Decision analytic protocol to guide the assessment of thyrotropin alfa-rch for use in the diagnosis of recurrent thyroid cancer

May 2011

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Minister for Health and Ageing (the Minister) to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister 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 provides a decision analytic protocol that is intended to guide the assessment of an intervention for a particular population of patients. The protocol has taken into account input from various stakeholders.

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 question for public funding that the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use

Intervention – specification of the proposed intervention and how it is delivered

Comparator – specification of the therapy most likely to be replaced by the proposed intervention

Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Acknowledgements

The PASC and the MSAC wish to thank Professor Robin Mortimer and Professor Roger Allison for their valuable contributions to the development of this protocol.

Summary of matters for consideration by the application

The PASC requests that the applicant note the following issues and consider addressing the issues in its application:

- it is likely that MSAC would only consider extending the current listing if a systematic review of the evidence confirmed that the diagnostic accuracy associated with thyrotropin alfa-rch is no worse than that associated with withdrawal from THT (see p.6)
- the comparison of the administration of thyrotropin alfa-rch followed by Tg assessment (i.e., stimulated Tg assessment) with unstimulated Tg assessment should be conducted using the current standard for Tg assay i.e., assays that have a detection threshold of 0.1ng/mL (see p.9)
- there is uncertainty around the application's assumptions with respect to duration of hypothyroidism when a patient prepares for stimulated Tg assessment by withdrawing from THT; the economic evaluation presented to MSAC should permit sensitivity analysis around the duration of symptomatic hypothyroidism (see p.9)
- it is possible that there could be increased use of stimulated Tg assessment for monitoring of patients with at least two successive negative assessments if thyrotropin alfa-rch were made available on the MBS (in patients who would otherwise be managed by unstimulated Tg assessment); both the economic and financial analyses should allow for sensitivity analysis around increased use of stimulated Tg assessment in these patients (see p.9). Furthermore, as the data demonstrating benefit from repeated TSH-stimulated Tg assessment in patients with two or more successive negative stimulated Tg assessments is likely to be limited; sensitivity analysis around the results of the economic analyses presented in the application should include the possibility that no incremental benefit is associated with increased use of stimulated Tg assessment compared with unstimulated Tg assessment in these patients (see p.9)
- there may be a clinical place for the use of thyrotropin alfa-rch in a small group of patients who would not be assessed for recurrence of thyroid cancer by assessment of serum Tg due to the presence of Tg antibodies because such testing in these patients has reduced sensitivity to detection of recurrence (see p.11); the applicant may wish to consider providing evidence to support listing of thyrotropin alfa-rch in these patients (i.e., evidence comparing stimulated total body iodine scan versus unstimulated total body iodine scan in these patients)
- ideally, the assessment of the clinical need, the clinical evidence, and economic evidence for thyrotropin alfa-rch should be conducted only for the incremental population that becomes eligible for reimbursed thyrotropin alfa-rch as a consequence of the proposed extension to the current listing given that thyrotropin alfa-rch is currently available for part of the total population covered by the proposed MBS item (see p.12)
- resource use associated with management of adverse events associated with thyrotropin alfa-rch should also be included in the economic analysis (see p.19)
- the inclusion of "lifetime thyroid cancer" costs in the economic analysis is likely to result in double counting of several resources; costs should be related more explicitly to use of specific resources (see p.19)
- the assumption of "additional costs" incorporating specialist visits and co-ordination of assessment for recurrence of thyroid cancer should be related more explicitly to use of specific resources (see p.19)

- the base case modelled economic evaluations presented in the application should be respecified to include more reasonable rates of: (i) non-compliance with stimulated Tg assessment (see p.17) ;and (ii) recurrence of thyroid cancer (see p.25)
- the assumption that unstimulated Tg assessment has no sensitivity in detecting recurrent thyroid cancer also is considered inappropriate; the inclusion of costs but no benefits from such testing in the economic evaluation was considered inappropriate (see p.25).

Purpose of application

An application has been received from Genzyme Australasia requesting extension of the current MBS listing for thyrotropin alfa-rch (recombinant human thyroid stimulating hormone). Genzyme Australasia are the distributors of the Thyrogen® brand of thyrotropin alfa-rch.

Background

Current arrangements for public reimbursement

Thyrotropin alfa-rch is currently available on the MBS as summarised in Table 1 on the following page. Essentially, availability is limited to patients in whom increase of endogenous thyroid stimulating hormone (TSH) by withdrawal of thyroid hormone therapy (THT) is either contraindicated on not tolerated.

The PASC noted that MSAC, in considering evidence in relation to thyrotropin alfa-rch at the time it was initially considered, concluded that increase in TSH by administration of thyrotropin alfa-rch was associated with a lower diagnostic accuracy of detection of recurrent thyroid cancer compared with increase in TSH by withdrawal from THT. Accordingly, the MBS item was restricted to patients in whom thyroid hormone therapy withdrawal is medically contraindicated or not tolerated. The PASC noted that it is likely that MSAC would only consider extending the current listing if a systematic review of the evidence confirmed that the diagnostic accuracy associated with thyrotropin alfa-rch is no worse than that associated with withdrawal from THT.

In the 2010 calendar year, 185 services for MBS Item 12201 (administration of thyrotropin alfa-rch) were claimed through Medicare. The associated cost to the MBS was $404,842. The distribution of services by patient demographic variables of gender and age are shown in Figure 1.

Figure 1: Distribution of utilisation of MBS item 12201 by gender and age

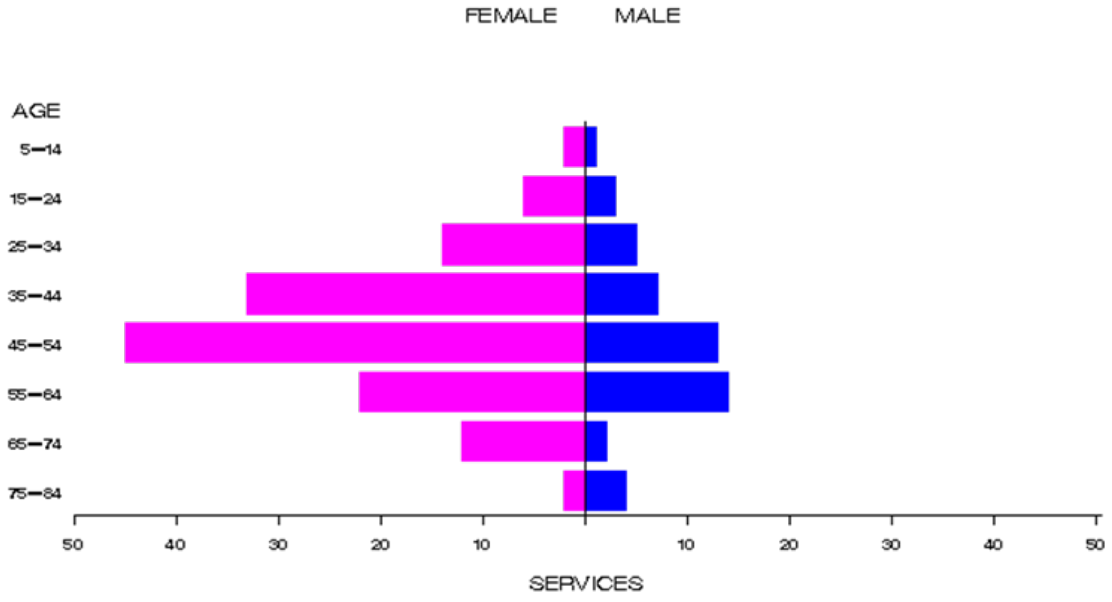


Table 1: Current MBS item descriptor for thyrotropin alfa-rch (MBS item 12201)

