medical device would fall into Class 2 under clause 1.5 if:

- k. a therapy decisions would usually be made only after further investigation; or
 - l. the device is used for monitoring.
2. Despite subsection (1) an IVD is classified as a Class 3 IVD medical device or a Class 3 in-house IVD if it is used to test for transmissible agents included in the Australian National Notifiable Diseases Surveillance System (NNDSS) list as published from time to time by the Australian government.

Source: <http://www.tga.gov.au/ivd/ivd-classification.htm> [accessed January 2011]

Intervention

Description

The intervention that will be assessed is mutation testing of the RET proto-onco-gene (REarranged during Transfection), which encodes a transmembrane tyrosine kinase receptor, a protein involved in processes such as neural crest differentiation, cell migration and proliferation (Burzynski et al. 2005). Mutations in the RET gene are associated with multiple endocrine neoplasia type II (MEN2A and B, and familial medullary thyroid cancer, FMTC) and the seemingly unrelated syndrome of congenital absence of the enteric ganglia

(Hirschsprung disease²). RET mutations that are causative of MEN2 are called gain in function mutations as they cause ligand-independent RET activation and constitutive cell signalling (Margraf et al. 2009).

Multiple endocrine neoplasia type II (MEN2) is a group of disorders, associated with tumours of the endocrine system (generally the thyroid, parathyroid and adrenals) (see Table 1). It includes three distinct phenotypes, the features of which are outlined in Table 1. Nearly all patients develop a medullary thyroid carcinoma (MTC), and half of patients with MEN2A or MEN2B develop pheochromocytomas (Margraf et al. 2009). Fifteen to thirty per cent of patients with MEN2A may also develop hyperparathyroidism, whereas patients with MEN2B are not at risk of parathyroid disease, but will show other abnormalities such as ganglioneuromas, medullated corneal nerves, and marfanoid body habitus (Eng 1999). Familial medullary thyroid cancer (FMTC) comprises families who only have MTC. However, some RET mutations are associated with both MEN2A and FMTC, so a clinical history is required to distinguish between the two conditions (Margraf et al. 2009).

Table 1: MEN2 phenotype definitions

Gene	Phenotype	Codon	Clinical characteristics	Risk	Timing of thyroidectomy
RET	MEN2A (55% of all cases)	634, 611, 618, 620 630, 631	Family (or individual) with MTC, and at least one individual developing hyperparathyroidism, pheochromocytoma, or both.	2 (Higher aggressiveness)	Age 5
	MEN2B (5-10% of all cases)	918, 883	MTC (with or without pheochromocytoma) and characteristic clinical features: mucosal ganglioneuromas, gastrointestinal ganglioneuromas, eye abnormalities including corneal nerve thickening, and skeletal abnormalities including marfanoid body habitus.	3 (Highest aggressiveness)	1 st year of life
	FMTC (35-40% of all cases)	609, 791, 790, 804, 649, 891, 768	Four or more family members with MTC only. No clinical evidence of pheochromocytoma, hyperparathyroidism, or any MEN2B-specific clinical features in affected or at-risk family members.	1 (High aggressiveness)	When calcitonin rises / 5 to 10 years of age

Source: (International RET mutation consortium 2006; Raue & Frank-Raue 2009, 2010); MTC: medullary thyroid carcinoma; FMTC: familial MTC

As can be seen in Table 1, a clinical diagnosis of MEN2 would only be given once a minimum of two features are identified in a family, as a means of distinguishing this inheritable disease from sporadic MTC. Seventy-five per cent of cases of MTC are sporadic, the remainder are hereditary ie MEN2A, MEN2B or FMTC (Wells & Santoro 2009). In the absence of genetic testing, patients with an MTC, would be considered to potentially have MEN2 and would consequently, along with their first degree family members, be recommended to undergo annual surveillance for additional clinical features of MEN2³.

² The initial application proposed the use of genetic testing of the RET gene for patients suspected of having MEN2, or in those diagnosed with Hirschsprung disease. However, no clinical benefit of using RET testing in Hirschsprung disease could be determined through scoping searches of the literature or consultation with clinical experts (MESP members or through public consultation), so PASC decided that the assessment of RET testing should not include Hirschsprung disease as an indication.

³ MESP member and endocrinologist, R Clifton-Bligh, email received on 12th July 2011

Most cases of MEN2 are caused by mutations on the RET proto-oncogene (over 98% of MEN2 families have known RET mutations) (Margraf et al. 2009). Furthermore, over 90% of people who have a RET mutation will develop MEN2 (Toledo et al. 2006). MEN2 is autosomal dominant, which means that offspring with one affected parent have a 50% chance of having MEN2 themselves. Mutation testing of the RET gene is used as a means of diagnosing MEN2 in those with symptoms (distinguishing between those who have MEN2, and those who have the more common sporadic form of MTC), and as a way of predicting which family members will develop MEN2, based on whether they carry the pathogenic mutation of the RET gene. Given that specific genotype-phenotype relationships have become evident, the type of specific mutation found may also be used to determine the age at which a prophylactic thyroidectomy should be performed (Raue & Frank-Raue 2009).

Delivery of the intervention

Testing of the RET gene for mutations would occur once a person has clinical features of MEN2, or in first or second degree family members, at genetic risk, of someone who has been diagnosed with MEN2. Testing would occur subsequent to genetic counselling.

Each person being tested for RET genetic mutations would only need to be tested once (in duplicate as recommended by the Royal College of Pathologists of Australia) (RCPA 2007). However, those who are found to have a RET gene mutation corresponding to MEN2 would require lifelong surveillance.

Clinical need and burden of disease

It is estimated that the prevalence of MEN2 is 2.5 per 100,000 in the general population (Raue & Frank-Raue 2010). In a population of 22.6 million people (ABS 2011), it is therefore estimated that 565 Australians have this rare disorder.

The best estimate of the population suspected of having MEN2, are those who are diagnosed with MTC. In 2007, there were a total of 456 males and 1,331 females newly diagnosed with thyroid carcinomas (AIHW 2010). Approximately 5 to 10% of thyroid

carcinomas are medullary (Keatts & Itano 2006), so it is estimated that of the 1,787 thyroid carcinomas diagnosed, 89 to 179 of them would be medullary. In 2007, there were 150 diagnostic tests performed on the RET gene in Australia (Suthers 2008). This is within the range of what would be expected given the estimated rate of MTCs diagnosed. It is not expected that having item numbers on the MBS to allow reimbursement for genetic testing of the RET gene would significantly impact on the number of genetic tests being performed, given that it is already considered standard practice in Australia⁴, and conversely, not testing would be considered contrary to best practice guidelines (Brandi et al. 2001).

Only 25 - 30% of MTCs are hereditary (Raue & Frank-Raue 2010), so the use of the genetic test in the proband would rule out the need for further familial genetic testing in 65 – 70% of cases. It is therefore expected that only 22 to 54 Australian patients per year would have MTC caused by MEN2, resulting in their first degree relatives requiring genetic screening. Based on data from the Familial Cancer Unit in South Australia, there are approximately 11.5 unaffected first or second degree relatives per proband (Suthers et al. 2006). In a study assessing uptake of genetic screening, when family members were contacted both by the proband and directly by letter from the Familial Cancer Unit, 40% of relatives undertook genetic screening within 2 years (Suthers et al. 2006). Based on this, it is estimated that per proband, on average, 4.6 family members would agree to predictive genetic testing. In 2007, there were 49 presymptomatic tests performed on the RET gene in Australia (Suthers 2008), which is below the rate of what would be expected assuming that more than one relative per proband would be tested. It is therefore estimated that having an item number on the MBS for detection of a known mutation in the RET gene in first or second degree relatives at genetic risk would increase the number of the presymptomatic tests to approximately 101 – 248 per year.

Prerequisites

It is a requirement that all patients undergoing predictive testing should first receive genetic counselling and give informed consent (or assent in the case of children). It is also recommended that all patients undergoing diagnostic genetic testing should undergo genetic counselling. It is therefore suggested that the ordering of the genetic test for RET mutations should be limited to specialised genetic services that can provide accredited genetic counselling to patients and their family members.

⁴ MESP member and endocrinologist, R Clifton-Bligh, email received on 20th June 2011

Co-administered and associated interventions

In the absence of genetic testing, patients with clinical features suggestive of MEN2 were investigated for other features of MEN2, as well as for hereditary disorders that may cause the features detected (Genetics Subcommittee of PSTC 2010). Those with early onset adrenal pheochromocytoma or hyperparathyroidism (in combination with a family history of a medullary thyroid carcinoma or pheochromocytoma) would have been investigated for a medullary thyroid carcinoma by pentagastrin-stimulated serum calcitonin and neck ultrasound. However, these investigations have been replaced by RET testing for the purpose of diagnosing medullary thyroid carcinomas and MEN2. In the absence of a RET mutation, the person would be assumed to have a spontaneous medullary thyroid carcinoma, and investigations for other features of MEN2 would not occur.

In the current clinical setting with RET testing as standard practice, RET testing occurs as a triage to further investigations. If patients are found to have pathological RET mutations, they would be investigated for further MEN2 features, prior to receiving a total thyroidectomy. However, if patients are found to have no pathological RET mutations, they would either be assumed to have a sporadic medullary thyroid carcinoma or hyperparathyroidism, or would be investigated for other hereditary disorders which are associated with pheochromocytoma.

