Recombinant human thyroid-stimulating hormone (rhTSH)

Diagnostic agent for use in well-differentiated thyroid cancer

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Assessment report

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The Medical Services Advisory Committee is an independent committee that has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Adèle Weston, Mr Lachlan Standfield and Mr Paul Mernagh from M-TAG Pty Ltd. The report was endorsed by the Commonwealth Minister for Health and Ageing on 16 October 2002.

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MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Thyrogen™ (thyrotropin alpha for injection) contains a highly purified recombinant form of human thyroid-stimulating hormone (rhTSH[1]). This report summarises the efficacy, safety and cost-effectiveness of rhTSH as a diagnostic agent for well-differentiated thyroid cancer, on the basis of the currently available evidence and in the context of the Australian public health care setting. This review is specific to well-differentiated papillary and follicular cancer, for which current practice guidelines recommend regular follow-up monitoring by radioiodine whole body scanning (WBS) and serum thyroglobulin (Tg) testing.

The treatment for the majority of patients with well-differentiated papillary or follicular thyroid cancer is a total or near-total thyroidectomy followed by an ablative dose of radioiodine (^{131}I). Patients are then treated with synthetic thyroid hormones, predominantly thyroxine sodium (T_4), to replace endogenous hormones and suppress TSH secretion. The synthetic hormone T_4 suppresses serum levels of TSH and hence minimises TSH-induced tumour growth. Lower levels of TSH also reduce iodine uptake and Tg secretion by the remaining thyroid tissue or cancer. Therefore, periodic withdrawal of thyroid hormone therapy (THT withdrawal) is required to raise endogenous serum TSH levels for diagnostic radioiodine scanning and to enhance serum Tg testing sensitivity.

Currently, patients are monitored for the presence of thyroid cancer by Tg testing alone or in combination with radioiodine imaging, after withdrawal of thyroid hormone therapy. During withdrawal, patients may experience a period of severe hypothyroidism, which can produce fatigue, weight gain, depression, inability to carry out normal activities, and occasional significant illness. For patients in whom withdrawal is medically contraindicated, Tg testing while remaining on thyroid hormone therapy is performed. However, the diagnostic accuracy of this approach is known to be poor. In contrast, exogenous rhTSH artificially stimulates the uptake of iodine and Tg secretion by the thyroid tissue or cancer. This allows patients to remain on hormone suppression therapy and avoid hypothyroidism while being assessed for the presence of residual or recurrent cancer.

Reconstituted rhTSH is administered by a medical practitioner via intramuscular injection. Two doses are given, 24 hours apart, such that the second dose is given 24

[1]This assessment is based on evidence relating to Thyrogen™, a product marketed by Genzyme Australasia Pty Ltd. Notwithstanding any difference between Thyrogen™ and other current or future rhTSH compounds, it is intended that the findings of this health technology assessment will be applicable to all brands of rhTSH.

hours prior to radioiodine administration. Diagnostic scanning occurs 48 hours later. A blood sample is obtained at the time of scanning for the measurement of serum Tg.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government 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.

A rigorous assessment of the available evidence is thus the basis of decision-making when funding is sought under Medicare. Medical Technology Assessment Group (M-TAG) Pty Ltd was contracted to conduct a systematic review and economic evaluation of rhTSH. A supporting committee with appropriate expertise then evaluated this evidence and provided advice to MSAC.

MSAC's assessment of rhTSH

Clinical need

Incidence

The Australian Institute of Health and Welfare (AIHW) statistics indicate that approximately 1000 patients were diagnosed with thyroid cancer in 1998 (273 males, 723 females). This represents approximately one per cent of all cancers diagnosed (excluding non-melanoma skin cancers). At diagnosis the vast majority of these patients have well-differentiated papillary or follicular thyroid cancer.

Mortality

Sixty-nine patients died from thyroid cancer in Australia in 1998. The number of patients diagnosed annually with thyroid cancer is approximately fourteen times the number who die from the disease, reflecting the high survival rate in this disease (AIHW and AACR 2001). Australian data indicate a 5-year relative survival rate of approximately 94 per cent for females and 92 per cent for males (Threlfall and Brameld 2000). Overseas sources report 5-year survival rates of treated patients with well-differentiated thyroid cancer ranging from 65–95 per cent (Lin *et al* 2001, National Statistics 2000, Tzavara *et al* 1999).

Long-term survival of patients with well-differentiated thyroid cancer is common, but patients are at risk of tumour recurrence for decades after diagnosis (Cobin *et al* 2002). Therefore, long-term surveillance of these patients is necessary.

Morbidity

Morbidity associated with well-differentiated thyroid cancer usually arises from treatment and monitoring procedures rather than disease *per se*. After initial diagnosis, patients

require surgical resection of the thyroid gland, a procedure which is associated with a risk of hypoparathyroidism and laryngeal nerve injury (Cobin *et al* 2002). Generally, patients are then required to undergo radioiodine ablation which requires a period of hospitalisation and may be associated with a number of short to long-term adverse effects (Alexander *et al* 1998). Patients then require lifetime daily treatment with thyroid hormone therapy, which may have adverse effects on the heart and bones (Burman 1995). Patients also require lifetime monitoring to detect disease recurrence. Currently, monitoring for differentiated thyroid cancer requires patients to endure up to 12 weeks of hypothyroidism. Hypothyroidism is associated with fatigue, decreased appetite, pain, sleep disturbance, constipation, impaired motor skills, psychological changes and fluid retention. Hypothyroidism also has the potential to result in temporary swelling of a tumour, which is undesirable in some tumour locations. Progression to metastatic disease may be associated with significant morbidity.

Therefore, periods of morbidity associated with hypothyroidism and hospitalisations associated with radioiodine ablation/treatment of recurrent or residual disease are features of the disease. These have the potential to impact on work productivity and family life, particularly as the disease is normally diagnosed in patients who are of working age.

Safety

To date, approximately 800 patients have received rhTSH in clinical trials. In general, the adverse events associated with the use of rhTSH appear to be mild in nature. The most commonly reported adverse events reported in association with rhTSH use are headache and nausea. However, there are also individual case studies that report serious adverse events associated with the swelling of metastases after rhTSH administration. To reduce the incidence of these serious adverse events, pre-treatment with corticosteroids may be considered prior to the administration of rhTSH in patients with metastatic disease in confined spaces. Furthermore, the adverse events associated with rhTSH should be considered in the context of the hypothyroidism experienced by patients undergoing THT withdrawal.

Effectiveness

This assessment focuses primarily on the cohort of patients who had already had one negative follow-up using the current THT withdrawal method. However, for completeness, implications for use in a broader population of patients are also considered.

Accuracy and precision

The primary efficacy measure was the diagnostic accuracy using rhTSH compared with the comparator of THT withdrawal. Two studies classified as containing level 2 diagnostic evidence were considered, as these represented the best available evidence.

When used with concurrent serum Tg testing and whole body scanning (a positive patient being defined as a positive result in *either* detection method), the unadjusted

sensitivity of rhTSH was 87 per cent, specificity was 95 per cent and accuracy 89 per cent.

When used with serum Tg testing alone (as may be the case in remote locations), the unadjusted sensitivity of rhTSH was 69 per cent, specificity was 100 per cent and accuracy 77 per cent.

These results were considered generalisable to the broader population of patients that includes those presenting for their first diagnostic follow-up.

Quality of life

Quality of life (QOL) evidence in this assessment comes from open-labelled trials in which the order of the diagnostic interventions was neither balanced nor randomised. Nevertheless, this evidence indicates a poorer general and thyroid-specific quality of life during THT withdrawal compared with rhTSH. The magnitude of the differences was considerable.

The quality of life data from the SF-36 survey were used to derive health utility values. The resultant utilities for the temporary health state of hypothyroidism is 0.650 compared with 0.825 for patients receiving rhTSH. These utility values summarise the quality of life advantage of rhTSH relative to THT withdrawal, although it is important to remember that this benefit is transient and infrequent. This factor is incorporated in the decision-analytic model that estimates the time spent in each health state in the first five years post-thyroidectomy, while also considering the diagnostic accuracy of rhTSH and the comparator.

Improved compliance with disease status monitoring

The effectiveness of THT withdrawal is reduced as some patients fail to comply with follow-up in order to avoid a period of hypothyroidism. However, the extent of the non-compliance is not known.