Category 2 – MISCELLANEOUS DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
12201 Administration, by a specialist or consultant physician in the practice of his or her specialty, of thyrotropin alfa-rch (recombinant human thyroid-stimulating hormone), and arranging services to which both items 61426 and 66650 apply, for the detection of recurrent well-differentiated thyroid cancer in a patient who: (a) has had a total thyroidectomy and one ablative dose of radioactive iodine; and (b) is maintained on thyroid hormone therapy; and (c) is at risk of recurrence; and (d) on at least one previous whole body scan or serum thyroglobulin test when withdrawn from thyroid hormone therapy did not have evidence of well differentiated thyroid cancer; and i. withdrawal from thyroid hormone therapy resulted in severe psychiatric disturbances when hypothyroid; or ii. withdrawal is medically contraindicated because the patient has: • unstable coronary artery disease; or • hypopituitarism ; or • a high risk of relapse or exacerbation of a previous severe psychiatric illness. Payable once only in any twelve month period. Fee: $2,302.25; Benefit: 75% = $1,726.70; 85% = $2,231.05 (See para D1.25 of explanatory notes to this Category) Para D1.25: Administration of Thyrotropin Alfa-rch for the Detection of Recurrent Well-differentiated Thyroid Cancer - (Item 12201) Thyrotropin alfa-rch is a diagnostic agent that allows patients to remain on thyroid hormone therapy while being assessed for recurrent cancer. This item was introduced following an assessment by the Medical Services Advisory Committee (MSAC) of the available evidence relating to the safety, effectiveness and cost-effectiveness of thyrotropin alfa-rch. MSAC found that the use of thyrotropin alfa-rch is associated with a lower diagnostic accuracy than when the patient has withdrawn from thyroid hormone therapy. Accordingly, benefits are payable under the item only for patients in whom thyroid hormone therapy withdrawal is medically contraindicated and where concurrent whole body study using radioactive iodine and serum thyroglobulin are undertaken. Services provided to patients who do not demonstrate the indications set out in item 12201 do not attract benefits under the item. "Severe psychiatric illness" is defined as patients with a severe pre-existing psychiatric illness who are currently under specialist psychiatric care. The item includes the cost of supplying thyrotropin alfa-rch and the equivalent of a subsequent specialist attendance. "Administration" means an attendance by the specialist or consultant physician (the administering practitioner) that includes: • an assessment that the patient meets the criteria prescribed by the item; • the supply of thyrotropin alfa-rch; • ensuring that thyrotropin alfa-rch is injected (either by the administering practitioner or by another practitioner) in two doses at 24 hour intervals, with the second dose being administered 72 hours prior to whole body study with radioactive iodine and serum thyroglobulin test; and • arranging the whole body radioactive iodine study and the serum thyroglobulin test. Where thyrotropin alfa-rch is injected by the administering practitioner, benefits are not payable for an attendance on the day the second dose is administered. Where thyrotropin alfa-rch is injected by: a general practitioner - benefits are payable under a Level A consultation (item 3); other practitioners - benefits are payable under item 52.

Regulatory status

The Thyrogen® brand of thyrotropin alfa-rch is approved by the TGA for the following indications:

- Use with serum thyroglobulin (Tg) testing, with or without radioactive iodine imaging, undertaken for the detection of thyroid remnants and well differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy.
- Therapeutic use in post-thyroidectomy patients maintained on hormone suppression therapy in the ablation of thyroid remnant tissue in combination with radioactive iodine. Note: Thyrogen® is listed on the PBS as a single treatment per lifetime for the ablation of thyroid remnant tissue in post thyroidectomy adults.

Intervention

Description

The requested listing of thyrotropin alfa-rch (recombinant human thyroid-stimulating hormone) involves use of the product as a single component of a diagnostic procedure.

Patients who have had well differentiated thyroid cancer and who have been successfully treated by thyroidectomy followed by an ablative dose of radioactive iodine require monitoring for recurrence of thyroid cancer. Patients who have had total thyroidectomy are typically treated with synthetic THT. THT is administered with two objectives: (i) to keep thyroid hormone levels within a range that maintains basic bodily function; and (ii) to suppress serum levels of TSH in order to minimise TSH-induced thyroid tissue and thyroid tumour growth.

Recurrence of thyroid cancer is typically assessed by measurement of serum Tg, which may or may not be used in combination with a total-body scan following administration of radioactive iodine and/or neck ultrasound. In order to increase the sensitivity of assessment of recurrence of thyroid cancer by measurement of serum Tg or by total body radioactive iodine scan, it is recommended that levels of TSH be increased to promote the release of Tg and the uptake of radioactive iodine. In the absence of availability of thyrotropin alfa-rch, this is achieved by having the patient discontinue their THT in order to stimulate the production of endogenous TSH. Thyrotropin alfa-rch is an exogenous form of TSH, which averts the need for a patient to discontinue their THT.

In a minority of patients who have antibodies to Tg, assessment for recurrence of thyroid cancer may not include measurement of serum Tg because such testing in these patients has reduced sensitivity to detection of recurrence. In these patients, total-body scan following administration of radioactive iodine and/or neck ultrasound is used to monitor for recurrence of thyroid cancer.

Delivery of the intervention

The recommended dose regimen for Thyrogen® is 0.9 mg, administered by intramuscular injection twice (once every 24 hours for two doses). The second dose should be given 24 hours prior to administration of radioactive iodine and 72 hours prior to quantitation of serum Tg and, if necessary, a diagnostic scan.

The application notes that, in contrast, patients being prepared for assessment of serum Tg (and if necessary a diagnostic scan) by withdrawal of THT undertake withdrawal over a period of four weeks. At four weeks, TSH levels should be sufficiently elevated for patients to be able to undergo diagnostic testing. In total, the application assumes that patients experience a 13-week period of hypothyroidism (five weeks of significant symptomatic hypothyroidism while preparing for and undergoing assessment of serum Tg and eight weeks post-assessment where patients gradually return to euthyroid levels). The PASC questioned the estimate of the period over which a patient experiences hypothyroidism and queried whether the duration of hypothyroidism is overestimated by the application. Advice from clinical experts was that, although it did take four weeks of withdrawal from THT to achieve desired TSH levels, patients did not typically experience significant symptoms of hypothyroidism until the third and fourth weeks after withdrawing from THT. The clinical experts also advised that, although return to euthyroid levels can take up to six weeks, the duration of clinical hypothyroid symptoms is shorter, with significant symptoms generally being resolved by the third week after recommencing THT. The PASC agreed that the economic evaluation presented to MSAC should permit sensitivity analysis around the duration of symptomatic hypothyroidism.