Table 2 summarises the investigations for MEN2 and other hereditary disorders that would be in use in the setting without RET testing, and with RET testing

Table 2: Co-administered and associated investigations

Clinical feature	Historical setting (RET testing not available) ^a	Current setting (RET testing available)
Medullary thyroid carcinoma	<ul style="list-style-type: none"> Investigate for pheochromocytoma: Plasma or urine catecholamines (and adrenal imaging – e.g. adrenal computed tomography (CT) scan or magnetic resonance imaging (MRI) and/or meta-iodobenzylguanidine scintigraphy (MIBG scan) – if these are elevated) Investigate for hyperparathyroidism: Serum calcium (and parathyroid hormone if calcium is elevated) to assess for hyperparathyroidism 	<ul style="list-style-type: none"> Investigate for MEN2 with RET genetic testing <p><i>Use RET testing to triage further investigations.</i></p> <p>Those with RET mutations:</p> <ul style="list-style-type: none"> Investigate for pheochromocytoma: Plasma or urine catecholamines (and adrenal imaging – e.g. adrenal computed tomography (CT) scan or magnetic resonance imaging (MRI) and/or meta-iodobenzylguanidine scintigraphy (MIBG scan) – if these are elevated) Investigate for hyperparathyroidism: Serum calcium (and parathyroid hormone if calcium is elevated) to assess for hyperparathyroidism. <p>Those without RET mutations:</p> <ul style="list-style-type: none"> No further investigations required
Adrenal pheochromocytoma (under 50 years)	<ul style="list-style-type: none"> Investigate for MTC: pentagastrin stimulated calcitonin and neck ultrasound Investigate for hyperparathyroidism: serum calcium (and parathyroid hormone if elevated) Investigate for other hereditary disorders: genetic testing of the VHL gene for von Hippel Lindau disease; genetic testing for 	<ul style="list-style-type: none"> Investigate for MEN2 with RET genetic testing <p><i>Use RET testing to triage further investigations</i></p> <p>Those with RET mutations:</p> <ul style="list-style-type: none"> Investigate for hyperparathyroidism: serum calcium (and parathyroid hormone if elevated) <p>Those without RET mutations:</p> <ul style="list-style-type: none"> Investigate for other hereditary disorders: genetic

Clinical feature	Historical setting (RET testing not available) ^a	Current setting (RET testing available)
	SDHB, SDHC and SDHD mutations; if serum calcium and parathyroid hormone are elevated, then assess for MEN1 (serum gastrin, insulin, glucagon, pancreatic polypeptide, vasoactive intestinal peptide, calcium, prolactin, adrenocorticotrophic hormone (ACTH), growth hormone, and somatomedin C (IGF-1))	testing of the VHL gene for von Hippel Lindau disease; genetic testing for SDHB, SDHC and SDHD mutations; if serum calcium and parathyroid hormone are elevated, then assess for MEN1 (serum gastrin, insulin, glucagon, pancreatic polypeptide, vasoactive intestinal peptide, calcium, prolactin, adrenocorticotrophic hormone (ACTH), growth hormone, and somatomedin C (IGF-1))
Hyperparathyroidism (plus a diagnosis of MTC or phaeochromocytoma in a close relative)	Hyperparathyroidism (plus a diagnosis of MTC or phaeochromocytoma in a close relative)	<ul style="list-style-type: none"> Investigate for MEN2 with RET genetic testing <p><i>Use RET testing to triage further investigations</i></p> <p>Those with RET mutations:</p> <ul style="list-style-type: none"> Investigate for phaeochromocytoma: plasma or urine catecholamines (and adrenal imaging e.g. adrenal CT scan or MRI and/or MIBG scan if elevated) <p>Those without RET mutations:</p> <ul style="list-style-type: none"> No further investigations required

^aThe comparative situation is termed "historical" to illustrate a scenario that existed without the use of RET testing. However, of interest is what tests *would be used currently in the absence of RET testing*. Therefore, genetic testing for other diseases have been included in the comparative setting, despite not being available prior to introduction of RET testing.

MTC = medullary thyroid carcinoma

Table 3 outlines the MBS items that correspond to these investigations. The use of these tests within those suspected of having MEN2 has likely reduced since the introduction of RET testing as a triage test for further investigations.

Table 3: MBS items for investigating clinical features of MEN2

Type of resource and identifier	Description	Fees
MBS item 66695	Quantitation in blood or urine of hormones and hormone binding proteins - ACTH , aldosterone, androstenedione, C-peptide, calcitonin , cortisol, DHEAS, 11-deoxycortisol, dihydrotestosterone, FSH, gastrin , glucagon , growth hormone , hydroxyprogesterone, insulin , LH, oestradiol, oestrone, progesterone, prolactin , parathyroid hormone , renin, sex hormone binding globulin, somatomedin C (IGF-1) , free or total testosterone, urine steroid fraction or fractions, vasoactive intestinal peptide , - 1 test	(see item below)
MBS item 66707	5 or more tests described in item 66695 (Item is subject to rule 6)	Fee: \$83.90 Benefit: 75% = \$62.95 85% = \$71.35
MBS item 12527	RENAL FUNCTION TEST (with imaging and at least 2 blood samples)	Fee: \$81.70 Benefit: 75% = \$61.30 85% = \$69.45

Patients with MEN2, thought to potentially have MEN2, or are at risk of developing MEN2, require lifelong surveillance. The tests offered are listed in Table 4. In current Australian practice, the assessment of risk of family members is already predominantly done by genetic testing of the RET gene (Fleming 2011). The listing of RET mutation testing on the MBS is therefore unlikely to have much impact on the use of current surveillance regimens. However, for the purposes of evaluating the cost-effectiveness of mutation testing of the

RET gene, the historic clinical setting whereby genetic testing is not available and there is a reliance on annual surveillance for patients with an MTC and all close family members, will be assessed.

Prior to the introduction of RET mutation testing, decisions regarding the requirement for lifelong screening in asymptomatic family members were made based on family history. All first degree relatives of a patient with an MTC would have been recommended to undergo lifelong surveillance. If a first degree family member developed clinical features, then their first degree relatives (ie second degree relatives of the proband) would then undergo annual surveillance using the principles of cascade testing.

With the introduction of RET genetic testing, the frequency of initial biochemical screening and imaging and surveillance within family members is likely to have changed for a variety of reasons:

- a) A better distinction between sporadic and hereditary cases of MTC (i.e. a more accurate diagnosis of the index case) meaning that fewer index cases require lifelong surveillance for MEN2.
- b) Greater certainty regarding an individual's risk of developing MEN2, due to knowledge of the presence/absence of the RET mutation and understanding of the biomarker, facilitating better compliance with surveillance recommendations in those with a mutation.
- c) A better distinction between sporadic and hereditary cases of MTC in the index case meaning that fewer families require screening and surveillance.
- d) The ability to distinguish between first degree relatives who are and who are not at risk of developing MEN2 on the basis of RET mutations. Only those first degree family members who have a RET mutation would undergo surveillance for clinical features of MEN2. Those family members who are free from pathogenic RET mutations would avoid the need for lifelong surveillance. Thus the genetic test would replace (and has replaced to date) routine lifelong screening of family members without RET mutations (resulting in fewer people undergoing annual surveillance).
- e) Earlier screening in second degree relatives (and possibly broader) on the basis of genetic mutations in first degree relatives, rather than waiting for the emergence of clinical features. Once a first degree family member is found to have a RET mutation, their first degree relatives may be genetically tested (using cascade testing). Although similar in principle to clinical practice prior

to the introduction of genetic testing, identification of a RET mutation may occur years before the presentation of clinical features. It is therefore likely that a proportion of additional second degree (and more distant) relatives are currently undergoing annual surveillance much earlier than they would have been prior to the introduction of RET genetic testing.

Points a, c and d above are likely to have greatly reduced the number of index cases and family members recommended to undergo annual surveillance, while points b and e are likely to have resulted in a slight increase in surveillance utilisation in specific populations.

Table 4: Lifelong surveillance regimen for MEN2

Age	Surveillance
From age 1-5 years	<p><i>Annual</i></p> <p>General clinical examination</p> <p>Examination of thyroid (or thyroid bed if post-thyroidectomy) by neck ultrasound (and biopsy of any suspicious masses)</p> <p>Biochemical screen for phaeochromocytoma</p> <p>Screen for hyperparathyroidism (total and ionised serum calcium)</p> <p>± calcitonin and carcinoembryonic antigen after surgery for MTC</p>

Source: (Genetics Subcommittee of PSTC 2010); MTC = medullary thyroid carcinoma

Table 5: MBS items for lifelong surveillance regimen for MEN2

Type of resource	Description	Fees
MBS item number 23	<p>LEVEL B CONSULTATION AT CONSULTATION ROOMS</p> <p>Professional attendance at consulting rooms by a general practitioner (not being a service to which any other item in this table applies) lasting less than 20 minutes, including any of the following that are clinically relevant:</p> <ul style="list-style-type: none"> a) Taking a patient history b) Performing a clinical examination c) Arranging any necessary investigation d) Implementing a management plan e) Providing appropriate preventive health care <p>In relation to 1 or more health-related issues, with appropriate documentation.</p>	<p>Fee: \$34.90</p> <p>Benefit: 100% = \$34.90</p>
MBS item 55032	<p>NECK, 1 or more structures of, ultrasound scan of, where:</p> <ul style="list-style-type: none"> (a) the patient is referred by a medical practitioner for ultrasonic examination not being a service associated with a service to which an item in Subgroups 2 or 3 of this Group applies; and (b) the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member (R) 	<p>Fee: \$109.10</p> <p>Benefit: 75% = \$81.85 85% = \$92.75</p>
MBS item 66500	<p>Quantitation in serum, plasma, urine or other body fluid (except amniotic fluid), by any method except reagent tablet or reagent strip (with or without reflectance meter) of: acid phosphatase, alanine aminotransferase, albumin, alkaline phosphatase, ammonia, amylase, aspartate aminotransferase, bicarbonate, bilirubin (total), bilirubin (any fractions), C-reactive protein, calcium (total or corrected for albumin), chloride, creatine kinase, creatinine, gamma glutamyl transferase, globulin, glucose, lactate dehydrogenase, lipase, magnesium, phosphate, potassium, sodium, total protein, total cholesterol, triglycerides, urate or urea - 1 test</p>	<p>Fee: \$9.75</p> <p>Benefit: 75% = \$7.35 85% = \$8.30</p>