Increased compliance resulting from avoidance of a hypothyroid period when using rhTSH is incorporated into the analysis.

Cost-effectiveness

This assessment used a decision-analytic cost-utility model to determine the cost-effectiveness of rhTSH relative to THT withdrawal, in the cohort of patients who have already had one negative follow-up using THT withdrawal. The average cost per patient in the rhTSH arm was $6761 for the five-year period. The equivalent cost for THT withdrawal was $2309, resulting in an incremental cost of $4452. The average number of quality-adjusted life-years (QALYs) for rhTSH arm was 3.81, only marginally greater than that on THT withdrawal, 3.72. Therefore, the incremental utility was 0.09. The difference in utilities is small because the hypothyroid state induced by THT withdrawal prior to scanning is brief. With significantly increased cost and only a marginal improvement in average utility, the incremental cost-effectiveness in this specific patient group is $51,344 per QALY.

The total population for whom the diagnostic use of rhTSH is indicated is small. For this reason, the total financial impact of public reimbursement is likely to be modest.

Recommendation

MSAC recommended that on the strength of evidence pertaining to the diagnostic use of recombinant thyroid-stimulating hormone in well-differentiated thyroid cancer, public funding should be supported for this procedure only in patients in whom THT withdrawal is medically contraindicated. In addition, on the basis of the current evidence, both rhTSH-stimulated whole body scanning and serum Tg testing should be undertaken concurrently. MSAC recommends that public funding for rhTSH should not be supported in patients who are able to tolerate THT withdrawal, on the basis of lower diagnostic accuracy and a high cost-effectiveness ratio.

The Minister for Health and Ageing accepted this recommendation on 16 October 2002.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of recombinant human thyroid-stimulating hormone (rhTSH), which is a diagnostic agent for well-differentiated thyroid cancer. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for rhTSH for use with radioiodine imaging and serum thyroglobulin (Tg) testing, undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy and at risk of recurrence. This assessment focuses primarily on the cohort of patients who have already had one negative follow-up using the current THT withdrawal method.

Background

Recombinant human thyroid-stimulating hormone (rhTSH)

The procedure

Thyrogen™ (thyrotropin alpha for injection) contains a highly purified recombinant form of human thyroid-stimulating hormone (rhTSH[2]). Genzyme Australasia Pty Ltd has proposed the following listing for Thyrogen™.

> "For use with radioactive iodine imaging and serum thyroglobulin (Tg) testing, undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy and at risk of recurrence."

The treatment for the majority of patients with thyroid cancer is a total or near-total thyroidectomy followed by an ablative dose of radioiodine (^{131}I). Patients are then treated with synthetic thyroid hormones, predominantly thyroxine sodium (T_4), to replace endogenous hormones. The synthetic hormone T_4 also suppresses serum levels of thyroid-stimulating hormone (TSH), and hence minimises TSH-induced tumour growth. Lower levels of TSH reduce iodine uptake and Tg secretion by the thyroid tissue. Therefore, periodic thyroid hormone therapy withdrawal (THT withdrawal) is required to raise endogenous serum TSH levels for radioiodine scanning and enhance serum Tg testing sensitivity.

Currently, patients are monitored for residual or recurrent thyroid cancer by Tg testing alone or in combination with radioiodine imaging, after withdrawal of thyroid hormone therapy. During withdrawal, patients may experience a period of severe hypothyroidism, which can produce fatigue, weight gain, depression, inability to carry out normal activities and occasional significant illness. For patients in whom THT withdrawal is medically contraindicated, Tg testing is carried out while the patient remains on thyroid hormone therapy; however, the diagnostic accuracy of this approach is known to be poor.

In contrast, exogenous rhTSH artificially stimulates the uptake of iodine and thyroglobulin (Tg) secretion by the thyroid tissue, allowing patients to remain on THT and avoid hypothyroidism while being assessed for the presence of residual or recurrent cancer.

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[2]This assessment is based on evidence relating to Thyrogen™, a product marketed by Genzyme Australasia Pty Ltd. Notwithstanding any difference between Thyrogen™ and other current or future rhTSH compounds, it is intended that the findings of this health technology assessment will be applicable to all brands of rhTSH.

Reconstituted rhTSH is administered via intramuscular injection to the buttock. Thyrogen™ is supplied as a sterile, non-pyrogenic, lyophilised product. It is available as a kit containing two 1.1 mg vials (> 4 IU) of rhTSH. The powder is reconstituted immediately prior to use with 1.2 mL of the diluent provided. Each vial of rhTSH is intended for single use. Two doses of rhTSH 0.9 mg are administered 24 hours apart. It is proposed that patients will collect the refrigerated medication from the pharmacy, and take it to their medical practitioner for injection over two consecutive days. Radioiodine administration would then take place 24 hours after the second injection, with scanning being carried out a further 48 hours later. A blood sample is obtained at the time of scanning for the measurement of serum Tg.

Intended purpose

The TGA-listed indication for rhTSH is for use with radioiodine imaging and Tg testing, undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy and at risk of recurrence. This assessment focuses primarily on the cohort of patients who have already had one negative follow-up using the current THT withdrawal method.

Clinical need/burden of disease

Incidence of thyroid cancer

The Australian Institute of Health and Welfare (AIHW) has published statistics on the incidence of various cancers occurring each year in the Australian population. The most recent data show that 996 new cases of thyroid cancer were diagnosed in 1998 (273 males, 723 females; (AIHW and AACR 2001)). This compares with 860 new cases diagnosed in 1997, 897 new cases diagnosed in 1996, and 808 cases in 1995. In total, there were 80,864 patients diagnosed with any type of cancer in 1998 (excluding non-melanoma skin cancers) and therefore the proportion diagnosed with thyroid cancer was approximately 1 per cent. In 1997, thyroid cancer was the twenty-sixth most commonly diagnosed cancer (AIHW and AACR 2000). At diagnosis the vast majority of these patients have well-differentiated papillary or follicular thyroid cancer.

Mortality due to thyroid cancer

The numbers of patients who died from thyroid cancer in Australia in 1998, 1997 and 1996 were 69, 71, and 72, respectively. Of the 69 deaths in 1998, 37 were males and 32 were females. In total, there were 34,270 deaths attributed to cancer for that year, and the proportion of patients who died from thyroid cancer was 0.2 per cent. The number of patients diagnosed annually with thyroid cancer is approximately fourteen times the number who die from the disease, reflecting the high survival rate in this disease (AIHW and AACR 2001).

In Australia, cancer data are collated by cancer registries in each state. Data available from Western Australia indicate a 5-year relative survival of approximately 94 per cent

for females and 92 per cent for males (Threlfall and Brameld 2000). Overseas sources report the 5-year survival with treatment for well-differentiated thyroid cancer as approximately 95 per cent in the US, Greece and Taiwan. Other areas, such as the UK and other European countries, report lower 5-year survival rates in the range 65–80 per cent (Lin *et al* 2001, National Statistics 2000, Tzavara *et al* 1999)

The prognosis of patients with thyroid cancer is affected by factors related to the patient, the disease and treatment. Favourable patient and disease-related factors are a young age, a small and histologically well-differentiated primary tumour and a tumour limited to the thyroid gland or at least the neck. The prognostic factors related to treatment are less clear due to the lack of randomised and appropriately controlled therapeutic clinical trials (Cobin *et al* 2002). Currently debated treatment issues include the following: the extent of primary surgical resection; the need for and the extent of regional lymph node resection; the role of postoperative radioiodine remnant ablation; and the degree of suppression needed in long-term management.

Morbidity

Morbidity associated with well-differentiated thyroid cancer arises primarily from treatment and monitoring procedures rather than the disease *per se*. After initial diagnosis, patients require surgical resection of the thyroid gland followed by radioiodine ablation.

Thyroid surgery and radioiodine ablation have a low risk of significant complications (Cobin *et al* 2002). Radioiodine treatment requires a period of hospitalisation and may be associated with short-term (Lin *et al* 1996) or longer term adverse reactions (Alexander *et al* 1998).

Currently, routine monitoring requires a period of withdrawal from thyroid hormone therapy. Depending on the duration of withdrawal and subsequent restoration of euthyroid status, the patient may be rendered hypothyroid for up to 12 weeks. Hypothyroidism is associated with fatigue, decreased appetite, pain, sleep disturbance, constipation, impaired motor skills, psychological changes and fluid retention. However, the extent of the hypothyroidism will be variable throughout this period, with the worst symptoms occurring around the time of scanning. Hypothyroidism also has the potential to result in temporary swelling of a tumour, which is undesirable in some tumour locations.