The current MBS item for thyrotropin alfa-rch is payable once only in any 12 month period. Although the item descriptor proposed by the application does not limit the number of times the item is payable, the PASC considered that the item descriptor should include a stipulation that the item be payable once only in any 12 month period. The economic analysis presented in the application assumes patients are withdrawn from THT or are given thyrotropin alfa-rch and have both serum Tg assessment and a radioactive iodine scan at 10 months post ablation. The analysis assumes that, if patients test negative, this assessment is followed up by another stimulated Tg assessment (but no radioactive iodine scan) 18 months later (i.e., at 28 months post total thyroidectomy). Beyond this time point, the economic analysis presented in the application assumes that patients testing negative twice in succession are monitored by unstimulated Tg assessment every two years (i.e., patients are monitored by assessment of serum Tg but with no need for withdrawal from THT or thyrotropin alfa-rch and no radioactive iodine scan). The PASC accepted advice from clinical experts that this was a reasonable approach to monitoring of patients for recurrence of well differentiated thyroid cancer. It noted that the need for further stimulated Tg assessment is uncertain for patients found to be free of disease on two previous successive occasions because of the paucity of data demonstrating benefit from repeated stimulated Tg assessment in this patient cohort. The PASC noted that it was possible that there could be increased use of stimulated Tg assessment for monitoring of patients with at least two successive negative assessments if thyrotropin alfa-rch were made available on the MBS and it was advised that the proposed item descriptor be modified to restrict use accordingly. The inclusion of such a requirement would also be consistent with the recommendations of the American Thyroid Association. It was agreed that both the economic and financial analyses should allow for sensitivity analysis around increased use of stimulated Tg assessment in patients who had been found to be free of disease on two successive occasions. Sensitivity analysis should include the possibility that no incremental benefit is associated with increased use of stimulated Tg assessment compared with unstimulated Tg assessment in patients who have previously tested negative on two successive occasions for recurrence of thyroid cancer.

The PASC noted and agreed with stakeholder input that there had been substantial development in terms of the threshold Tg level that is able to be detected by Tg assays (i.e., functional sensitivity)

since MSAC's original consideration of thyrotropin alfa-rch. It was considered that ultrasensitive thyroglobulin assays with detection limits of 0.1ng/mL are likely to represent the standard used in practice. The PASC therefore advised that any comparison of the diagnostic accuracy of stimulated Tg assessment versus unstimulated Tg assessment should be conducted considering studies that used the ultrasensitive assays for Tg. Presentation of studies that used outdated assays for Tg (i.e., with higher detection thresholds) would be of limited relevance to MSAC decision-making. The PASC advised that the question of whether assays for Tg that have a detection threshold (or functional sensitivity) as low as 0.1 ng/ml allow for the detection of smaller amounts of thyroid tissue, even when TSH is suppressed, should be addressed by the assessment considered by MSAC. Comparisons of stimulated versus unstimulated radioactive iodine scans would remain relevant.

Prerequisites

Both the current and proposed MBS item descriptors require that administration of thyrotropin alfa-rch be arranged by "a specialist or consultant physician in the practice of his or her speciality". The PASC and the clinical experts agreed that no change to this requirement was necessary provided there were no indications that thyrotropin alfa-rch was not being used in line with the intent of the item descriptor.

Co-administered and associated interventions

As noted in the description of thyrotropin alfa-rch above, thyrotropin alfa-rch is used as a single component of a diagnostic procedure. It is administered to promote the release of Tg and the uptake of radioactive iodine, which are monitored to assess a patient for recurrence of thyroid cancer. Quantitation of serum Tg for detection of recurrence of thyroid cancer is reimbursed under MBS item 66650 and whole body study using radioactive iodine is reimbursed under MBS item 61426. The clinical experts advised that neck ultrasound (reimbursed under MBS items 55032 and 55033) is increasingly also being used in assessing patients for recurrence of thyroid cancer.

In the current scenario where thyrotropin alfa-rch is not available, patients are also assessed for recurrence of thyroid cancer by quantitation of serum Tg with or without whole body study using radioactive iodine and/or neck ultrasound. However, release of Tg and the uptake of radioactive iodine are stimulated by having the patient discontinue their THT in order to stimulate the production of endogenous TSH (rather than by administration of thyrotropin alfa-rch as occurs in the proposed scenario).

Listing proposed and options for MSAC consideration

Proposed MBS listing

The application to MSAC requests an item descriptor for thyrotropin alfa-rch as summarised in Table 2.

Table 2: Proposed MBS item descriptor for thyrotropin alfa-rch (MBS item 12201)

Category 2 – MISCELLANEOUS DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
12201 Administration arranged by a specialist or consultant physician in the practice of his or her specialty, of thyrotropin alfa-rch (recombinant human thyroid-stimulating hormone) for use with serum thyroglobulin (Tg), with or without radioactive iodine imaging, undertaken for the detection of thyroid remnants and well differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy.

The requested MBS listing is consistent with the TGA approved indication for Thyrogen®.

The PASC noted that the proposed item descriptor for thyrotropin alfa-rch is broader than the current MBS listing in various ways:

1. The current MBS listing is limited to use in patients who are susceptible to psychiatric disturbance or those in whom THT-withdrawal is medically contraindicated for various reasons whereas the requested expanded MBS listing of thyrotropin alfa-rch does not include such a limitation;
2. The current MBS item descriptor requires patients to be having both radioactive iodine imaging and Tg assessments arranged whereas the requested expanded MBS listing of thyrotropin alfa-rch also permits use in patients having Tg assessment only (without complementary radioactive iodine imaging).
3. The current MBS listing requires patients to have undertaken a whole body radioactive iodine scan or serum Tg test subsequent to withdrawal of THT whereas the requested expanded MBS listing of thyrotropin alfa-rch does not include such a requirement.
4. The current MBS listing requires patients to have had a total thyroidectomy and one ablative dose of radioactive iodine whereas the requested expanded MBS listing of thyrotropin alfa-rch permits use in "post-thyroidectomy patients" which may be interpreted more broadly (i.e., to include partial thyroidectomy and to not require a post-thryoidectomy ablative dose of radioactive iodine).
5. The current MBS listing only permits use of thyrotropin alfa-rch for the detection of recurrent well differentiated thyroid cancer whereas the requested expanded MBS listing of thyrotropin alfa-rch also permits use for detection of thyroid remnants in post-thyroidectomy patients maintained on hormone suppression therapy.

The PASC and the clinical experts agreed that consideration of the extension to the MBS listing of thyrotropin alfa-rch should be limited to a patient population who have had well differentiated thyroid cancer treated by total thyroidectomy and ablation of residual thyroid tissue by administration of radioactive iodine and who are being assessed for recurrence of thyroid cancer. It was agreed that extension of the listing to include patients who had not had complete ablation of the thyroid tissue performed was clinically inappropriate.

The PASC accepted advice from the clinical experts noting that there may be a clinical place for the use of thyrotropin alfa-rch in a small group of patients who would not be assessed for recurrence of thyroid cancer by assessment of serum Tg due to the presence of Tg antibodies because such testing in these patients has reduced sensitivity to detection of recurrence. In these patients, total-body scan following administration of radioactive iodine with or without neck ultrasound is used to monitor for recurrence of thyroid cancer.