Type of resource	Description	Fees
MBS item 66584	Quantitation of ionised calcium (except if performed as part of item 66566) - 1 test	Fee: \$9.75 Benefit: 75% = \$7.35, 85% = \$8.30
MBS item 66695	Quantitation in blood or urine of hormones and hormone binding proteins - ACTH, aldosterone, androstenedione, C-peptide, calcitonin , cortisol, DHEAS, 11-deoxycortisol, dihydrotestosterone, FSH, gastrin, glucagon, growth hormone, hydroxyprogesterone, insulin, LH, oestradiol, oestrone, progesterone, prolactin, parathyroid hormone , renin, sex hormone binding globulin, somatomedin C(IGF-1), free or total testosterone, urine steroid fraction or fractions, vasoactive intestinal peptide, - 1 test	Fee: \$30.70 Benefit: 75% = \$23.05, 85% = \$26.10
MBS item 66650	Alpha-fetoprotein, CA-15.3 antigen (CA15.3), CA-125 antigen (CA125), CA-19.9 antigen (CA19.9), cancer associated serum antigen (CASA), carcinoembryonic antigen (CEA), human chorionic gonadotrophin (HCG), neuron specific enolase (NSE), thyroglobulin in serum or other body fluid, in the monitoring of malignancy or in the detection or monitoring of hepatic tumours, gestational trophoblastic disease or germ cell tumour - quantitation - 1 test (Item is subject to rule 6)	Fee: \$24.50 Benefit: 75% = \$18.40 85% = \$20.85
MBS item 66779	Adrenaline, noradrenaline, dopamine, histamine, hydroxyindoleacetic acid (5HIAA), hydroxymethoxymandelic acid (HMMA), homovanillic acid (HVA), metanephrines , methoxyhydroxyphenylethylene glycol (MHPG), phenylacetic acid (PAA) or serotonin quantitation - 1 or more tests	Fee: \$40.20 Benefit: 75% = \$30.15 80% = \$34.20

NB: A maximum of three pathology costs are claimable under MBS arrangements due to coning.

Treatment for MEN2 will depend on the presentation. Standard chemotherapy regimens and radiation therapy have been found to be ineffective methods of treatment for MTC, so treatment of MTC largely depends on the adequacy of surgical removal of the thyroid (Brandi et al. 2001). MTCs are treated with total thyroidectomy and central lymph node dissection at a minimum (Brandi et al. 2001 Lundgren et al. 2007). Following thyroidectomy, patients are required to take thyroxine over their remaining lifetime. The primary treatment for pheochromocytoma is resection, most often performed laparoscopically (Alderazi et al. 2005). The current treatment for hyperparathyroidism is parathyroidectomy, with the timing based on the degree of hypercalcaemia and/or associated clinical features (cognitive symptoms, renal stones, osteoporosis)⁵. Bisphosphonate treatment may be used in milder degrees of hypercalcaemia when patients show osteoporosis on bone densitometry testing⁵. Treatment costs associated with the different clinical features of MEN2 are outlined in Table 6, Table 7 and Table 8.

It is not expected that treatment for those diagnosed with MEN2 who have an MTC at presentation will change with greater use of genetic testing. However, those who have an MTC who are found not to have a RET mutation (and therefore do not have MEN2) can avoid the need for lifelong surveillance of additional features of MEN2.

It is expected that those who are diagnosed with MEN2 prior to the development of a MTC (ie through initial presentation with early onset pheochromocytoma) would receive a prophylactic thyroidectomy upon confirmation of having a RET mutation. As the penetrance of RET mutations in MEN2 patients is close to 100% (ie nearly all who have a mutation on the RET gene will eventually develop a MTC), the ideal treatment for MEN2 is a total thyroidectomy prior to clinical evidence of a MTC, to reduce disease-related morbidity and death (Margraf et al. 2009). MEN2A was the first disease in history where total removal of an organ was performed prior to development of a carcinoma, solely on the basis of genetic testing (Lundgren et al. 2007). It is expected that performing prophylactic thyroidectomies has resulted in fewer patients being diagnosed with metastatic MTC. The assumption is made that this has resulted in fewer patients needing to undergo more extensive surgery such as a lymphadenectomy and has replaced the need for palliation in some patients.

Treatment of family members who are found to have a RET mutation also involves a prophylactic total thyroidectomy (Brandi et al. 2001). MTCs produce calcitonin in the parafollicular or C cells of the thyroid gland. A case series from the United States reportedly performed prophylactic total thyroidectomies on 50 asymptomatic patients with RET mutations, aged 3 to 19 years. However, on gross or histological examination of the removed thyroid, only four patients had no evidence of disease at the time of surgery⁶.

⁵ MESP member and endocrinologist, R Clifton-Bligh, email received on 20th June 2011

⁶ Note: Only 10 of the 50 patients underwent the total thyroidectomy early enough to be consistent with the current guidelines for the timing of prophylactic total thyroidectomies (Brandi et al. 2001).

Thirteen patients had C-cell hyperplasia, and the remaining 33 patients had either microscopic or macroscopic evidence of MTC in the removed thyroid. After 5 years follow-up, six of these patients showed signs of persistent or recurrent MTC. None of the 17 patients (median age 7 years) who were free of MTC prior to total thyroidectomy showed signs of disease after 5 years (Skinner et al. 2005). Although this study did not have a comparative arm, expert opinion suggests this study provides evidence that prophylactic surgery can prevent the development of MTC.⁷

Historically, pentagastrin-stimulated serum calcitonin measurements were used to identify those who had developed a MTC. In the absence of genetic testing, removal of the thyroid would only occur once calcitonin levels had risen, indicating the presence of a carcinoma. The present strategy of performing prophylactic thyroidectomy would therefore have resulted in an increased need for thyroxine in the years between when a prophylactic total thyroidectomy is performed, and when that individual would have developed a MTC had prophylactic surgery not been performed.

⁷ MESP member and endocrinologist, R Clifton-Bligh, email received on 22nd June 2011

Table 6: Possible treatment costs associated with treatment of, or prophylaxis for, an MTC

Type of resource and identifier	Description	Fees
MBS item 30296	THYROIDECTOMY, total (Anaes.) (Assist.)	Fee: \$984.90 Benefit: 75% = \$738.70
MBS Item 17615	Pre-anaesthesia consultation -on a patient undergoing advanced surgery or -who has complex medical problems, involving a selective history and an extensive examination of multiple systems and the formulation of a written patient management plan documented in the patient notes <i>AND of more than 15 minutes but not more than 30 minutes duration, not being a service associated with a service to which items 2801 - 3000 applies</i>	Fee: \$82.30 Benefit: 75% = \$61.75 85% = \$70.00
MBS item 20320	INITIATION OF MANAGEMENT OF ANAESTHESIA for procedures on oesophagus, thyroid, larynx, trachea, lymphatic system, muscles, nerves or other deep tissues of the neck, not being a service to which another item in this Subgroup applies (6 basic units)	Fee: \$114.30 Benefit: 75% = \$85.75
MBS item 51303	Assistance at any operation identified by the word "Assist." for which the fee exceeds \$537.15 or at a series of operations identified by the word "Assist." for which the aggregate fee exceeds \$537.15 One fifth of the established fee for the operation or combination of operations	1/5 of \$984.90 = \$196.98
MBS item 25015 <i>For those with MEN2B or mutations in codons 883, 918, 922^a</i>	ANAESTHESIA, PERFUSION OR ASSISTANCE AT ANAESTHESIA - where the patient is less than 12 months of age or 70 years or greater (1 basic unit)	Fee: \$19.05 Benefit: 75% = \$14.30
NHCDC cost weights for K06Z	Accommodation costs for Thyroid procedure , average length of stay 2.04 days	Average total cost: \$4,039
PBS item 2173J	Thyroxine sodium, 200 µg	DPMQ: \$27.01
PBS item 2175L	Thyroxine sodium, 100 µg	DPMQ: \$23.98
PBS item 9287T	Thyroxine sodium, 75 µg	DPMQ: \$24.02
PBS item 2174K	Thyroxine sodium, 50 µg	DPMQ: \$23.37

MBS=Medicare Benefits Schedule; NHCDC=National Hospital Cost Data Collection private hospital costs, AR-DRG version 5.1 round 13 (2008-2009); PBS=Pharmaceutical Benefits Schedule;

^a Patients with MEN2 or mutations in codons 883, 918, 922 are recommended to undergo total thyroidectomies in the first month of life; DPMQ = Dispensed price for maximum quantity

Table 7: Possible treatment costs associated with hyperparathyroidism

Type of resource and identifier	Description	Fees
MBS item 30315	Parathyroid operation for hyperparathyroidism (Anaes.) (Assist.)	Fee: \$1,096.70 Benefit: 75% = \$822.55
MBS Item 17615	Pre-anaesthesia consultation -on a patient undergoing advanced surgery or -who has complex medical problems, involving a selective history and an extensive examination of multiple systems and the formulation of a written patient management plan documented in the patient notes <i>AND of more than 15 minutes but not more than 30 minutes duration, not being a service associated with a service to which items 2801 - 3000 applies</i>	Fee: \$82.30 Benefit: 75% = \$61.75 85% = \$70.00
MBS item 20320	INITIATION OF MANAGEMENT OF ANAESTHESIA for procedures on oesophagus, thyroid, larynx, trachea, lymphatic system, muscles, nerves or other deep tissues of the neck, not being a service to which another item in this Subgroup applies (6 basic units)	Fee: \$114.30 Benefit: 75% = \$85.75
MBS item 51303	Assistance at any operation identified by the word "Assist." for which the fee exceeds \$537.15 or at a series of operations identified by the word "Assist." for which the aggregate fee exceeds \$537.15 One fifth of the established fee for the operation or combination of operations	1/5 of \$1,096.70 = \$219.34
NHCDC cost weights for K05Z	Accommodation costs for Parathyroid procedure , average length of stay 1.96 days	Average total cost: \$3,481

MBS=Medicare Benefits Schedule; NHCDC=National Hospital Cost Data Collection private hospital costs, AR-DRG version 5.1 round 13 (2008-2009); PBS=Pharmaceutical Benefits Schedule; DPMQ = Dispensed price for maximum quantity