Therefore, periods of morbidity associated with hypothyroidism and, if necessary, hospitalisations associated with radioiodine ablation/treatment of recurrent or residual disease, are a feature of the disease. These have the potential to impact on work productivity and family life, particularly as the disease is normally diagnosed in patients who are of working age. Quantification of the impact of hypothyroidism on a patient's quality of life is discussed in more detail later in this report.

Furthermore, the need for medication (predominantly T_4) is required to suppress endogenous thyroid hormones for the remainder of the patient's life. Long-term thyroid hormone therapy may have adverse effects on bone and the heart, including accelerated bone turnover, osteoporosis and atrial fibrillation (Burman 1995, Cobin 1995, Sawin *et al* 1994). Consequently, individual dose titration is required, and many experts maintain that

long-term complete TSH suppression should be reserved for higher risk patients (Cobin *et al* 2002). Transient excessive doses of T_4 can lead to the manifestations of thyrotoxicosis. Importantly, the requirement for ongoing daily medication and monitoring may also impact on the patient's quality of life. Furthermore, as with all medications, the patient and physician need to consider potential drug interactions.

If progression to metastatic disease occurs, distant metastases may be associated with significant morbidity. Examples are tumours located in the lung, brain, bone or adjacent to the spinal cord. If progression to undifferentiated disease occurs, radioiodine ablation is ineffective. While surgical treatment remains an option in some situations, the prognosis deteriorates considerably. Patients who fail to comply with routine monitoring may progress to metastatic and/or undifferentiated disease without prior symptoms.

Estimation of clinical need for the rhTSH diagnostic use of rhTSH

To estimate the clinical need for rhTSH in a diagnostic role it is preferable to estimate the number of procedures undertaken in this group of patients annually, rather than the number of patients. This approach takes into account multiple use of diagnostic procedures by one patient within the year, as well as infrequent monitoring that occurs in later years when patients remain disease-free. It therefore reflects the likely clinical need for the diagnostic procedure.

Nevertheless, patient statistics are of interest and are presented here for completeness.

Estimated new patients annually

There were 2121 hospital separations recorded in 1999–2000 for patients who had a principle diagnosis code of malignant neoplasm of the thyroid gland (Principle Diagnosis Code C73). Of these, 1636 were in public hospitals and 485 in private hospitals; 538 were males and 1583 were females. Fifty-two per cent of the separations occurred in patients aged 30–55 years (AIHW 2002). The figure of 2121 separations may incorporate multiple visits to hospital by the same patient for a range of procedures, and therefore is an overestimation of the number of patients diagnosed with thyroid cancer.

Also available from AIHW are separations according to procedure block. The total number of separations for procedure block 115 (total thyroidectomy) in the year 1999–2000 was 5579 (public 3761, private 2832) (AIHW 2001b, AIHW 2001a).

Of the 2121 separations for thyroid cancer patients and the 5579 separations for thyroidectomy, 1581 separations occurred in patients who had a principal diagnosis of thyroid cancer *and* who underwent a total thyroidectomy (971 public, 610 private).[3] In summary, the annual number of patients with a principal diagnosis of thyroid cancer *and* who underwent a total thyroidectomy (1581) represents an estimation of the minimum number of new patients meeting the rhTSH indication annually.

[3]Personal communication from AIHW.

Estimated number of diagnostic procedures annually

Tertroxin (T_3; liothyronine sodium) is used by some clinicians to ease the symptoms of THT withdrawal. Statistics from the Pharmaceutical Benefits Schedule (CDHA 2002) and the Repatriation Pharmaceutical Benefits Schedule (RPBS) (CDHA 2002) show that a total of 5878 prescriptions for Tertroxin (item number 2318B, 100×20 μg) were filled on the PBS and RPBS in the year 2000–2001 (HIC 2002b). However, this figure is not representative of the number of patients undergoing T_4 withdrawal, as many clinicians do not use T_3 during T_4 withdrawal periods. Furthermore, T_3 is reimbursed for several indications (management of patients with thyroid cancer; replacement therapy for hypothyroid patients who have documented intolerance or resistance to thyroxine sodium; initiation of thyroid therapy in severely hypothyroid patients).

A better alternative is to review the number of whole-body diagnostic radioiodine scans conducted annually. A scan is usually conducted at each scheduled follow-up in conjunction with serum Tg testing, although some patients may have Tg testing alone, particularly when access to scanning is difficult. Statistics from the Medicare Benefits Schedule (2001) show that 985 patients underwent a whole-body diagnostic radioiodine scan (item number: 61426) in the year 2000–2001 (HIC 2002a). However, this represents only those patients treated outside of the public hospital system. Similarly, it excludes the smaller number of scans reimbursed by the Department of Veterans' Affairs.

If this figure is upscaled by the public:private ratio calculated for total thyroidectomy (1.56:1), then it is estimated that a total of 2526 scans are performed annually (1541 public:985 private).

Since patients do not have a radioiodine scan every year of follow-up, this figure should be viewed as 'number of procedures' rather than 'number of patients', and should equate with the potential number of courses of rhTSH given in one year. However, this estimate still excludes any patients currently monitored with a serum Tg test alone.

In summary, the best available estimate of the potential number of courses of rhTSH in one year, based on current treatment, is 2526. However, improved monitoring compliance and increased use by patients for whom THT withdrawal is medically contraindicated will inflate this estimate.

Patient subpopulations in whom rhTSH diagnostic use is indicated

Of the patients with thyroid cancer who have undergone a thyroidectomy and ablation, it is assumed that all would require follow-up testing for cancer recurrence by radioiodine uptake and serum Tg levels. At a minimum, patients suitable for rhTSH administration would be those who: are unable to raise endogenous TSH levels to that required for optimal radioiodine imaging (Ringel and Ladenson 1996); have a tumour adjacent to the central nervous system (Ladenson 1999); have a concomitant medical condition, such as renal failure or heart failure, that makes thyroid hormone withdrawal medically contraindicated (Mazzaferri and Kloos 2000); or have previously experienced a serious medical or psychiatric complication of short-term hypothyroidism. Of this group of patients, rhTSH may have a particularly important role in those who have a positive on-T_4 Tg test, who otherwise would require a battery of diagnostic imaging procedures.

It is evident that the majority of thyroid cancer patients with hypothyroidism due to THT withdrawal suffer a significant, albeit transient, decrease in their quality of life and, in many cases, losses in work productivity. A quality-of-life (QOL) study of thyroid cancer patients (Dow *et al* 1997) has shown that common physical changes associated with hypothyroidism include fatigue, decreased appetite, pain, sleep disturbance, constipation, motor skills and fluid retention. Psychological changes occur in the areas of perceived coping, overall QOL, happiness, sense of control, satisfaction, concentration, usefulness, appearance, anxiety and depression. However, it is important to remember that the periods of hypothyroidism are relatively brief (up to 12 weeks) and infrequent.

Patients who test positive for serum Tg antibodies cannot be accurately assessed with a serum Tg test, whether stimulated with THT withdrawal or rhTSH. Whole body scanning can be used instead in this patient subgroup, but this may be problematic for patients in rural and remote locations.

The primary review was limited to diagnostic use of rhTSH in the routine follow-up of patients whose post-thyroidectomy and/or ablation withdrawal scan was negative, as long as the scans remain negative.

Existing procedures

Currently, post-thyroidectomy/ablation patients are routinely monitored[4] for the presence of residual or recurrent cancer in one of the following three ways.

- Tg testing *and* radioiodine imaging after hormone suppression therapy withdrawal
- Tg testing after hormone suppression therapy withdrawal
- Tg testing while the patient remains on hormone suppression therapy.

No statistics are available to determine precisely the proportion of patients within each of these categories. For the purpose of this review, expert opinion estimated that the majority of patients have serum Tg testing *and* radioiodine scanning after THT withdrawal, whilst serum Tg testing alone is more common in patients living in rural and remote areas. A smaller proportion of patients have serum Tg testing while they remain on THT because THT withdrawal is medically contraindicated[5].