The PASC noted that there may be occasions where use of stimulated assessments of serum thyroglobulin or whole body study using radioactive iodine were indicated downstream (i.e., after a patient had had two consecutive assessments of stimulated serum thyroglobulin reporting undetectable levels of thyroglobulin) and therefore considered that it was appropriate that a second listing should permit the use of thyrotropin alfa-rch in patients where recurrence of thyroid cancer was clinically suspected. The PASC recommended item descriptors as shown in Table 3.

It was also agreed that the MBS item should only allow for reimbursement of diagnostic uses of the agent and should not include therapeutic applications of thyrotropin alfa-rch (i.e., the MBS listing should not extend to the use of thyrotropin alfa-rch in patients requiring further ablation of thyroid tissue). Therapeutic applications of thyrotropin alfa-rch are considered for inclusion on the PBS by the PBAC.

Table 3: Revised proposed MBS item descriptors for thyrotropin alfa-rch suggested by PASC

Category 2 – MISCELLANEOUS DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
12201 Administration, by a specialist or consultant physician in the practice of his or her specialty, of thyrotropin alfa-rch (recombinant human thyroid-stimulating hormone) for measurement of stimulated serum thyroglobulin (MBS item 66650) or for whole body study using radioactive iodine (MBS item 61426), undertaken for the detection of recurrent well differentiated thyroid cancer in a patient who has had a total thyroidectomy and at least one ablative dose of radioactive iodine and is maintained on thyroid hormone therapy. Payable once only in any twelve month period. Fee: $2,302.25; Benefit: 75% = $1,727.70; 85% = $2,231.05 Note: This item can only be used following ablation until the patient achieves two consecutive assessments of stimulated serum thyroglobulin reporting undetectable levels of thyroglobulin. Patients who have had two consecutive assessments of stimulated serum thyroglobulin where thyroglobulin was not detected should be monitored by assessment of unstimulated serum thyroglobulin.
New item Administration, by a specialist or consultant physician in the practice of his or her specialty, of thyrotropin alfa-rch (recombinant human thyroid-stimulating hormone) for measurement of stimulated serum thyroglobulin (MBS item 66650) or for whole body study using radioactive iodine (MBS item 61426), undertaken for the detection of recurrent well differentiated thyroid cancer in a patient who has had a total thyroidectomy and at least one ablative dose of radioactive iodine and is maintained on thyroid hormone therapy where there is a clinical suspicion of recurrence of thyroid cancer. Payable once only in any twelve month period. Fee: $2,302.25; Benefit: 75% = $1,727.70; 85% = $2,231.05

The PASC noted that, ideally, the assessment of the clinical need, the clinical evidence, and economic evidence for thyrotropin alfa-rch should be conducted only for the incremental population that becomes eligible for reimbursed thyrotropin alfa-rch as a consequence of the proposed extension to the current listing given that thyrotropin alfa-rch is currently available for part of the total population covered by the proposed MBS item. This is an important consideration as the current application presents an assessment of the clinical and economic performance of thyrotropin alfa-rch for the entire population covered by the new MBS item rather than just for the incremental population that becomes eligible for reimbursed thyrotropin alfa-rch as a consequence of the proposed extension to the current listing. It is possible, if not likely, that the average benefit in the total population may not be identical to the benefit experienced by the sub-group for whom thyrotropin alfa-rch is already available, such that the average benefit may comprise a large benefit in one subgroup of patients

(such as those for whom thyrotropin alfa-rch is already available) and only a small benefit in the complementary subgroup of patients (i.e., in the additional patients who will become eligible for thyrotropin alfa-rch should the MBS item be expanded as suggested). The PASC does, however, acknowledge that it might be difficult to present analyses only for the incremental population if studies have not reported outcomes for the two subgroups separately. Although MSAC would prefer to have evidence presented for the two subgroups separately, in the situation where evidence for the subgroups is not available, MSAC would consider evidence for the entire group.

Clinical place for proposed intervention

Thyrotropin alfa-rch (exogenous TSH) is used as a direct substitute for withdrawal of THT (to endogenously increase levels of TSH). Both approaches are used prior to assessment of serum Tg, with or without radioactive iodine imaging and/or neck ultrasound, for the purposes of detection of recurrence of well differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy.

The management algorithms that are assumed to apply in the application for the scenarios where thyrotropin alfa-rch is and is not available are summarised in Figure 2. The clinical experts considered that the management algorithms summarised in Figure 2 could be considered overly simplistic and explained that the strategy to manage patients post thyroidectomy and ablation could depend on the outcome of an assessment of risk of recurrence and an assessment of response to total thyroidectomy. Table 4 summarises a staging system that has been recommended for use by the American Thyroid Association to predict risk of recurrent/persistent disease in patients with differentiated thyroid cancer. In a sample of 588 patients[i], 23%, 50% and 27% of patients were classified as having low, intermediate and high risk of recurrence, respectively. Following total thyroidectomy, patients are recommended to be followed up with an assessment of stimulated serum Tg and neck ultrasound at 6 to 24 months. Response to thyroidectomy and ablation of any residual thyroid tissue by administration of radioactive iodine is then categorised in accordance with the classification provided in Table 5. Table 6 provides a matrix that summarises the likelihood of detection of persistence/recurrence of thyroid cancer in a sample of 471 patients by initial risk of recurrence and response to initial therapy at first follow-up assessment at 6-24 months after total thyroidectomy. Table 7 presents the proportion of patients who had no evidence of disease at the time of last follow-up (a median of 7 years after initial therapy).

Table 4: American Thyroid Association initial risk of recurrence classification

Low risk of recurrence	Intermediate risk of recurrence	High risk of recurrence
All the following are present: - No local or distant metastases - All macroscopic tumour has been resected - No invasion of locoregional tissues - Tumour does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma, Hurthle cell carcinoma, follicular thyroid cancer) - No vascular invasion - No uptake of radioactive iodine outside the thyroid bed on the post-treatment scan, if done	Any of the following is present: - Microscopic invasion into the perithyroidal soft tissues - Cervical lymph node metastases or uptake of radioactive iodine outside the thyroid bed on the post-treatment scan done after thyroid remnant ablation - Tumour with aggressive histology or vascular invasion (e.g., tall cell, insular, columnar cell carcinoma, Hurthle cell carcinoma, follicular thyroid cancer)	Any of the following is present: - Macroscopic tumour invasion - Incomplete tumour resection with gross residual disease - Distant metastases

Table 5: Response to initial therapy definitions (6-24 months after radioactive iodine ablation)

Excellent response	Acceptable response	Incomplete response
All of the following: - Suppressed (unstimulated) and stimulated Tg <1ng/mL - Neck ultrasound without evidence of disease - Cross-sectional and/or nuclear medicine imaging negative (if performed)	Any of the following: - Suppressed (unstimulated) Tg <1ng/mL and stimulated Tg ≥1 and <10ng/mL - Neck ultrasound with nonspecific changes or stable subcentimetre lymph nodes - Cross-sectional and/or nuclear medicine imaging with nonspecific changes, although not completely normal	Any of the following is present: - Suppressed (unstimulated) Tg ≥1ng/mL or stimulated Tg ≥10ng/mL - Rising Tg values - Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging

Table 6: Proportion of patients with persistent or recurrent disease at 2 years follow-up for 471 patients reported by Tuttle et al, 2010