Table 8: Possible treatment costs associated with adrenal phaeochromocytoma

Type of resource and identifier	Description	Fees
MBS item 30324	ADRENAL GLAND TUMOUR , excision of (Anaes.) (Assist.)	Fee: \$1,313.20 Benefit: 75% = \$984.90
MBS Item 17615	Pre-anaesthesia consultation -on a patient undergoing advanced surgery or -who has complex medical problems, involving a selective history and an extensive examination of multiple systems and the formulation of a written patient management plan documented in the patient notes <i>AND of more than 15 minutes but not more than 30 minutes duration, not being a service associated with a service to which items 2801 - 3000 applies</i>	Fee: \$82.30 Benefit: 75% = \$61.75 85% = \$70.00
MBS item 20320	INITIATION OF MANAGEMENT OF ANAESTHESIA for procedures on oesophagus, thyroid, larynx, trachea, lymphatic system, muscles, nerves or other deep tissues of the neck, not being a service to which another item in this Subgroup applies (6 basic units)	Fee: \$114.30 Benefit: 75% = \$85.75
MBS item 51303	Assistance at any operation identified by the word "Assist." for which the fee exceeds \$537.15 or at a series of operations identified by the word "Assist." for which the aggregate fee exceeds \$537.15 One fifth of the established fee for the operation or combination of operations	1/5 of \$1,313.20 = \$262.64
NHCDC cost weights for K03Z	Accommodation costs for Adrenal procedure , average length of stay 5.05 days	Average total cost: \$9,454
PBS item 1499X (for after bilateral adrenalectomy)	Hydrocortisone , 4 mg	DPMQ: \$10.92
PBS item 1500Y (for after bilateral adrenalectomy)	Hydrocortisone , 20 mg	DPMQ: \$14.33
PBS item 1433K (for after bilateral adrenalectomy)	Fludrocortisone acetate , 100 µg	DPMQ: \$46.50

MBS=Medicare Benefits Schedule; NHCDC=National Hospital Cost Data Collection private hospital costs, AR-DRG version 5.1 round 13 (2008-2009); PBS=Pharmaceutical Benefits Schedule; DPMQ = Dispensed price for maximum quantity

Listing proposed and options for MSAC consideration

Proposed MBS listing

Based on the populations expected to benefit from mutation testing in the RET gene (those with clinical features of MEN2 or their family members), the proposed MBS items are suggested as:

1. A diagnostic test to detect germline mutations in the RET gene
2. A predictive test to detect mutations in the RET gene of family members of a proband

The proposed MBS items are summarised in Table 9. The proposed fees are based on the current fees charged to patients by the Institute of Medical and Veterinary Science in Adelaide in South Australia.

Table 9: Proposed MBS item descriptor for RET gene testing

Category 6 – Pathology services
<p>MBS [item number]</p> <p>Detection of germline mutations in the RET gene in patients with:</p> <ul style="list-style-type: none"> a) Medullary thyroid carcinoma b) Adrenal phaeochromocytoma under the age of 50 years c) Hyperparathyroidism plus a diagnosis of thyroid cancer or phaeochromocytoma in a close relative^a <p>1 or more tests</p> <p>Fee: \$1150</p> <p>Prior to ordering these test the ordering practitioner should ensure the patient (or their parent/guardian in the case of children) has given informed consent. Testing can only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the treating practitioner, a genetic counselling service or by a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.</p>
<p>MBS [item number]</p> <p>Detection of a known mutation in the RET gene in:</p> <ul style="list-style-type: none"> a) Asymptomatic first or second degree relatives, at a risk of a patient with a documented pathogenic RET mutation <p>1 or more tests</p> <p>Fee: \$480</p> <p>Prior to ordering these tests the ordering practitioner should ensure the patient (or their parent/guardian in the case of children) has given informed consent. Testing can only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the treating practitioner, a genetic counselling service or by a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.</p>

^aIt has been suggested by PASC that the definition of a “close relative” be limited to first or second degree family members.

In a diagnostic setting, the use of RET gene screening would constitute Level 1 testing as defined by the National Pathology Accreditation Advisory Council, and would therefore not require formal pre-test genetic counselling or written consent (NPAAC 2007). However, expert opinion suggests that all patients undergoing RET testing should participate in genetic counselling⁸. Predictive testing in unaffected relatives would constitute Level 2 testing, and therefore needs to be restricted to services which can provide accredited genetic counselling (NPAAC 2007).

⁸ MESP member and endocrinologist, R Clifton-Bligh, email received on 22nd June 2011

Once first degree relatives of a proband are diagnosed as having a pathogenic RET mutation, then this allows for cascade testing of their first degree relatives (ie second degree relatives of the proband). However, rather than restrict the proposed MBS item to first degree relatives, the item has been worded to allow for situations where first degree relatives are unavailable (eg have died), so second degree relatives may be tested.

Clinical place for proposed intervention

For the diagnosis of MEN2, RET testing is used to triage (or replace in the case of pentagastrin stimulated calcitonin) biochemical screening and imaging in those patients with clinical features suggestive of MEN2.

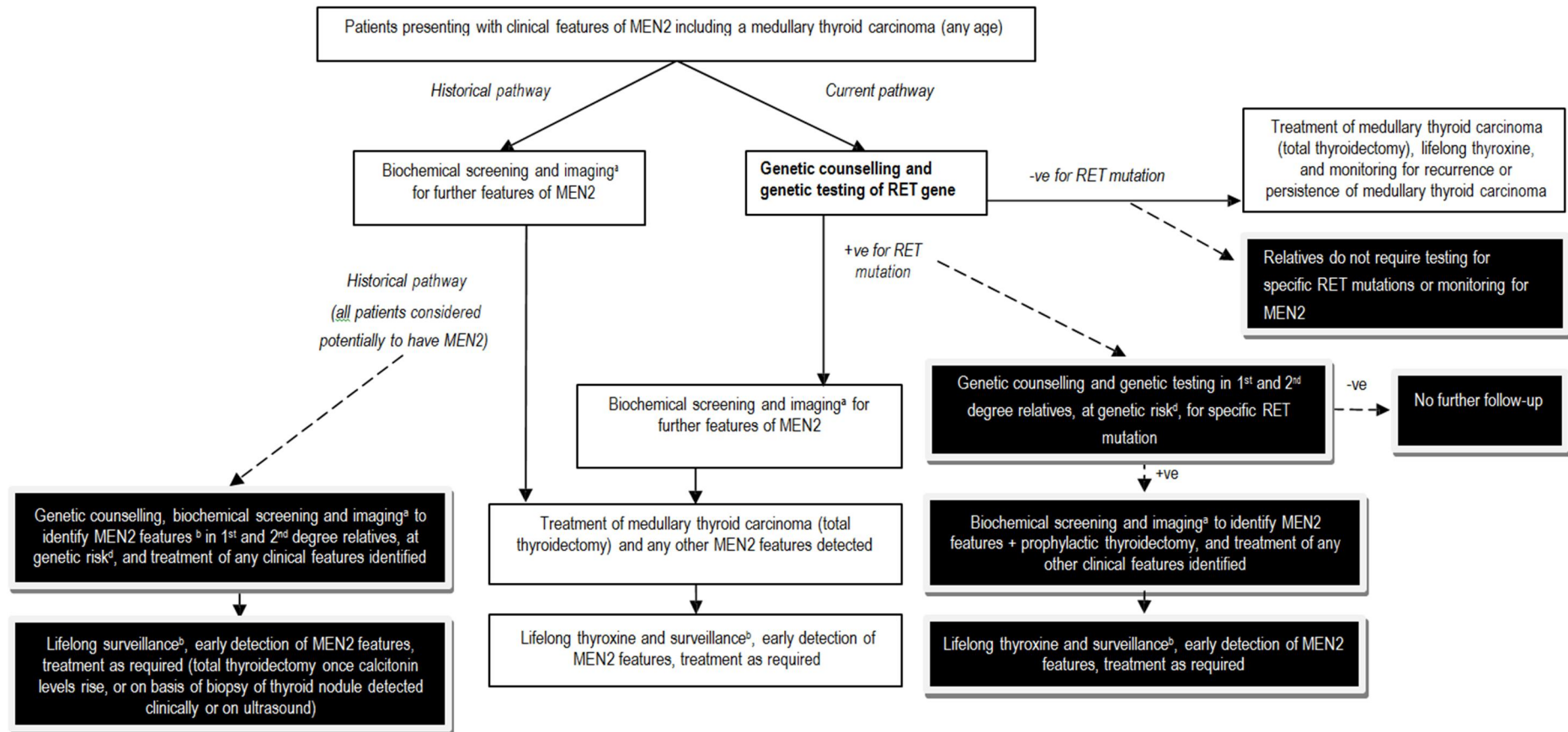
Two clinical management algorithms have been provided for RET genetic testing in index cases with a MTC (Figure 1), without a MTC (Figure 2) and for their close family members. The clinical scenario in Figure 1 is more common than Figure 2, as a MTC is the first symptom in most MEN2 families due to its earlier and higher penetrance (Brandi et al. 2001). The left side of each management algorithm outlines the approach to the diagnosis and prediction of MEN2 in a setting without genetic testing (as the historical comparator), while the right side shows current clinical practice, which includes the use of genetic testing. The white text boxes and solid arrows relate to the diagnosis and treatment of people with clinical features suggestive of MEN2, while the black boxes and dashed arrows correspond to the management of their close family members.

Special emphasis should be given to material differences between the algorithms outlining the "historical" and "current" clinical management strategies for MEN2 in the type of healthcare resources and the frequencies of their use. Figure 1 shows that in the absence of genetic testing (the historical setting), all patients with an MTC at presentation or detected through initial investigations would be monitored for further clinical features of MEN2, despite there being a 75% chance of the MTC being sporadic. It is also assumed that, in the absence of genetic testing, their first degree family members would receive annual surveillance for MEN2 features. Family members would undergo a total thyroidectomy once early signs of MTC are detected by elevated calcitonin levels. In comparison, the main differences between this historical setting and the current setting (with genetic testing available) are: a) the targeted use of life-long surveillance in patients and family members who have a definitive diagnosis of MEN2 or RET mutation, or the avoidance of this requirement in those patients and family members without a RET mutation; and b) the use of prophylactic total thyroidectomy in family members with a confirmed RET mutation.