[4]For the purpose of this review, expert opinion has estimated that, on average, Australian routine monitoring occurs at six months, one year, three years and five years after initial treatment. If patients subsequently test positive and require further treatment, they then recommence monitoring at the beginning of this schedule.

[5]Hypopituitarism, functional metastases, ischaemic heart disease, severe psychiatric disturbances when hypothyroid, very advanced disease or frailty.

Comparator

The comparator is considered to be the testing procedure most likely to be replaced in practice by the rhTSH testing procedure. In the majority of cases this is THT withdrawal. However, in some patients THT withdrawal is medically contraindicated and testing is undertaken while on THT (**Table 1**).

Table 1 Comparator regimens

	Detection mode	
	WBS + serum Tg result	**Serum Tg alone**
Primary evaluation Only patients who have had a negative post-treatment diagnostic test[a]	WBS + serum Tg after THT withdrawal	Serum Tg after THT withdrawal
Secondary evaluations		
All patients presenting for diagnostic testing	WBS + serum Tg after THT withdrawal	Serum Tg after THT withdrawal
Patients for whom THT withdrawal is medically contraindicated[b]	On-THT serum Tg, then: if negative, watchful waiting if positive, thallium scan and/or PET scan	

Abbreviations: Tg, thyroglobulin; THT, thyroid hormone therapy; PET, positron emission tomography; WBS whole body radioiodine scan

[a]Generally, post-treatment diagnostic tests are performed six months after treatment. However, at the suggestion of the applicant, the primary assessment excludes patients having their first post-treatment follow-up. The excluded group will include both new patients and patients with recurrent disease.

[b]Hypopituitarism, functional metastases, ischaemic heart disease, severe psychiatric disturbances when hypothyroid, very advanced disease, frailty.

Current practice guidelines recommend conducting both a whole body scan (WBS) and a serum Tg test. Therefore, this review will primarily consider the concurrent use of the two detection modes. In practice, patients receive treatment if *either* test is positive. In rural and remote areas of Australia, access to WBS may be limited. For this reason, the current assessment will also investigate the diagnostic accuracy of serum Tg testing alone.

Marketing status of the technology

Thyrogen™ obtained registration as an orphan drug from the Therapeutic Goods Administration (TGA) on the 14 September 2001.[6] The Australian Registry of Therapeutic Goods number for the drug is ARTG 79777. The TGA-listed indication for Thyrogen™ is:

> "For use with radioactive iodine imaging and serum thyroglobulin (Tg) testing, undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy and at risk of recurrence".

Thyrogen™ is *not* approved by the TGA for therapeutic use and therefore this role is specifically excluded from this review.

Thyrogen™ was registered in the US by the Food and Drug Administration on the 30 November 1998 (application number: 020898) (FDA CDER 1998). The FDA-listed indication for Thyrogen™ is:

> "As an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the follow-up of patients with thyroid cancer".

Thyrogen™ was authorised for use in the European Union (EU) on the 9 March 2000 (EU number: 1 vial, EU/1/99/122/001; 2 vials EU/1/199/122/002) (European Communities 2002). The EU indication for Thyrogen™ is:

> "Thyrogen™ (thyrotropin alpha) is indicated for use with radioiodine imaging together with serum testing undertaken for the detection of thyroid remnants and well differentiated thyroid cancer in thyroidectomy patients".

Current reimbursement arrangement

There is no current reimbursement arrangement for Thyrogen™ (rhTSH) or its administration in Australia. The radioiodine WBS (item number: 61426) and the serum Tg test (item number: 66650) are currently reimbursed through Medicare.

[6]Personal communication, TGA, 8 July 2002.

Approach to assessment

Review of literature

The medical literature was searched to identify relevant studies and reviews for the period between 1980 and 2002.

Searches were conducted via the following primary databases:

- Premedline
- Medline 1966 to current
- Embase 1980 to current
- Cancerlit 1975 to current
- Econlit 1969 to current
- HealthSTAR 1975 to current

The search terms used included the following terms:

- Thyroid neoplasms; thyroidectomy; thyroid cancer; thyroid carcinoma; differentiated thyroid; thyroid remnant; neoplasm recurrence, local; residual neoplasm.
- Thyrogen™; recombinant human thyrotropin; recombinant thyrotropin; recombinant human thyroid stimulating hormone; recombinant thyroid stimulating hormone; recombinant human TSH; recombinant TSH; exogenous human thyroid stimulating hormone; exogenous thyroid stimulating hormone; exogenous human TSH; exogenous TSH; exogenous human thyrotropin; exogenous thyrotropin; rhTSH; rTSH; thyrotropin alpha; thyrotropin; 194100-83-9.

Complete details of the literature searches performed using the Medline and Embase databases are presented in **Appendix D**.

Searches of the following secondary databases/sites were also performed:

- The Cochrane Library
- British Columbia Office of Health Technology Assessment
- Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
- Centre for Health Program Evaluation (Monash University, Australia)

- Centre for Reviews and Dissemination (University of York, UK)
- Health Economics Research Group (Brunel University, UK)
- Health Information Research Unit (HIRU) internal database (McMaster University, Ontario, Canada)
- International Network of Agencies for Health Technology Assessment (INAHTA) (Sweden)
- International Society of Technology Assessment in Health Care (Montreal, Canada)
- National Health and Medical Research Council Australia Publication list
- National Health Service (UK)
- National Information Center on Health Services Research and Health Care Technology (HSTAT database) (US)
- Swedish Council on Technology Assessment in Health Care (SBU)
- US Office of Technology Assessment 1974–1995 (closed)
- US Health Care Financing Administration (HCFA).

Inclusion criteria

- A study comparing rhTSH with an appropriate reference standard.
- A study of patients with differentiated thyroid cancer.
- A study of rhTSH used as a diagnostic aid in testing for recurrent thyroid cancer or thyroid remnants.
- A study using the correct rhTSH dose regimen.

Exclusion criteria

- Non-systematic reviews or opinion pieces.
- Non-human or *in vitro* studies.
- A study of the therapeutic or ablative use of rhTSH.
- A study with 20 or fewer patients (efficacy and QOL assessment only).

The flow chart in **Figure 1** summarises the exclusion of studies from the effectiveness review of rhTSH. A complete list of the citations identified in the literature search is included in **Appendix E**, together with reasons for exclusion from the effectiveness review.