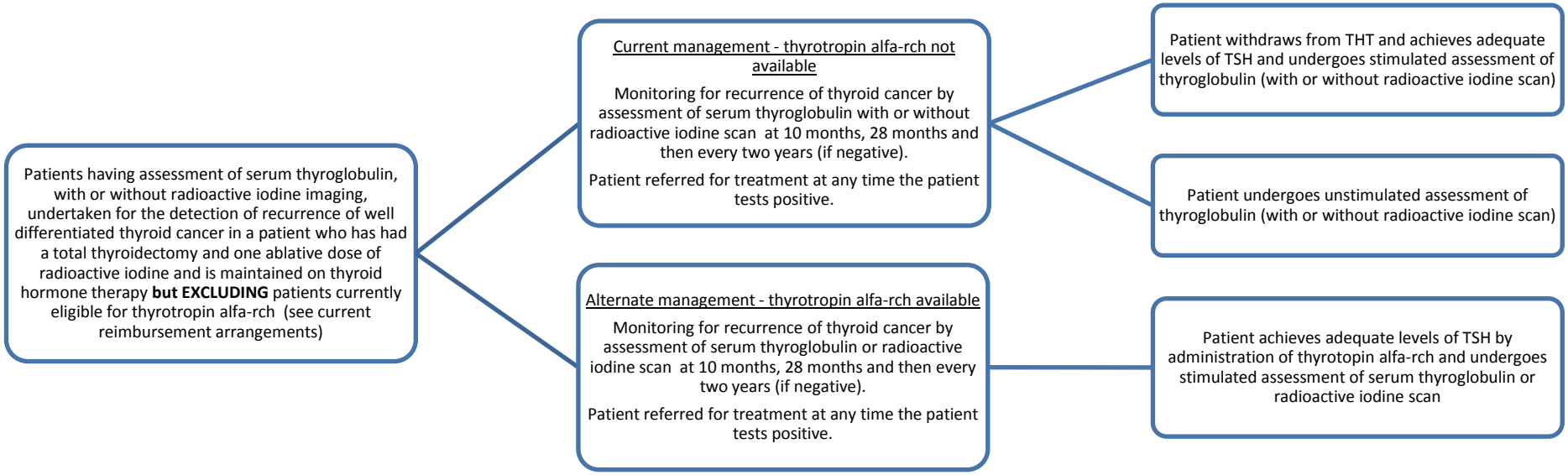
Initial classification of risk of recurrence → Response to initial therapy↓	Low risk of recurrence	Intermediate risk of recurrence	High risk of recurrence
Excellent response	1/59 (2%)	2/86 (2%)	2/14 (14%)
Acceptable response	0/30 (0%)	0/56 (0%)	0/9 (0%)
Incomplete response	2/15 (13%)	41/99 (41%)	81/103 (79%)
Average proportion of patients with persistent/recurrent disease at 2 year follow-up by initial risk classification	3/104 (3%)	43/241 (18%)	83/126 (66%)
Overall average proportion of patients with persistent/recurrent disease at 2 year follow-up	129/471 (27.4%)		

Table 7: Proportion of patients with no evidence of disease at final follow-up (a median of 7 years after initial therapy) up by initial classification of risk and by assessment conducted at 2 years follow-up as reported by Tuttle et al, 2010

Initial classification of risk of recurrence	Results of assessment of response at 2 years follow-up	Proportion of patients with no evidence of disease at final follow-up
Low risk (n=104)	Suppressed Tg<1 ng/mL alone	84%
	Stimulated Tg<1 ng/mL alone	89%
	Excellent response (imaging negative[a] and suppressed Tg<1 ng/mL)	94%
	Excellent response (imaging negative[a] and stimulated Tg<1 ng/mL)	97%
Intermediate risk (n=241)	Suppressed Tg<1 ng/mL alone	74%
	Stimulated Tg<1 ng/mL alone	80%
	Excellent response (imaging negative[a] and suppressed Tg<1 ng/mL)	90%
	Excellent response (imaging negative[a] and stimulated Tg<1 ng/mL)	94%
High risk (n=126)	Suppressed Tg<1 ng/mL alone	39%
	Stimulated Tg<1 ng/mL alone	55%
	Excellent response (imaging negative[a] and suppressed Tg<1 ng/mL)	80%
	Excellent response (imaging negative[a] and stimulated Tg<1 ng/mL)	82%

[a] Negative imaging: normal neck ultrasound in all patients. In addition, any other functional or cross-sectional imaging obtained at the discretion of the treating physician was interpreted as having no evidence of persistent/recurrent thyroid cancer.

Figure 2: Management algorithms in the scenario with and without thyrotropin alfa-rch



Comparator

The application nominates withdrawal of THT (to endogenously increase levels of TSH) as the appropriate comparator in all patients however the economic evaluation presented by the application suggests that thyrotropin alfa-rch might also be used in patients who, due to the unpleasantness of the hypothyroid state that occurs as a consequence of withdrawal of THT, are not compliant with recommendations to discontinue THT and who do not undergo TSH-stimulated quantitation of serum Tg (with or without radioactive iodine imaging) for the detection of recurrence of well differentiated thyroid cancer. Thus the application includes two comparators in its economic evaluation – withdrawal of THT for patients (followed by Tg assessment) who comply with instructions to withdraw from THT and unstimulated Tg assessment for patients who do not comply with withdrawal of THT. The application estimates that 20% of patients are non-compliant with monitoring recommendations and undergo unstimulated quantitation of serum Tg whereas 0% of patients of patients having TSH-levels increased by administration of thyrotropin alfa-rch undergo unstimulated Tg assessment.

The PASC sought expert clinical advice to determine how patients who are not compliant with monitoring recommendations are typically managed. The clinical experts consulted advised that unstimulated Tg assessment would be conducted in these patients and that this was therefore the appropriate comparator in these patients. It was noted that the application, appropriately, only suggested that patients would undergo unstimulated Tg assessment after they had undergone at least one stimulated Tg assessment. The clinical experts advised that it is a matter of debate as to whether a second stimulated Tg assessment was indicated at all in many patients. Therefore, it was considered likely that the primary reason for patients not undergoing a second stimulated Tg assessment (for both patients having TSH increased by withdrawal of THT and patients having TSH increased by administration of thyrotropin alfa-rch) was due to physician discretion rather than patient choice. The PASC considered that the estimate in the base case modelled economic evaluation, that 20% of patients were non-compliant with monitoring recommendations and undergo unstimulated quantitation of serum Tg, was likely to be an overestimate. The PASC requested that any estimate of non-compliance rates included in the base case should be supported by appropriate evidence that does not take into account use of unstimulated Tg assessment due to physician discretion rather than patient choice. Sensitivity analysis around this parameter in the model was requested. A rate of 0% non-compliance should be included in the sensitivity analysis. As noted above in the discussion of the delivery of the intervention, the clinical experts also noted that it was possible that there could be increased use of stimulated Tg assessment for monitoring of patients with two successive negative assessments if thyrotropin alfa-rch were made available on the MBS. The PASC agreed with the clinical experts and advised that both the economic and financial analyses should allow for sensitivity analysis around increased use of stimulated Tg assessment in patients who had been found to be free of disease on two successive occasions.