In Figure 2, it is shown that in the absence of genetic testing, all those who present with an early onset adrenal pheochromocytoma or hyperparathyroidism (plus a diagnosis of

medullary thyroid carcinoma or pheochromocytoma in a close relative), who are found not to have an MTC, would be assumed not to have MEN2. Therefore, the index case and their family members would not be screened or undergo surveillance. However, in the current setting where genetic testing is available, patients with this clinical profile who have a RET mutation would be diagnosed with MEN2, and therefore undergo prophylactic total thyroidectomy and lifelong surveillance. Their family members would also undergo cascade screening and those who also carry the RET mutation would undergo prophylactic thyroidectomy and lifelong surveillance.

Figure 1 Management algorithm for use of a RET gene test to diagnose and predict MEN2 (medullary thyroid carcinoma identified in index case prior to genetic testing)



Notes:

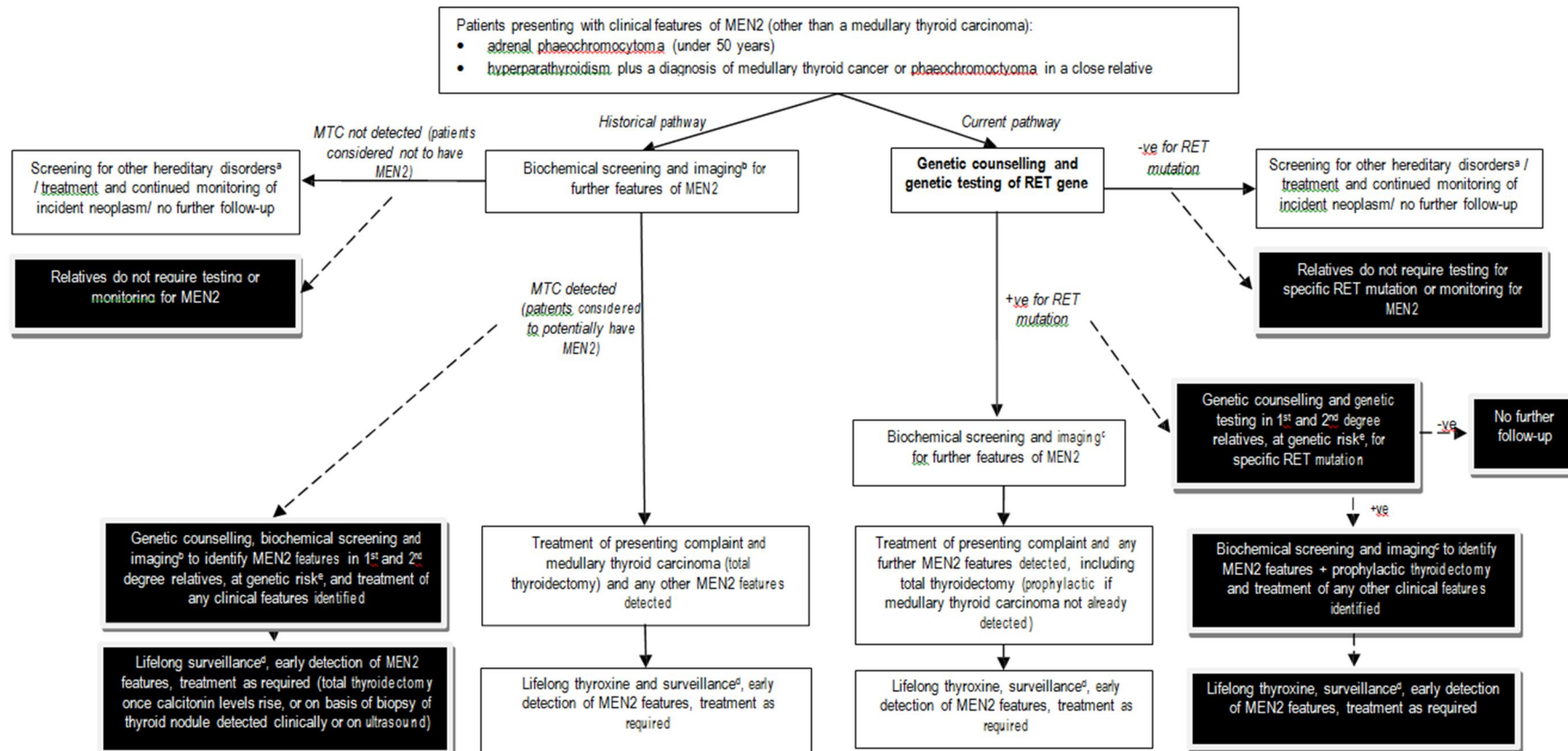
^a Biochemical screening and imaging for further features of MEN2: plasma or urine catecholamine (and adrenal imaging e.g. adrenal CT scan or MRI and/or MIBG scan if these are elevated) to assess for phaeochromocytoma, serum calcium (and parathyroid hormone if elevated) to assess for hyperparathyroidism

^b Surveillance in those who have had a total thyroidectomy: Annual general clinical examination, examination of thyroid (or thyroid bed if post-thyroidectomy), biochemical screen for phaeochromocytoma, screen for hyperparathyroidism (total and ionised serum Ca²⁺) and calcitonin and carcinoembryonic antigen to detect persistence or recurrence of MTC

^c Historical surveillance in those at risk of MEN2 who have not had a total thyroidectomy: Annual general clinical examination, examination of thyroid (or thyroid bed if post-thyroidectomy), biochemical screen for phaeochromocytoma, screen for hyperparathyroidism (total and ionised serum Ca²⁺); pentagastrin-stimulated serum calcitonin and neck ultrasound to assess for a medullary thyroid carcinoma

^d 2nd degree relatives would only be considered to be at genetic risk if 1st degree relatives have a RET mutation, clinical features of MEN2, or if information regarding 1st degree relatives is unavailable

Figure 2 Management algorithm for use of a RET gene test to diagnose and predict MEN2 (no medullary thyroid carcinoma in index case prior to genetic testing)



Notes: ^aScreening for other hereditary disorders: genetic testing of the VHL gene for von Hippel Lindau disease, genetic testing for SDHB, SDHC and SDHD mutations; if serum calcium and parathyroid hormone are elevated then additional testing for features of MEN1 (serum gastrin, serum insulin, serum glucagon, serum pancreatic polypeptide, serum vasoactive intestinal peptide, serum prolactin, growth hormone, and adrenocorticotrophic hormone (ACTH))

^bHistorical biochemical screening and imaging for further features of MEN2: pentagastrin-stimulated serum calcitonin and neck ultrasound to assess for a medullary thyroid carcinoma; plasma or urine catecholamine (and adrenal imaging e.g. adrenal CT scan or MRI and/or MIBG scan if these are elevated) to assess for pheochromocytoma if not the presenting clinical feature, or serum calcium (and parathyroid hormone if elevated) to assess for hyperparathyroidism if not the presenting clinical feature

^cCurrent biochemical screening and imaging for further features of MEN2: plasma or urine catecholamine (and adrenal imaging e.g. adrenal CT scan or MRI and/or MIBG scan if these are elevated) to assess for pheochromocytoma if not the presenting clinical features, or serum calcium (and parathyroid hormone if elevated) to assess for hyperparathyroidism if not the presenting feature

^dHistorical surveillance: Annual general clinical examination, examination of thyroid (or thyroid bed if post-thyroidectomy), biochemical screen for pheochromocytoma, screen for hyperparathyroidism (total and ionised serum Ca²⁺); plus pentagastrin-stimulated serum calcitonin and neck ultrasound to assess for a medullary thyroid carcinoma or calcitonin and carcinoembryonic antigen after surgery for medullary thyroid carcinoma

Current surveillance: Annual general clinical examination, examination of thyroid (or thyroid bed if post-thyroidectomy), biochemical screen for pheochromocytoma, screen for hyperparathyroidism (total and ionised serum Ca²⁺) ± calcitonin and carcinoembryonic antigen after surgery for MTC

Comparator

Comparators are usually selected by determining the technology (including testing strategy) most likely to be replaced, or added to, by the technology submitted for a new MBS item number. However, in the situation of genetic testing within patients suspected of having MEN2 or their close family members, genetic testing is already standard practice. For the financial implications, the comparator is considered to be genetic testing paid for by either the patient or by the States and Territories.

In order to assess the safety, effectiveness and cost-effectiveness of testing for mutations in the RET gene as a means of triaging biochemical screening and imaging in patients suspected of having MEN2 (and a replacement for pentagastrin stimulated calcitonin measurements), or in first or second degree family members of those diagnosed with MEN2, the comparator is biochemical screening and imaging alone for the diagnosis of MEN2. The investigations patients receive depend on their presenting feature. For index patients, the comparator is outlined in the second column of Table 2 (page 12). Table 3 on page 13 outlines the MBS items that correspond to these investigations.

There is no specific alternative test to diagnose individual susceptibility to MEN2. Without genetic testing, the diagnosis of MEN2 would rely on tumour type and location, which is not possible to assess prospectively. However, close family members of someone with MEN2 would have lifelong surveillance to ensure early detection of disease. The surveillance regimen for those with MEN2 or at risk of MEN2 is outlined in Table 10. The MBS items corresponding to these surveillance measures are outlined in Table 5, page 15. The comparison for first and second degree relatives is therefore between genetic counselling and genetic testing plus a prophylactic thyroidectomy, lifelong thyroxine and lifelong surveillance in those who carry a RET mutation, versus genetic counselling and lifelong surveillance (with a total thyroidectomy and lifelong thyroxine after a rise in calcitonin levels) for all first degree relatives.