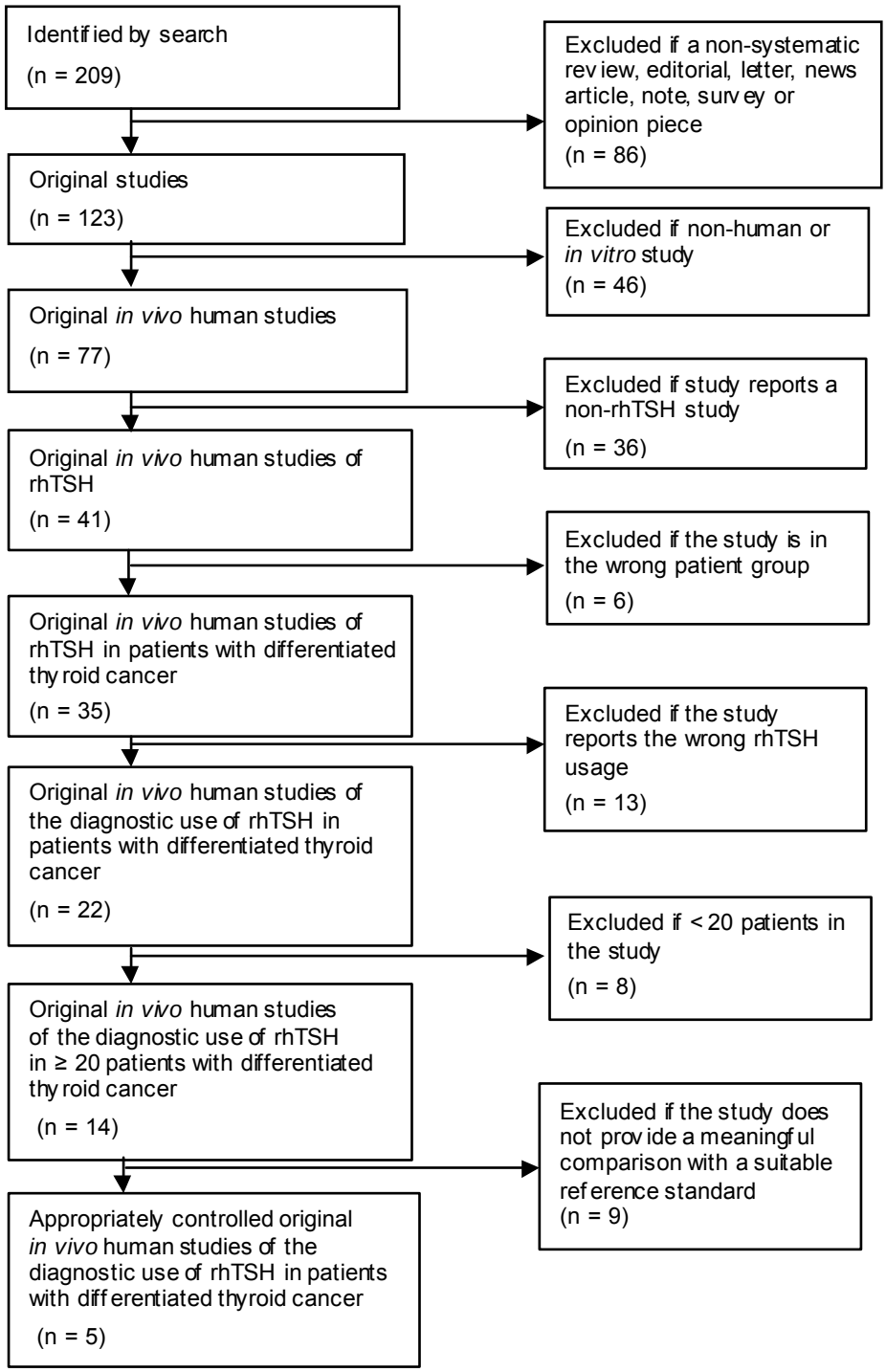

Figure 1 Reasons for exclusion of published and unpublished reports identified by the literature search

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000). These dimensions (**Table 2**) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the identified literature as informing a particular intervention. The last two require expert clinical input as part of the determination.

Table 2 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The *p* value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a]*See* ***Table 3***.

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in **Table 3**. These designations are specific to evidence relating to diagnostic tests (Bandolier 2002).

Table 3 Designations of levels of evidence

Level of evidence	Study design
1	An independent, masked comparison with reference standard among an appropriate population of consecutive patients
2	An independent, masked comparison with reference standard among non-consecutive patients or confined to a narrow population of study patients
3	An independent, masked comparison with an appropriate population of patients, but reference standard not applied to all study patients
4	Reference standard not applied independently or masked
5	Expert opinion with no explicit critical appraisal, based on physiology, bench research, or first principles

Source: Bandolier (2002).

A more detailed assessment of study quality was undertaken using a modification of the diagnostic-specific checklist published by the Cochrane Screening and Diagnostic Tests Methods group. Two evaluators independently scored each of the included studies. This enabled a quality score to be assigned to each study. Details of the checklist and scoring are provided in **Appendix F**.

Additional searches

Additional searches were conducted to examine the following:

- Quality of life data associated with hypothyroidism
- Economic evaluations of rhTSH
- Information required for the modelled economic evaluation.

Expert advice

A supporting committee with expertise in general surgery, endocrinology, endocrine surgery, nuclear medicine and radiation oncology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the supporting committee is provided at **Appendix B**.

Results of assessment

As shown in **Table 4,** a total of 14 relevant publications were identified by the literature search.

The literature search identified six comparative studies of rhTSH. One of these studies had fewer than 20 patients and, in accordance with the exclusion criteria, was excluded from the effectiveness assessment (Meier *et al* 1994). However, for completeness this study was reviewed for safety. Four of the comparative studies identified were prospectively designed and two were retrospective in design. Three studies reported blinding of the WBS evaluation and no studies reported blinding of the serum Tg tests. Eight non-comparative studies of rhTSH were also identified in the literature search. In line with the exclusion criteria, these trials were omitted from the effectiveness assessment. However, all non-comparative trials were reviewed for the safety assessment of rhTSH.

Due to the nature of THT withdrawal, it was not possible to blind the patients or clinicians to the diagnostic modes used. Therefore, all the studies identified were performed in an open-label fashion.

Table 4 Relevant studies identified

Study	Study design	Reviewed for safety assessment	Reviewed for effectiveness assessment
Comparative studies			
Haugen (1999)[a]	Prospective, evaluator-blinded[b], with sequential diagnostic measurements	✓	✓
Ladenson (1997)	Prospective, evaluator-blinded, with sequential diagnostic measurements	✓	✓
Mazzaferri and Kloos (2002)	Retrospective, with a combination of variable reference standards	✓	✓
Pacini (2001)	Prospective, with sequential diagnostic measurements	✓	✓
Robbins (2001)	Retrospective, parallel cohort	✓	✓
Meier (1994)	Prospective, dose ranging, evaluator blinded, with sequential diagnostic measurements	✓	x
Non-comparative studies			
Giovanni (2002)	Case series	✓	x
Braga (2001)	Case study	✓	x
David (2001)	Case series	✓	x
Lippi (2001)	Case series	✓	x
Petrich (2001)	Single-arm clinical trial in consecutive patients with historical controls	✓	x
Durski (2000)	Case series	✓	x
Mariani (2000)	Case series	✓	x
Vargas (1999)	Case study	✓	x

[a]Only arm 1 of the Haugen study utilised the dose and schedule of rhTSH recommended in the Product Information. Arm II was excluded from further analysis, including safety, as it used a higher dose than is recommended in the Product Information.
[b]Only blinded for WBS, not serum Tg.

Is it safe?

Assessment of the safety of rhTSH in the diagnostic testing of patients with differentiated thyroid cancer included comparative and non-comparative studies. Studies that described the use of rhTSH for the treatment of differentiated thyroid cancer were excluded from the safety review. Only patients who were administered the correct dosage of rhTSH in line with the manufacturer's recommended schedule were included in the safety review.

Table 5 summarises the safety data reported in three of the six identified comparative studies of rhTSH (Haugen *et al* 1999, Ladenson *et al* 1997, Meier *et al* 1994). The other three studies did not report adverse event data (Mazzaferri and Kloos 2002, Pacini *et al* 2001, Robbins *et al* 2001). The most commonly reported adverse events associated with the use of rhTSH were: headache (3.5–11.1%) and nausea (7.7–17.4%).

The publication by Meier (1994) reported only those adverse events occurring in the rhTSH phase of the study. Furthermore, only three patients received the correct dosage of rhTSH in line with the manufacturer's recommended schedule. As shown in **Table 5**, none of these patients experienced adverse events. However, three patients receiving the highest doses of rhTSH (30–40 U) complained of nausea, which was mild in two patients and moderate in one patient. In the latter patient, the nausea was accompanied by emesis and hot flushes. One of the two patients who complained of mild nausea also experienced mild weakness, dizziness and headaches for 48 hours after treatment.

Two patients in the trial by Ladenson (1997) discontinued the study due to adverse events associated with rhTSH. One patient experienced moderate nausea and dizziness following the first dose of rhTSH, and the other patient experienced nausea and vomiting after two doses of rhTSH. There were no serious adverse events reported that were associated with the use of rhTSH in the Haugen (1999) or Ladenson (1997) studies.

There was no evidence of development of antibodies specific to rhTSH reported in three of the comparative trials assessed (Haugen *et al* 1999, Ladenson *et al* 1997, Meier *et al* 1994). The other three comparative trials did not assess rhTSH-specific antibody levels (Mazzaferri and Kloos 2002, Pacini *et al* 2001, Robbins *et al* 2001).