Clinical claim

The implicit fundamental clinical claims made in the application are as follows:

(i) In patients who currently comply with monitoring recommendations, administration of thyrotropin alfa-rch (exogenous TSH) compared with withdrawal of THT (to endogenously increase levels of TSH) is no worse in terms of effectiveness (i.e., results in an equivalent promotion of the release of Tg and the uptake of radioactive iodine such that there is no impact on diagnostic accuracy of tests to quantify Tg or the outcome of whole body studies using radioactive iodine) and is associated with advantages in terms of safety (i.e., any adverse events associated with thyrotropin alfa-rch are offset by the effects of hypothyroidism that is associated with withdrawal of THT).

(ii) In patients who currently do not comply with monitoring recommendations (i.e., who choose not to withdraw from THT), administration of thyrotropin alfa-rch prior to Tg assessment has advantages in terms of effectiveness compared to unstimulated Tg assessment (i.e., recurrence is more likely to be diagnosed in patients administered thyrotropin alfa-rch prior to Tg assessment compared to those who have unstimulated Tg assessment). Administration of thyrotropin alfa-rch prior to Tg assessment and is no worse in terms of safety than unstimulated Tg assessment (i.e., adverse events associated with thyrotropin alfa-rch are negligible from a clinical perspective).

The PASC confirmed that the claims that should be assessed in the application are of the clinical superiority of thyrotropin alfa-rch compared with withdrawal of THT or of non-compliance with monitoring recommendations. PASC confirmed that the appropriate economic analysis to inform MSAC decision-making will be a cost-effectiveness analysis.

Outcomes and health care resources affected by introduction of proposed intervention

Either directly or indirectly, the application suggests that the clinical and economic performance of thyrotropin alfa-rch should be assessed considering comparative impact on the following health outcomes and comparative impact on the utilisation of the following healthcare resources.

Clinical outcomes:

- Diagnostic accuracy of TSH-stimulated (endogenously or exogenously) serum Tg with or without whole body study using radioactive iodine
- Compliance with follow-up (assumed in the application to impact on rates of detection of recurrence of thyroid cancer and, consequently, on survival over the long term)
- Quality of life over time (patients in the hypothyroid state are assumed to experience a poorer quality of life compared with euthyroid patients)

Health care resources:

- Administration of Thryogen®
- Quantitation of serum TSH levels (used to determine whether patient is adequately hypothyroid when stimulating TSH by withdrawal of THT)
- Medical consultations
- Assessment of serum Tg
- Whole body study using radioactive iodine
- Interventions aimed at managing symptoms of hypothyroidism
- Interventions aimed at managing recurrence of thyroid cancer (e.g., hospitalisations)

The PASC agreed with advice from clinical experts suggesting that resource use associated with management of adverse events associated with thyrotropin alfa-rch should also be included in the economic analysis.

Table 8 summarises the healthcare resources that are considered in the economic analysis presented in the application. The PASC agreed with the clinical experts suggestion that inclusion of "lifetime thyroid cancer" costs in the analysis was likely to result in double counting of several resources. This is because such costs may include costs of initial and subsequent detection and treatment of thyroid cancer (e.g., ablation costs, medical care costs, costs associated with monitoring). The PASC recommended the explicit listing of resources used in the management of recurrent thyroid cancer. The PASC also suggested that the incorporation of any "additional costs" relating to specialist visits and co-ordination of assessment for recurrence of thyroid cancer should be related more explicitly to use of specific resources.

Table 8: Summary list of resources to be considered in the economic analysis

	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					Total cost per unit
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	
Resources provided to identify eligible population (at point A in Figure 3)										
- None										
Resources provided to deliver thyrotropin alfa-rch (at point G of the Thyrogen arm in Figure 3)										
- Administration of thyrotropin alfa-rch MBS Item 12201	Specialist	Community	100% of patients in thyrotropin alfa-rch arm	1 at 10 months and 1 at 28 months unless there is recurrence of cancer	Not specified					$2,302.25 / administration
Resources provided in having a patient withdraw from THT (at point G of the THT withdrawal arm in Figure 3)										
- Quantitation of TSH MBS Item 66716	Laboratory	Laboratory	100% of patients in withdrawn from THT arm	1.1 at 10 months and 1.1 at 28 months unless patient is non-compliant or there is recurrence of cancer	Not specified					$25.20/test
- "Additional costs" incorporating specialist visits and co-ordination of assessment for recurrence of thyroid cancer	Not specified	Not specified	100% of patients in withdrawn from THT arm	1 at 10 months and 1 at 28 months unless patient is non-compliant or there is recurrence of cancer	Not specified					$400.83 / assessment [a]

	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					Total cost per unit
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	
Resources provided in assessing a patient who is non-compliant with withdrawal from THT (at point O in both arms in Figure 3)										
- Quantitation of TSH MBS Item 66716	Laboratory	Laboratory	100% of patients in withdrawn from THT arm	1 every 24 months unless patient experiences late stage cancer	Not specified					$25.20/test
Resources provided in conducting assessments for recurrence of thyroid cancer (at point G in both arms in Figure 3)										
- Quantitation of serum Tg levels MBS Item 66650	Laboratory	Laboratory	100% of patients in both arms	1 at 10 months and 1 at 28 months unless patient is non-compliant or there is recurrence of cancer and then 1 every 24 months unless patient experiences late stage cancer	Not specified					$24.50/test
- Tg antibody test MBS Item 71165	Laboratory	Laboratory	100% of patients in both arms	1 at 10 months and 1 at 28 months unless patient is non-compliant or there is recurrence of cancer	Not specified					$34.80/test
- Follow-up specialist consultation MBS Item 108	Specialist	Clinic			Not specified					$76.40/visit
- Whole body study using radioactive iodine MBS Item 61426	Approved provider	Approved facilities	100% of patients in both arms	1 at 10 months only	Not specified					$554.80/study
- GP visits to manage hypothyroidism MBS Item	GP	Clinic	57.4% of patients managed by THT withdrawal	1 at 10 months and 1 at 28 months unless patient is non-compliant or there is recurrence of cancer	Not specified					$34.90/visit
- Specialist visits to manage hypothyroidism MBS Item 108	Specialist	Clinic	42.1% of patients managed by THT withdrawal		Not specified					$76.40/visit

	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					Total cost per unit
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	
Resources used to manage recurrent cancer (at point L and point R in both arms in Figure 3)										
- Ablation with radioactive iodine MBS Item 16006	Approved provider	Approved facility	100% of patients diagnosed with recurrence of thyroid cancer	1 per patient diagnosed with recurrent thyroid cancer	Not specified					$480.95
- Time in radioprotective ward	Hospital	Hospital			Not specified					$1,376.83/day
- Administration of Thyrogen® for ablation	PBS	Community			Not specified					$2,302.25 / administration
- Quantitation of serum Tg levels MBS Item 66650	Laboratory	Laboratory			Not specified					$24.50/test
- Tg antibody test MBS Item 71165	Laboratory	Laboratory			Not specified					$34.80/test
- Follow-up specialist consultation MBS Item 108	Specialist	Clinic			Not specified					$76.40/visit
- Whole body study using radioactive iodine MBS Item 61426	Approved provider	Approved facilities			Not specified					$554.80/study
- "Lifetime thyroid cancer" costs [breakdown not provided by application]	Not specified	Not specified	100% of those who develop late stage cancer over the time horizon examined	1 (assigned upon death due to cancer)	Not specified					$14,122.25 / patient
Other resources provided to patients										
- Thyroxine sodium 200mcg tablets (T4)	PBS	Community	100% of patients in both arms over time horizon examined[b]	1 week's supply per week	Not specified					$27.43/pack of 200; converted to $0.96 per week
- Liothryoxine sodium 20mcg tablets (T3)	PBS	Community	5% of patients in the withdrawal of THT arm for 4 weeks prior to assessment for recurrence of thyroid cancer	1 pack prior to assessment for recurrence of thyroid cancer	Not specified					$82.30/pack of 100