Table 10: Lifelong surveillance regimen for MEN2

Age	Surveillance
From age 1-5 years	<i>Annual</i> General clinical examination Examination of thyroid (or thyroid bed if post-thyroidectomy) by neck ultrasound (and biopsy of any suspicious masses) Biochemical screen for pheochromocytoma Screen for hyperparathyroidism (total and ionised serum calcium) ± calcitonin and carcinoembryonic antigen after surgery for MTC

Source: (Genetics Subcommittee of PSTC 2010)

The effectiveness of a diagnostic test depends on whether it improves patient health outcomes. This can be assessed by studies that directly investigate the impact of the test on health outcomes or alternatively, in some situations, by linking evidence from studies.

Should there be no direct evidence (eg clinical trials) available assessing the impact of genetic testing for the RET gene on patient outcomes, a linked evidence approach will be undertaken using the methods outlined in the MSAC (2005) Guidelines for the assessment of diagnostic technologies.

A linked evidence approach involves narratively linking evidence reporting on three aspects of a diagnostic test intervention, if certain conditions are met. These aspects are:

test accuracy - measured for example, by sensitivity, specificity, positive or negative predictive values or likelihood ratios. This involves comparing the diagnostic test results against a reference standard ('truth').

impact on clinical decision making - measured as the change in treatment decision made by clinicians in response to the information provided by the diagnostic test; and

effectiveness of treatment – measured as the impact of on the change in management on health outcomes.

In current practice, due to the high penetrance of RET mutations (ie nearly all patients who have a mutation will develop MTC eventually), those who are mutation positive would undergo total thyroidectomy (Lundgren et al. 2007). Once the thyroid has been removed, it is impossible to know whether it would have become diseased or not, other than by testing the RET genetic mutation status and determining prognosis in those whom have the mutation. There is therefore no perfect reference standard in those who have undergone prophylactic treatment as a result of mutation status (treatment bias). The (imperfect) reference standard is long-term clinical assessment, using all available information.

Outcomes for safety and effectiveness evaluation

The health outcomes, upon which the comparative clinical performance of mutation testing of the RET gene plus current clinical investigations versus the comparator of current clinical investigations alone will be measured, are:

Effectiveness outcomes

Primary (patient relevant)

- Mortality
- Progression free survival
- Quality of life
- Incidence and severity (TNM stage) of MTC, pheochromocytoma, parathyroid hyperplasia/neoplasia and hyperparathyroidism

Secondary

- Incidence of symptoms arising from MTC, pheochromocytoma, parathyroid hyperplasia/neoplasia and hyperparathyroidism
- Timing of thyroidectomy
- Age at diagnosis
- Rates and impact (physical and psychological) of surveillance

Safety outcomes

- Psychological and physical harms from testing

Summary of PICO to be used for assessment of evidence (systematic review)

Table 11 provides a summary of the PICO used to:

- (1) define the question for public funding,
- (2) select the evidence to assess the safety, effectiveness and cost-effectiveness of mutation testing of the RET gene; and
- (3) provide the evidence-based inputs for any decision-analytic modelling to determine the cost-effectiveness of mutation testing of the RET gene.

Cost-effectiveness outcomes have been included in Table 11 so that literature on economic models and trial-based economic evaluations published in the peer-reviewed literature can be canvassed. Their applicability to the Australian health system is, however, likely to be limited and so their utility is primarily to inform the decision analytic modelling that will be conducted according to the perspective of the Australian health system.

Table 11 Summary of PICO to define clinical questions that assessment will investigate

Patients	Intervention	Comparator	Reference Standard	Outcomes to be assessed
Patients presenting with clinical features of MEN2: • medullary thyroid cancer (any age)	Mutation testing of the RET gene <i>In those with RET mutation:</i> clinical investigations for <u>phaeochromocytoma</u> and <u>hyperparathyroidism</u> , plus total thyroidectomy, lifelong thyroxine and surveillance <i>In those without RET mutation:</i> total thyroidectomy and lifelong thyroxine	Clinical investigations for <u>phaeochromocytoma</u> and hyperparathyroidism plus total thyroidectomy, lifelong thyroxine and surveillance for all	Long-term clinical assessment	Safety Psychological and physical harms from testing Effectiveness <i>Direct evidence</i> Primary outcomes: Mortality Progression free survival Quality of life Incidence and severity (TNM stage) of MTC, <u>phaeochromocytoma</u> , parathyroid hyperplasia/neoplasia and hyperparathyroidism Secondary outcomes: Incidence of symptoms arising from MTC, <u>phaeochromocytoma</u> , parathyroid hyperplasia/neoplasia and hyperparathyroidism Timing of thyroidectomy Age at diagnosis Rates and implications (physical and psychological) of surveillance
Patients presenting with clinical features of MEN2: • adrenal <u>phaeochromocytoma</u> (under 50 years)	Mutation testing of the RET gene <i>In those with RET mutation:</i> clinical investigations for hyperparathyroidism, plus prophylactic total thyroidectomy, lifelong thyroxine and surveillance <i>In those without RET mutation:</i> investigations for other hereditary disorders	Clinical investigations for MTC and hyperparathyroidism <i>In those with an MTC:</i> total thyroidectomy, lifelong thyroxine and surveillance <i>In those without an MTC:</i> investigations for other hereditary disorders		
Patients presenting with clinical features of MEN2: • hyperparathyroidism plus a diagnosis of medullary thyroid cancer or <u>phaeochromocytoma</u> in a close relative	Mutation testing of the RET gene <i>In those with RET mutation:</i> clinical investigations for <u>phaeochromocytoma</u> , plus prophylactic total thyroidectomy, lifelong thyroxine and surveillance <i>In those without RET mutation:</i> no further investigations	Clinical investigations for MTC and <u>phaeochromocytoma</u> <i>In those with an MTC:</i> total thyroidectomy, lifelong thyroxine and surveillance <i>In those without an MTC:</i> no further investigations		
First degree relatives of patients with a known pathogenic RET mutation	Genetic counselling plus genetic testing for known RET mutation <i>In those with RET mutation:</i> prophylactic total thyroidectomy, lifelong thyroxine and surveillance <i>In those without RET mutation:</i> no further follow-up	Genetic counselling plus lifelong surveillance Total thyroidectomy once calcitonin levels rise, or on the basis of biopsy of thyroid nodule detected clinically or on <u>ultrasound</u> , followed by lifelong thyroxine		Cost-effectiveness Cost, cost per event avoided, cost per life year gained, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio
Clinical Questions				
1. Is mutation testing of the RET gene safe, effective and cost-effective, in the diagnosis of patients suspected of having MEN2, when used as a replacement or triage for investigating further features of MEN2 or other hereditary disorders, determining who should receive a prophylactic total thyroidectomy, and triaging lifelong surveillance?				
2. Is mutation testing of the RET gene safe, effective and cost-effective, in first and second degree family members of patients diagnosed with MEN2, when used to determine who should receive prophylactic total thyroidectomy and triage lifelong surveillance?				

Clinical claim

The application claims that mutation testing of the RET gene in patients with MEN2 paves the way for presymptomatic testing within family members to determine who should undergo a prophylactic thyroidectomy, followed by lifelong thyroxine and lifelong surveillance for MEN2. Genetic testing should result index cases requiring surveillance, and the claim is that the health outcomes of people with MEN2 are better when they are diagnosed prior to symptoms occurring, as early intervention decreases morbidities and mortality. This scenario would also likely occur in those suspected of having MEN2, but in whom an MTC has not yet developed. It is expected that the use of genetic testing in both the index case and their family members would result in non-inferior safety outcomes, and superior effectiveness versus clinical testing alone for patients suspected of having MEN2. As shown in Table 12, a cost-effectiveness or cost-utility analysis would be performed under these conditions.

Table 12: Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator			
		Superior	Non-inferior	Inferior	
Comparative safety versus comparator	Superior	CEA/CUA	CEA/CUA	Net clinical benefit	CEA/CUA
				Neutral benefit	CEA/CUA*
				Net harms	None [^]
	Non-inferior	CEA/CUA	CEA/CUA*	None [^]	
	Inferior	Net clinical benefit	CEA/CUA	None [^]	
		Neutral benefit	CEA/CUA*		
		Net harms	none [^]		

None[^]

None[^]

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

[^] No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes for economic evaluation

It is expected that for patients suspected of having MEN2 and their relatives, genetic testing of the RET gene would result in benefits in terms of overall survival, progression-free survival, quality of life, and incidence and severity (TNM stage) of MTC, phaeochromocytoma, parathyroid hyperplasia/neoplasia and hyperparathyroidism. Therefore the health outcomes for the economic evaluation should be life-years gained and quality-adjusted life-years gained over a life-time horizon.

Health care resources

For the diagnosis of MEN2 in the index case, genetic testing has replaced the use of pentagastrin-stimulated calcitonin measurements, and is used to triage patients to either investigations for further MEN2 features (if RET+), or investigations for other hereditary disorders (if RET-). As such, the costs associated with these investigations would likely have been reduced, and should be taken into account. Additionally, the genetic test helps determine who should undergo lifelong annual surveillance, so the costs associated with the surveillance need to be taken into account. Furthermore, in those patients who present with clinical features of MEN2, other than MTC (ie an adrenal phaeochromocytoma (when under 50 years), or present with hyperparathyroidism plus have a close family member with a diagnosis of MTC or phaeochromocytoma), there is expected to be a change in treatment, as well as surveillance strategies. Those who undergo genetic testing and have a RET mutation would be recommended to undergo a prophylactic total thyroidectomy followed by lifelong thyroxine. In comparison, those who do not undergo genetic testing would only undergo a total thyroidectomy (and lifelong thyroxine) upon evidence of the development of MTC (detected by evaluating serum calcitonin or on the basis of a biopsy of a thyroid nodule detected clinically or by ultrasound), by which time there would possibly be local or distant metastases, which would require either more extensive surgical intervention, or lead to palliative therapy.