Table 5 Adverse events reported in comparative studies of rhTSH

Adverse event	Haugen (1999)		Ladenson (1997)		Meier (1994)[a]
	rhTSH phase (Arm 1)	THT withdrawal phase (Arm 1)	rhTSH phase	THT withdrawal phase	rhTSH and THT withdrawal phase
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Digestive					
Nausea	9/117 (7.7%)	nr	25/144 (17.4%)	8/144 (5.6%)	0/3 (0.0%)
Vomiting	2/117 (1.7%)	nr	2/144 (1.4%)	3/144 (2.1%)	0/3(0.0%)
Diarrhoea	nr	nr	1/144 (0.7%)	0/144 (0.0%)	nr
Dyspepsia	3/117 (2.6%)	nr	nr	nr	nr
Nausea with vomiting	2/117 (1.7%)	nr	0/144 (0.0%)	1/144 (0.7%)	0/3(0.0%)
Moniliasis oral	nr	nr	1/144 (0.7%)	0/144 (0.0%)	nr
Thirst	nr	nr	1/144 (0.7%)	0/144 (0.0%)	nr
Body as a whole					
Headache	13/117 (11.1%)	nr	5/144 (3.5%)	4/144 (2.8%)	0/3(0.0%)
Asthenia	6/117 (5.1%)	nr	5/144 (3.5%)	0/144 (0.0%)	nr
Paraesthesia	3/117 (2.6%)	nr	nr	nr	nr
Hot flushes	nr	nr	nr	nr	0/3(0.0%)
Fever	2/117 (1.7%)	nr	nr	nr	nr
Chills	nr	nr	2/144 (1.4%)	0/144 (0.0%)	nr
Pain	1/117 (0.9%)	nr	1/144 (0.7%)	0/144 (0.0%)	nr
Abdominal pain	1/117 (0.9%)	nr	1/144 (0.7%)	0/144 (0.0%)	nr
Neck pain	nr	nr	1/144 (0.7%)	0/144 (0.0%)	nr
Weakness	nr	nr	nr	nr	0/3(0.0%)
Nervous					
Dizziness	2/117 (1.7%)	nr	2/144 (1.4%)	1/144 (0.7%)	0/3(0.0%)
Confusion	nr	nr	1/144 (0.7%)	0/144 (0.0%)	nr
Insomnia	nr	nr	1/144 (0.7%)	0/144 (0.0%)	nr
Nervousness	nr	nr	1/144 (0.7%)	0/144 (0.0%)	nr
Cardiovascular					
Embolism pulmonary	nr	nr	0/144 (0.0%)	1/144 (0.7%)	nr
Left external ear canal bleeding	nr	nr	0/144 (0.0%)	1/144 (0.7%)	nr
Hypotension	nr	nr	1/144 (0.7%)	0/144 (0.0%)	nr
Other					
Hypercholesterolemia	1/117 (0.9%)[b]	11/117 (9.4%)	nr	nr	nr
Hyperlipidemia	0/117 (0.0%)	4/117 (3.4%)	nr	nr	nr

Abbreviations: nr, not reported; THT, thyroid hormone therapy.
[a]Only patients receiving the correct dosage of rhTSH were assessed.
[b]Possibly related to rhTSH administration.

Table 6 summarises the adverse event data reported in the non-comparative studies of rhTSH. The most common adverse events reported in these studies were headache and nausea. Two reports of severe adverse events in patients with brain metastases were reported: one patient had severe headaches (Giovanni *et al* 2002) and the other developed right hemiplegia (Vargas *et al* 1999). Two patients with papillary thyroid carcinoma experienced tumour growth 12–48 hours after the second rhTSH injection, reflected by acute respiratory distress or a palpable, tender mass (Braga *et al* 2001). Two patients experienced transient swelling and pain in bone lesions. In one of these patients, who had a very large metastatic invasion of the pelvis from bone metastasis, bone-lesion pain was very severe and required analgesic drugs (Lippi *et al* 2001). To reduce the incidence of severe adverse events, pre-treatment with corticosteroids may be considered prior to the administration of rhTSH in patients with metastatic disease in confined spaces.

It should be noted that this assessment is specific to patients who have had a previous negative THT withdrawal test. In general, such patients will have less aggressive disease and may be less likely to experience the severe adverse events reported in these non-comparative studies.

Table 6 Adverse events reported in non-comparative studies of rhTSH

Study	Adverse event	n/N	Comments
Giovanni (2002)	Mild nausea	2/104	
	Moderate headache	4/104	
	Severe headache	1/104	Patient with brain metastases
	Violent skeletal pain	3/104	Patients with bone metastases
Braga (2001)	Tumour enlargement	2/2	In patients with local recurrent thyroid tumour
David (2001)	Nausea	3/33	
	Headache	1/33	
Lippi (2001)	Bone pain	2/12	Pain in bone lesions, severe in one patient
	Mild fever	3/12	
	Mild nausea	2/12	
	Death of patient due to tumour cachexia 40 days after treatment.	1/12	Patient with diffuse metastatic involvement
Petrich (2001)	Headache	6/30	
	Upper abdominal symptoms	1/30	
Durski (2000)	Mild headache	6/38	Two patients had mild headache and nausea
	Mild nausea	9/38	
	Light-headedness	2/38	
	Stomach ache	1/38	
Mariani (2000)	Mild nausea and general malaise with shivers	~ 20% [a]	
	Moderately severe headache	1/22	
	"Hypothyroidism-like" symptoms, such as cold intolerance	Sporadic[a]	
Vargas (1999)	Right hemiplegia and haemorrhage of the left parietal and clival masses.	1/1	Patient with follicular thyroid cancer metastatic to the brain

[a]Number of patients not reported.

In summary, it appears that the adverse events associated with the diagnostic use of rhTSH are generally mild or moderate. They are usually transient in nature. The most common adverse events are headache and nausea, although there are isolated reports of adverse events that appear to be the result of tumour swelling.

The impact of the adverse events associated with rhTSH on patients' quality of life should be considered in the context of the hypothyroidism experienced by patients undergoing THT withdrawal (see **Tables 15–17**).

Is it effective?

Available evidence

Table 7 provides a summary of the five studies meeting the criteria for inclusion in the effectiveness review of rhTSH. These studies were classified according to levels of evidence specific to diagnostic tests (**Table 3**) (Bandolier 2002). Two studies contained level 2 evidence (Haugen *et al* 1999, Ladenson *et al* 1997) and four studies contained level 4 evidence (Haugen *et al* 1999, Mazzaferri and Kloos 2002, Pacini *et al* 2001, Robbins *et al* 2001). For more detailed information on these studies see **Appendix G**. The studies containing level 2 evidence were the focus of the rhTSH effectiveness assessment as they represented the best available evidence. The original study reports for these two studies were made available by the applicant, allowing calculation of outcomes not reported in the publications.

Table 7 Comparative trial characteristics

Level of evidence	Quality score[a]	Study / publication	Patient number (N)	Reference standard reported in publication	Reference standard used in this assessment	rhTSH			THT withdrawal		
						Data on Tg and WBS	Data on Tg alone	Data on WBS alone	Data on Tg and WBS	Data on Tg alone	Data on WBS alone
2/4[b]	9	Haugen (1999)	Arm 1: 123	Concordance with THT withdrawal WBS and/or serum Tg	THT withdrawal WBS and serum Tg	✓	✓	✓	✓	✓	✓
2	9	Ladenson (1997)	152	Concordance with THT withdrawal WBS	THT withdrawal WBS	x	x[c]	✓	x	x[c]	✓
4	2	Mazzaferri and Kloos (2002)	107	Variable	Not used	✓	✓	✓	v[d]	v[d]	x
	9	Pacini (2001)	72	THT withdrawal WBS and serum Tg	THT withdrawal WBS and serum Tg	x	✓	x	✓	✓	✓
	0	Robbins (2001)	289	Composite of all clinical information	Not used	✓	✓	✓	✓	✓	✓

Abbreviations: rhTSH, recombinant human thyroid-stimulating hormone; THT, thyroid hormone therapy; Tg, serum thyroglobulin test; WBS, radioiodine whole body scan; V, variable.

[a](0 = poor, 16 = excellent). The Quality score is based on the scale described in **Appendix F**.

[b]WBS classified as level 2 evidence. Serum Tg classified as level 4 evidence.

[c]Serum Tg was not a prospectively identified end point and was not uniformly measured.

[d]Tests performed varied between patients; these included: physical examination, chest X-ray, diagnostic WBS, post-therapy WBS, neck ultrasound, fine needle cytology, surgical pathology, and whole body positron emission tomography.

The study by Haugen (1999) provides the primary evidence for the assessment of the sensitivity, specificity, and accuracy of rhTSH-stimulated serum Tg testing and WBS compared to THT withdrawal and serum Tg testing and WBS. This study contained level 2 evidence (blinded assessment of the WBS), and level 4 evidence (unblinded serum Tg test). However, as the serum Tg test is an objective laboratory measure, it is somewhat less likely to introduce bias into the study results. The manufacturer's recommended dosage and schedule of rhTSH (0.9 mg once per day for two days) was used only in arm 1 of the study. Therefore, only the results of arm 1 were considered in this assessment.