[a] estimated by subtracting PBS dispensed price from MBS schedule fee for thyrotropin alfa-rch

[b] The only exception is that these costs are not included for 4 weeks prior to assessment for recurrence of cancer in patients managed by withdrawal of THT

Proposed structure of economic evaluation (decision analytic)

Table 9 presents a summary of the extended PICO for comparisons of thyrotropin alfa-rch with withdrawal from THT (in patients who would withdraw from THT prior to assessment of serum Tg) and with no withdrawal from THT (in patients who refuse to withdraw from THT prior to assessment of serum Tg).

Table 9: Summary of extended PICO to define question for public funding that assessment will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
Patients who have had well differentiated thyroid cancer and who have been successfully treated by thyroidectomy followed by an ablative dose of radioactive iodine who are maintained on thyroid hormone therapy and who require monitoring for recurrence of thyroid cancer	Thyrotropin alfa-rch followed by assessment for recurrence of thyroid cancer either by assessment of serum Tg or whole body study of radioactive iodine	For patients who are compliant with instructions to withdraw from thyroid hormone therapy, the appropriate comparator is withdrawal of thyroid hormone therapy prior to assessment for recurrence of thyroid cancer (by assessment of serum Tg [with or without whole body study of radioactive iodine and/or neck ultrasound]) For patients who are not compliant with instructions to withdraw from thyroid hormone therapy, the appropriate comparator is unstimulated Tg assessment for recurrence of thyroid cancer (with or without whole body study of radioactive iodine and/or neck ultrasound)	• Diagnostic accuracy of TSH-stimulated (endogenously or exogenously) serum Tg or whole body study using radioactive iodine • Compliance with follow-up (assumed in the application to impact on rates of detection of recurrence of thyroid cancer and, consequently, on survival over the long term) • Quality of life over time (patients in the hypothyroid state are assumed to experience a poorer quality of life compared with euthyroid patients)	• Administration of thyrotropin alfa-rch • Quantitation of serum TSH levels (used to determine whether patient is adequately hypothyroid when stimulating TSH by withdrawal of THT) • Medical consultations • Assessment of serum Tg • Whole body study using radioactive iodine • Resources used to manage symptoms of hypothyroidism • Resources used to manage recurrence of thyroid cancer • Resources used to manage adverse events associated with thyrotropin alfa-rch

The application presents a stepped economic evaluation to examine the cost-effectiveness of thyrotropin alfa-rch.

- Step 1 (preliminary economic analysis) only captures the costs and effects accrued during the diagnostic testing period for both thyrotropin alfa-rch and THT-withdrawal-stimulated arm over a 13 week period.
- Step 2 (20 year analysis) also captures the costs and effects accrued during the diagnostic testing period, however, Step 2 also captures any therapeutic radioiodine ablation episodes, the waiting periods between tests and ablation periods, the impact of poor compliance with follow up in the THT-withdrawal-stimulated arm and the impact of late stage cancer and premature cancer mortality.
- Step 3 (lifetime analysis – base case) is identical to Step 2 except that the time horizon of the economic model is extended to the patient's lifetime.

The structure of the base case economic evaluation presented in the application is summarised in Figure 3. As shown in this figure, a Markov model is used to conduct the economic evaluation. The same Markov processes are used in each arm of the model although the probability of transitions across health states sometimes varies across the arms. The model includes the following health states and transitions:

1. All patients enter the model immediately after thyroidectomy (point A in Figure 3).
2. All patients are assumed to be scheduled for an initial post-thyroidectomy assessment of Tg and whole body study using radioactive iodine following TSH-stimulation (either exogenously by thyrotropin alfa-rch [in the arm representing the proposed scenario] or endogenously by withdrawal of THT [in the comparator arm]). The economic analysis assumes this assessment occurs, on average, 10 months after the initial treatment for well differentiated thyroid cancer.
    - Patients are assumed to be alive & free of late-stage cancer or to have late-stage cancer or be dead at the time of this scheduled post thyroidectomy assessment (points B & C in Figure 3).
        - Patients with late-stage cancer are progressed through a Markov process where they are either survive or die at the end of each cycle (i.e., move to health state labelled Q in Figure 3).
        - Patients who are alive & free of late stage cancer are classified as having recurrence of thyroid cancer (disease positive) or not (disease negative). At 10 months, 50% are assumed to have recurrence of disease and 50% are assumed to be disease negative (point D in Figure 3).
        - All patients are assumed to be compliant with monitoring by stimulated thryoglobulin assessment that is scheduled at 10 months (i.e., at point E in Figure 3).
            - Patients treated with endogenous TSH stimulation are assumed to experience "pre-test" and "post-test" periods (at points F and H, respectively, in Figure 3) associated with hypothyroidism whereas patients treated with exogenous TSH do not experience these periods.
            - Quantitation of Tg together with whole body study using radioactive iodine is assumed to be 100% accurate in determining whether a patient has recurrence of thyroid cancer (at point J in Figure 3).

- Patients who test positive are assumed to be treated with further ablation (i.e., move to health state labelled K in Figure 3). Following treatment (at point M in Figure 3), patients are returned to the health state described in 1. above and are assumed to have another assessment scheduled 10 months following treatment.
- Patients who test negative are assumed to have another monitoring test scheduled, on average, in 18 months' time (i.e., at 28 months post total thyroidectomy).
    - Patients are assumed to be alive & free of late-stage cancer or to have late-stage cancer or be dead at the time of this scheduled post thyroidectomy assessment (points B & C in Figure 3).
        - Patients with late-stage cancer are progressed through a Markov process where they are either survive or die at the end of each cycle (i.e., move to health state labelled Q in Figure 3).
        - Patients who are alive & free of late stage cancer are classified as having recurrence of thyroid cancer (disease positive) or not (disease negative) – at point D in Figure 3. At 28 months, 20% of patients (all of whom tested negative at 10 months) are assumed to have recurrence of disease and 80% are assumed to be disease negative.
        - 20% of patients having TSH stimulated endogenously are assumed to be non-compliant with withdrawal from THT prior to assessment of serum Tg (point E in Figure 3). These patients are assumed to be managed by low intensity follow-up (unstimulated Tg testing every 12 months). These patients move to health state labelled O in Figure 3)
            - Unstimulated Tg testing every 12 months is implicitly assumed to have no sensitivity in detecting recurrence. Patients are assumed to be alive with or without progression of recurrent disease (if present) or dead at the time of their next scheduled low-intensity post thyroidectomy assessment.
        - 80% of patients are assumed to undergo TSH stimulated Tg assessment.
            - Patients treated with endogenous TSH stimulation are assumed to experience "pre-test" and "post-test" periods (at points F and H, respectively, in Figure 3) associated with hypothyroidism whereas patients treated with exogenous TSH do not experience these periods.
            - Quantitation of Tg alone (without whole body radioactive iodine scan) is assumed to have 81% sensitivity and 100% specificity in determining whether a patient has recurrence of thyroid cancer (at point J in Figure 3).
                - Patients who test positive are assumed to be treated with ablation (i.e., move to health state labelled K in Figure 3). Following treatment, patients are returned to the health state described in 1. above and are assumed to have another assessment scheduled 10 months following treatment.