For family members of a patient diagnosed with a RET mutation corresponding to MEN2, those who do not have a RET mutation would avoid the need for lifelong surveillance which would be required in the absence of genetic testing. The costs associated with genetic testing and surveillance need to therefore be considered. In those family members who are found to have a RET mutation, the costs of a prophylactic total thyroidectomy and subsequent thyroxine sodium medication should be considered, and compared against the costs of treatment or palliation once evidence of an MTC is found through biochemical screening or imaging.

The costs associated with treatment of adrenal phaeochromocytoma or hyperparathyroidism

are not expected to differ, so do not need to be considered.

Table 13: List of resources to be considered in the economic analysis for those suspected or diagnosed with having MEN2

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
Resources provided to deliver genetic testing to index case and family members										
- Genetic counselling	Accredited genetic counsellor	Outpatient	100%	Once						
- RET gene screen	Ordered by specialised genetics service, clinical geneticist or endocrinologist	Outpatient	100%	Once	Proposed fee \$1,150					\$1,150
- RET known mutation testing	Ordered by specialised genetics service, clinical geneticist or endocrinologist	Outpatient	100%	Once	Proposed fee \$250					\$250
Resources provided to deliver biochemical screening and imaging in index case and family members										
- Consultation	GP Endocrinologist	Outpatient	100% of mutation positive patients	Once per year	Item 23 \$34.90					
- Neck ultrasound	Sonographer or radiologist	Outpatient	100% of mutation positive patients	Once per year	Item 55032 \$109.10					
- Blood test for calcium (total or corrected for albumin)	Pathologist	Outpatient	100% of mutation positive patients	Once per year	Item 66500 \$9.75					
- Blood test for ionised calcium	Pathologist	Outpatient	100% of mutation positive patients	Once per year	Item 66584 \$9.75					
- Blood test for calcitonin	Pathologist	Outpatient	100% of mutation positive patients	Once per year	Item 66695 \$30.70					
- Blood test for carcinoembryonic antigen (CEA)	Pathologist	Outpatient	100% of mutation positive patients	Once per year	Item 66650 \$24.50					

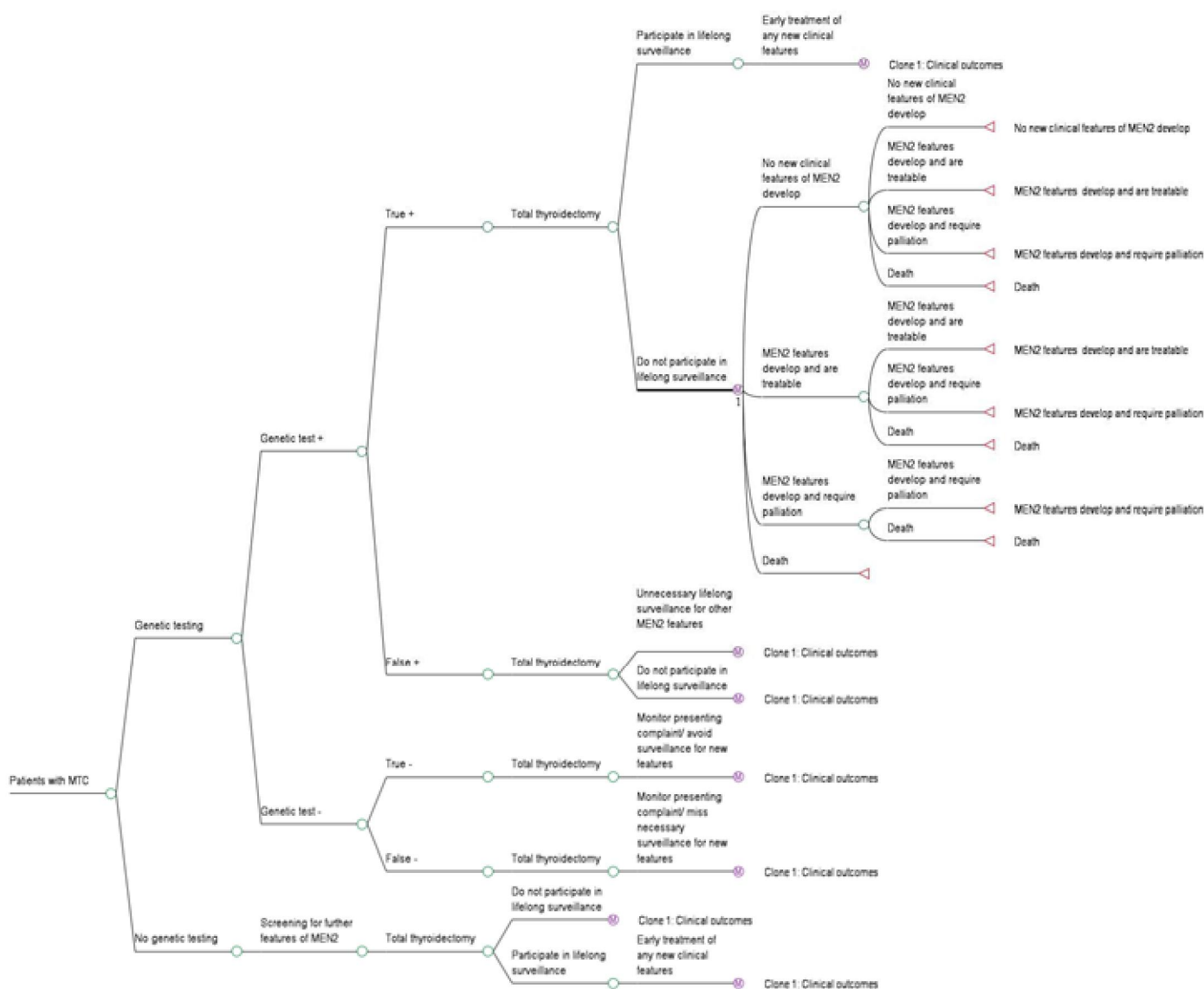
	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
- Biochemical screen for phaeochromocytoma	Pathologist	Outpatient	100% of mutation positive patients	Once per year	Item 66779 \$40.20					
<u>Resources provided to deliver prophylactic thyroidectomy surgery in index cases and family members</u>										
- Thyroidectomy	Surgeon	Inpatient	100% of mutation positive patients	Once	Item 30296 \$738.70				\$246.20	\$984.90
- Pre-anaesthetic consultation	Anaesthetist	Inpatient	100% of mutation positive patients	Once (between 15 and 30 minutes)	Item 17615 \$70.00				\$12.30	\$82.30
- Anaesthesia	Anaesthetist	Inpatient	100% of mutation positive patients	Once	Item 20320 \$85.75				\$28.55	\$114.30
- Age modifier for anaesthesia	Anaesthetist	Inpatient	5-10% of mutation positive patients (MEN2B)	Once	Item 25015 \$14.30					\$19.05
- Assistant		Inpatient	100% of mutation positive patients	Once	Item 51303 \$167.43				\$29.54	\$196.98
- Hospital accommodation for thyroid operation	Private hospital	Inpatient	100% of mutation positive patients	Average length of stay 2.04 days				NHCDC cost weights for K06Z \$3,481		\$3,481
- Thyroxine sodium	Pharmacist, script by endocrinologist	Outpatient	100% of mutation positive patients	In adults: 100 - 200 µg/day In children: 1.6 µg/kg/day ^a			PBS 2173J \$27.01			TBD

* Include costs relating to both the standard and extended safety net; TBD=to be determined; ^aDosage estimates from the Australian Prescriber, <http://www.australianprescriber.com/magazine/31/6/159/61>

Proposed structure of economic evaluation (decision-analysis)

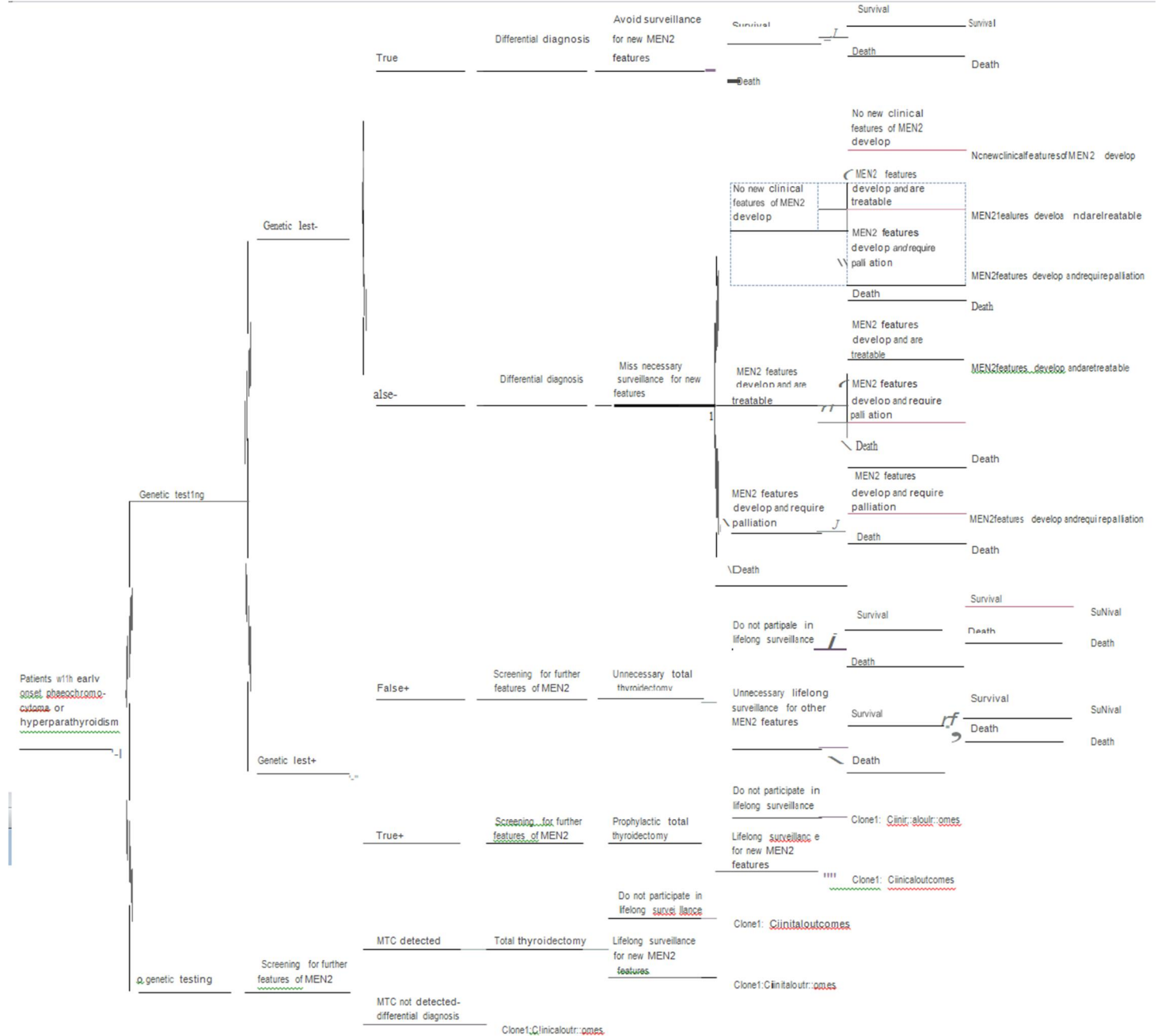
Figure 3 and Figure 4 outline the proposed decision analytics as a means of summarising the comparisons the assessment report should investigate and present for those patients who are suspected of having MEN2, and present with (Figure 3) or without (Figure 4) an MTC. Figure 5 and Figure 6 outline the decision analytics for family members of those who present with an MTC, or with early onset pheochromocytoma or hyperparathyroidism (plus a diagnosis of an MTC or pheochromocytoma in a close relative).