The study by Ladenson (1997) was prospectively designed to assess the diagnostic accuracy of rhTSH-stimulated WBS. The study was not prospectively designed to assess the diagnostic utility of rhTSH-stimulated serum Tg testing. Specifically, serum Tg measurements were performed in a number of laboratories, with potential assay variability. Furthermore, the majority of patients had their post-rhTSH serum Tg levels measured at a suboptimal time point (24 hours after rhTSH administration). Therefore, the serum Tg data reported in this study were excluded from the effectiveness assessment. As the primary assessment required the concurrent use of WBS and serum Tg results, this study was not suitable for the primary efficacy assessment of rhTSH.

The Mazzaferri and Kloos (2002) study was of a retrospective-cohort design. All patients were clinically free of disease after thyroid ablation and had undetectable or low on-T_4 serum Tg levels. The study was designed to determine the diagnostic accuracy of rhTSH-stimulated serum Tg alone. The study employed a range of clinical assessments as a reference standard. The clinical assessments were not administered uniformly in all patients. In general, the clinical assessments were more thorough as the rhTSH-stimulated serum Tg level increased. The variation in the reference standard is likely to introduce partial verification bias and differential reference bias into the study results (Lijmer *et al* 1999). Therefore, the results of this study were excluded from further consideration in the effectiveness analysis of rhTSH. For completeness, the results of this trial are reported in **Appendix G**.

The study by Pacini (2001) was prospectively designed and conducted in 72 consecutive patients with undetectable on-T_4 serum Tg levels. The study was designed to determine the diagnostic accuracy of rhTSH-stimulated serum Tg alone. The results of this study are examined in the assessment of the effectiveness of rhTSH-stimulated serum Tg testing alone.

The study by Robbins (2001) was of a retrospective, open-label, parallel cohort design. Patients were assigned to the study arms by need (patients who could not produce sufficient endogenous TSH, or those unable to tolerate hypothyroidism) or by patient choice in a non-randomised manner. The use of a non-randomised, parallel cohort design in this setting is likely to introduce significant bias into the study results (Lijmer *et al* 1999). Therefore, the results of this study were excluded from the analysis of rhTSH effectiveness. For completeness, the results of this trial are reported in **Appendix G**.

Diagnostic accuracy

The effectiveness measure used for this assessment was the diagnostic accuracy of rhTSH-stimulated serum Tg testing and WBS compared with THT withdrawal serum Tg testing and WBS. The accepted methodology for investigating the accuracy of new diagnostic tests is to compare the diagnosis made with the new test with the true disease status. However, it is often not feasible to determine the disease status of a patient unequivocally. Therefore, in many disease states a proxy measure, such as another diagnostic test or clinical judgement, must be used. The best available measure of disease is called the reference standard. Both the rhTSH result and the comparator result must be independently compared to the reference standard to assess accuracy, before the difference in accuracy between rhTSH and the comparator can be determined.

Currently, the best available indicator of the presence of thyroid remnants or thyroid cancer in patients who had near-total thyroidectomy is an elevated serum Tg, *or* a positive WBS after THT withdrawal. While this is the most appropriate reference standard available, it is recognised that it is imperfect (Robbins *et al* 2001). For the purpose of this evaluation, a positive classification was assigned to all patients with a THT withdrawal serum Tg ≥ 2 ng/mL or a WBS classification ≥ 1 (ie, including thyroid bed uptake; **Appendix H**). Definitions of positive classifications for rhTSH, the comparator, and the reference standard are outlined in **Table 8**. It is important to note that in several situations the comparator is the same as the reference standard.

Table 8 Definitions of positive classifications for rhTSH, comparator, and reference standard

Definition of a positive classification	Reference standard
rhTSH	
1. rhTSH-stimulated serum Tg ≥ 2 ng/mL or WBS ≥ 1[a]	THT withdrawal serum Tg ≥ 2 ng/mL or WBS ≥ 1[a]
2. rhTSH-stimulated serum Tg ≥ 5 ng/mL or WBS ≥ 1[a]	As above
3. rhTSH-stimulated serum Tg ≥ 2 ng/mL	As above
4. rhTSH-stimulated serum Tg ≥ 5 ng/mL	As above
5. rhTSH-stimulated serum Tg ≥ 2 ng/mL or WBS ≥ 1[a]	As above
Comparator	
1. THT withdrawal serum Tg ≥ 2 ng/mL or WBS ≥ 1[a]	As above
2. THT withdrawal serum Tg ≥ 5 ng/mL or WBS ≥ 1[a]	As above
3. THT withdrawal serum Tg ≥ 2 ng/mL	As above
4. THT withdrawal serum Tg ≥ 5 ng/mL	As above
5. On-THT serum Tg ≥ 2 ng/mL	As above

Abbreviations: rhTSH, recombinant human thyroid-stimulating hormone; THT, thyroid hormone therapy; Tg, serum thyroglobulin test; WBS, radioiodine whole body scan.
[a]WBS classifications defined in **Appendix H.**

For each of the rhTSH and comparator measures listed in **Table 8,** the following markers of diagnostic effectiveness were calculated.

- Sensitivity – the ability to detect thyroid remnants or thyroid cancer among patients in whom they are present.

- Specificity – the ability to detect no thyroid remnants or thyroid cancer among patients in whom they are absent.

- Accuracy – the proportion of all tests giving the correct result, as proportion of all results (calculated as a diagnostic odds ratio (DOR) from the sensitivity and specificity).

- Positive predictive values (PPV) – the ability to detect positive patients only among positive scans (ie, avoid false-positives).

- Negative predictive values (NPV) – the ability to detect negative patients only among negative scans (ie, avoid false-negatives).

Primary assessment: patients presenting for diagnostic testing subsequent to a negative test

The primary assessment refers to rhTSH use in patients presenting for diagnostic testing subsequent to a negative WBS following THT withdrawal. Data specific to this subpopulation were not available. However, it was possible to extract individual patient data for just those patients whose thyroid tissue had been successfully ablated sometime in the past from the Haugen (1999) study. Nevertheless, this group is likely to be more closely representative of patients included in the assessment than a population that includes patients who have not yet had proof of successful ablation.

WBS and serum Tg

Only one study adequately reported both serum Tg and WBS results after rhTSH administration and THT withdrawal (Haugen *et al* 1999). This study provides the clinical evidence for the primary evaluation of rhTSH diagnostic effectiveness (**Table 9**).

Table 9 rhTSH-stimulated/THT withdrawal WBS and serum Tg effectiveness in successfully ablated patients

Trial	Serum Tg assay positive definition	Testing mode	Sensitivity	Specificity	Accuracy	PPV	NPV
Haugen (1999)[a]	≥ 2 ng/mL	rhTSH	87% *	95%	89%	98%	74%
	≥ 2 ng/mL[b]	THT withdrawal	100%	100%	100%	100%	100%
	≥ 5 ng/mL	rhTSH	81% *	95%	85%	98%	67%
	≥ 5 ng/mL	THT withdrawal	91%	100%	94%	100%	81%

Abbreviations: Tg, thyroglobulin; rhTSH, recombinant human thyroid-stimulating hormone; THT, thyroid hormone therapy; PPV, positive predictive value; NPV, negative predictive value.
*Denotes a significant difference between rhTSH and THT-withdrawal ($p < 0.05$) (method 10 of Newcombe (1998)).
[a]Patients who tested positive for Tg antibodies were excluded from the evaluation of rhTSH accuracy.
[b]This measure is identical to the reference standard, so 100 per cent accuracy is implicit.

Using the 2 ng/mL serum Tg criterion, there were 67 concordant and 8 discordant tests in the primary analysis; this was comprised of 47 true-positive, 20 true-negative, 1 false-positive, and 7 false-negative results. It should be noted that the differences in specificity between rhTSH and THT withdrawal were not statistically significant. **Table 9** shows that rhTSH has relatively high sensitivity, specificity and accuracy in comparison with the reference standard. Altering the serum Tg positive cut-off level has a modest effect on the accuracy of diagnosis using rhTSH. Interpreting the diagnostic effectiveness of rhTSH relative to the comparator is difficult when the comparator serves as the reference standard and is recognised as somewhat imperfect.