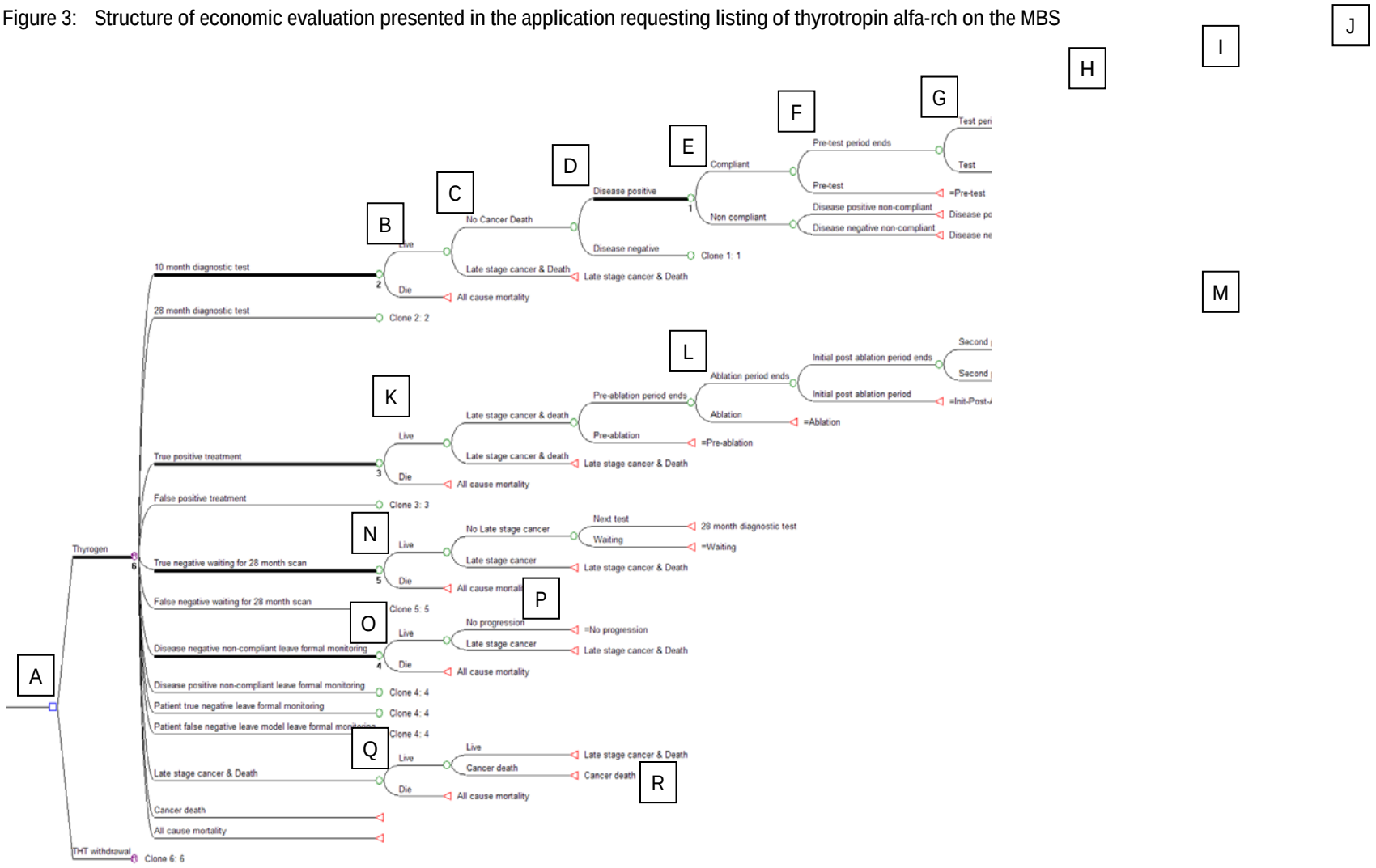
- Patients who test negative (i.e., have tested negative at both 10 months and 28 months post thyroidectomy) are assumed to be at low risk of recurrence of thyroid cancer and are assumed to be followed up by low-intensity unstimulated Tg assessment every 24 months.
  - Unstimulated Tg testing every 24 months is implicitly assumed to have no sensitivity in detecting recurrence. Patients are assumed to be alive with or without progression of recurrent disease (if present) or dead at the time of their next scheduled low-intensity post thyroidectomy assessment.

The PASC and the clinical experts were concerned that insufficient evidence would be available to support the assumption in the economic evaluation that patients having TSH levels increased by administration of thryotropin alfa-rch were more compliant with monitoring by stimulated Tg assessment at 28 months post total thyroidectomy and that this had a consequent significant impact on rates of detection of recurrence of thyroid cancer and on survival over the long term. As discussed on p.17, the PASC considered that the estimate in the base case modelled economic evaluation, that 20% of patients were non-compliant with monitoring recommendations and undergo unstimulated quantitation of serum Tg, was likely to be an overestimate. The PASC requested that any estimate of non-compliance rates included in the base case should be supported by appropriate evidence that does not take into account use of unstimulated Tg assessment due to physician discretion rather than patient choice. Sensitivity analysis around this parameter in the model was requested. A rate of 0% non-compliance should be included in the sensitivity analysis. The PASC and the clinical experts also expressed concern that inadequate evidence would be available to support the assumption of a 50% recurrence rate at 10 months and another 20% recurrence rate at 28 months. As shown in Table 6 and Table 7, the proportion of patients with persistent/recurrent disease at initial follow-up and over time in practice appears to be substantially lower than assumed in the economic evaluation presented in the application. The PASC advised that the base case modelled economic analysis presented in the application should be respecified to include more reasonable estimates of non-compliance and recurrence rates.

The PASC agreed with considerations by the clinical experts that the application's implicit assumption that unstimulated Tg assessment had no sensitivity in detecting recurrent thyroid cancer was also inappropriate. The inclusion of costs but no benefits from such testing in the economic evaluation was considered inappropriate.

The PASC advised that presentation of a stepped analysis that included steps that addressed assumptions associated with substantial uncertainty would be appropriate.

Figure 3: Structure of economic evaluation presented in the application requesting listing of thyrotropin alfa-rch on the MBS



References

[i] Tuttle RM et al. Estimating Risk of Recurrence in Differentiated Thyroid Cancer After Total Thyroidectomy and Radioactive Iodine Remnant Ablation: Using Response to Therapy Variables to Modify the Initial Risk Estimates Predicted by the New American Thyroid Association Staging System. *Thyroid*. 2010; 20(12):1341-9