Figure 3 Decision tree representing decision options in patients suspected of having MEN2 who present with MTC



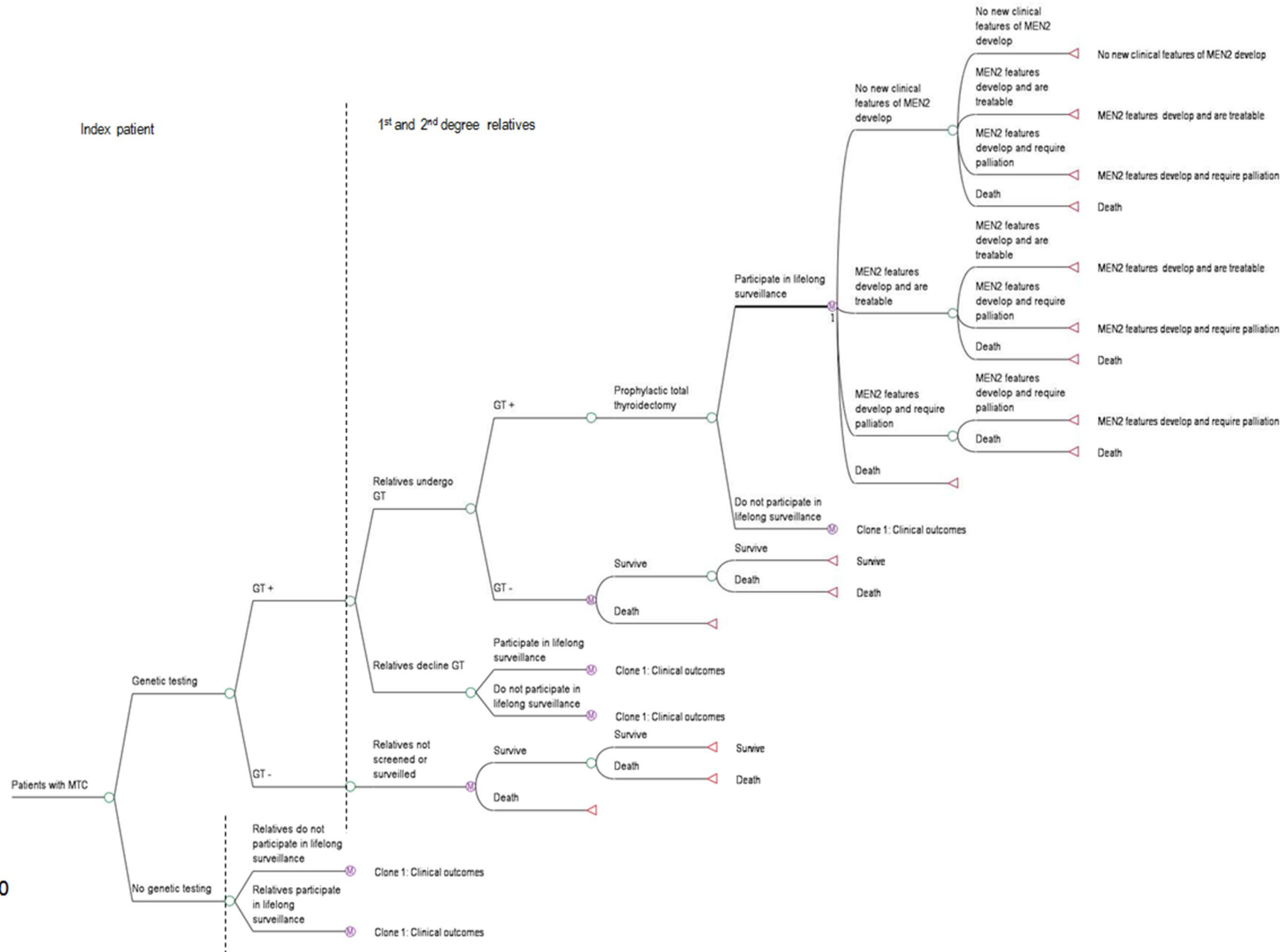
MTC=medullary thyroid carcinoma

Figure 4 Decision tree representing decision options in patients suspected of having MEN2 who present with pheochromocytoma or hyperparathyroidism



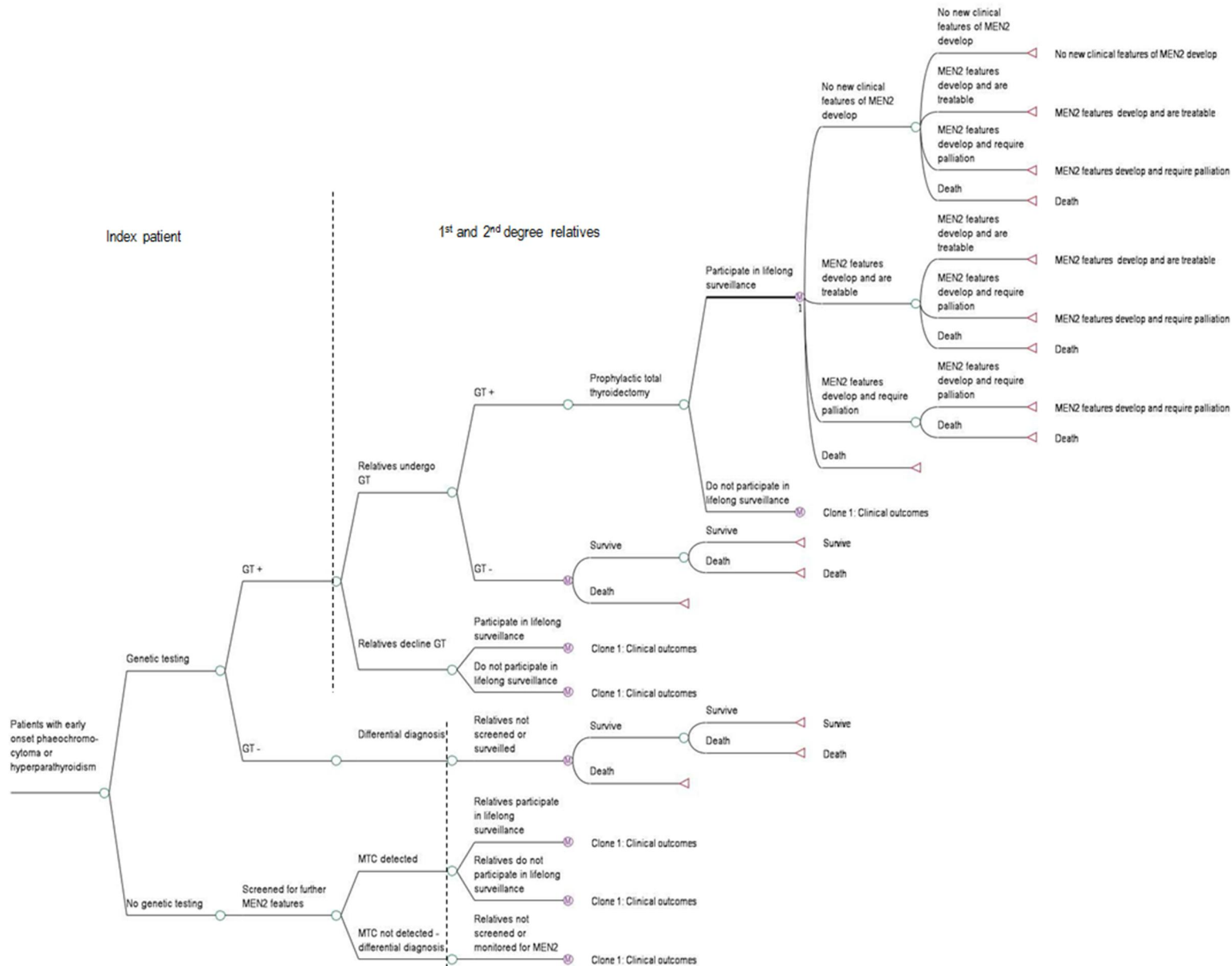
MTC=medullary thyroid carcinoma

Figure 5 Decision tree representing decision options in family members of those suspected of having MEN2 who present with MTC



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Figure 6 Decision tree representing decision options in family members of those suspected of having MEN2 who present with pheochromocytoma or hyperparathyroidism



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