Sensitivity and specificity are the two most widely used measures of test performance. When an imperfect gold standard is used to determine disease status, a bias is introduced into both of these measures. Therefore, to correct for this bias, the sensitivity and specificity measurements derived in the primary evaluation (serum Tg cut-off level ≥2 ng/mL) were adjusted using the method described by Valenstein *et al,* (1990). The level of imperfection associated with THT withdrawal stimulated serum Tg and WBS was estimated using data from the THT withdrawal arm of the Robbins (2001) study. While this study was not useful in providing comparative efficacy data it did compare THT withdrawal WBS and serum Tg with a clinical assignment of disease based on all available clinical information. This provided the best estimation available of the actual accuracy of the THT withdrawal WBS and serum Tg proxy measurements. Data from the Robbins (2001) study were recalculated according to the following criteria for a positive test; a WBS ≥ 1 and/or a serum Tg >2.0 ng/mL, giving an estimated sensitivity and specificity for THT withdrawal of 98 per cent and 81 per cent, respectively. On this basis, the adjusted sensitivity and specificity for rhTSH were 86 per cent and 65 per cent, respectively.

Serum Tg alone

Only one study adequately reported the serum Tg results after rhTSH administration and THT withdrawal for this patient subgroup (Haugen *et al* 1999). This study provides the clinical evidence for the primary evaluation of rhTSH diagnostic effectiveness (**Table 10**).

Table 10 rhTSH-stimulated/THT withdrawal serum Tg effectiveness in successfully ablated patients

Trial	Serum Tg assay positive definition	Testing mode	Sensitivity	Specificity	Accuracy	PPV	NPV
Haugen (1999)[a]	≥ 2 ng/mL	rhTSH	69%	100%	77%	100%	55%
	≥ 2 ng/mL	THT withdrawal	78%	100%	84%	100%	64%
	≥ 5 ng/mL	rhTSH	60%	100%	72%	100%	51%
	≥ 5 ng/mL	THT withdrawal	65%	100%	75%	100%	53%

Abbreviations: Tg, thyroglobulin; rhTSH, recombinant human thyroid-stimulating hormone; THT, thyroid hormone therapy; PPV, positive predictive value; NPV, negative predictive value.
[a]Patients who tested positive for Tg antibodies were excluded from the evaluation of rhTSH accuracy.

The use of serum Tg measurement alone significantly decreases the diagnostic accuracy of rhTSH and THT withdrawal against a reference standard that incorporates the results of both serum Tg and WBS. Furthermore, the negative predictive value (NPV) of serum Tg alone is markedly lower than when serum Tg and WBS are used in combination. This

may impact on the clinician's ability to confidently exclude the presence of disease in patients. Again, it must be noted that interpreting the diagnostic effectiveness of rhTSH relative to the comparator is difficult when the comparator is imperfect.

These results clearly indicate the importance of using WBS and serum Tg testing concurrently for the purposes of patient follow-up. Using serum Tg testing alone significantly diminishes the accuracy of the diagnosis.

Secondary assessment: all patients presenting for diagnostic testing

As there is potential for rhTSH use in a broader population than that suggested by the applicant, a secondary assessment was undertaken for completeness. In addition to the subgroup of patients in the primary evaluation, this evaluation includes those patients who have had surgical or ablative treatment but are yet to have diagnostic follow-up.

WBS and serum Tg

One study reported patients analysed with both serum Tg tests and WBS after THT withdrawal and rhTSH administration and included patients having their first post-test follow-up (Haugen *et al* 1999). This study provides the evidence for the secondary evaluation of the accuracy of rhTSH-stimulated serum Tg testing and WBS (**Table 11**).

Table 11 rhTSH-stimulated/THT withdrawal WBS and serum Tg effectiveness in all patients

Trial	Serum Tg assay positive definition	Testing mode	Sensitivity	Specificity	Accuracy	PPV	NPV
Haugen (1999)[a]	≥ 2 ng/mL	rhTSH	86% **	95%	89%	98%	70%
	≥ 2 ng/mL[b]	THT withdrawal	100%	100%	100%	100%	100%
	≥ 5 ng/mL	rhTSH	82% *	95%	85%	98%	64%
	≥ 5 ng/mL	THT withdrawal	91%	100%	93%	100%	79%

Abbreviations: Tg, thyroglobulin; rhTSH, recombinant human thyroid-stimulating hormone; THT, thyroid hormone therapy; PPV, positive predictive value; NPV, negative predictive value; WBS, whole body scanning.
*Denotes a significant difference between rhTSH and THT withdrawal ($p < 0.05$) (method 10 of Newcombe (1998)).
**Denotes a significant difference between rhTSH and THT withdrawal ($p < 0.01$) (method 10 of Newcombe (1998)).
[a]Patients who tested positive for Tg antibodies were excluded from the evaluation of rhTSH accuracy.
[b]This measure is identical to the reference standard, so 100% accuracy is implicit.

This analysis of rhTSH demonstrates relatively high sensitivity, specificity, and accuracy in comparison to the reference standard. Altering the serum Tg positive cut-off level has a modest effect on the accuracy of rhTSH. The diagnostic accuracy of rhTSH in this broader patient group is very similar to that found in the primary analysis and implies the diagnostic results are broadly generalisable between the different patient groups. Again, interpreting the diagnostic effectiveness of rhTSH relative to the comparator is difficult when the comparator serves as the reference standard and is imperfect.

Serum Tg alone

Evidence relating to the effectiveness of rhTSH use for serum Tg testing alone in this broader patient group was available from two studies (Haugen *et al* 1999, Pacini *et al* 2001).

All patients in the Pacini (2001) study were previously treated with near-total thyroidectomy and I^{131} ablation and were scheduled for routine diagnostic follow-up.

Data from the entire patient group in the Pacini (2001) study were utilised to derive rhTSH effectiveness data.

Table 12 rhTSH-stimulated/THT withdrawal serum Tg effectiveness in all patients

Trial	Serum Tg assay positive definition	Testing mode	Sensitivity	Specificity	Accuracy	PPV	NPV
Haugen (1999)[a]	≥ 2 ng/mL	rhTSH	71% *	100%	78%	100%	54%
	≥ 2 ng/mL	THT withdrawal	81%	100%	85%	100%	63%
	≥ 5 ng/mL	rhTSH	65% *	100%	74%	100%	50%
	≥ 5 ng/mL	THT withdrawal	70%	100%	78%	100%	52%
Pacini (2001)[ab]	> 1 ng/mL	rhTSH	74%	100%	85%	100%	73%
	> 1 ng/mL	THT withdrawal	86%	100%	92%	100%	83%

Abbreviations: Tg, thyroglobulin; rhTSH, recombinant human thyroid-stimulating hormone; THT, thyroid hormone therapy; PPV, positive predictive value; NPV, negative predictive value.
*Denotes a significant difference between rhTSH and THT withdrawal ($p < 0.05$) (method 10 of Newcombe (1998)).
[a]Patients who tested positive for Tg antibodies were excluded.
[b]Data not available to calculate statistical significance.

The use of serum Tg measurement alone significantly decreases the diagnostic accuracy of rhTSH and THT withdrawal against a reference standard that incorporates the results of both serum Tg and WBS. Furthermore, the negative predictive value (NPV) of serum Tg alone is markedly lower than when serum Tg and WBS are used in combination. This may impact on the clinician's ability to confidently exclude the presence of disease in patients. Again, it must be noted that interpreting the diagnostic effectiveness of rhTSH relative to the comparator is difficult when the comparator is imperfect.

These results clearly indicate the importance of using a WBS and serum Tg testing concurrently for the purposes of patient follow-up. Using serum Tg testing alone significantly diminishes the accuracy of the diagnosis.

Secondary assessment: patients for whom THT withdrawal is medically contraindicated

There are no comparative rhTSH effectiveness data available specific to this subgroup of patients. Therefore, the effectiveness of rhTSH in this patient group is uncertain. As an estimate, the accuracy of serum Tg measurements taken while patients were on THT was compared to the accuracy of the rhTSH-stimulated WBS and serum Tg measurements for all patients in the Haugen (1999) study (**Table 13**).

Table 13 rhTSH-stimulated WBS and serum Tg effectiveness versus on-THT Tg effectiveness in all patients

Trial	Serum Tg assay positive definition	Testing mode	Sensitivity	Specificity	Accuracy	PPV	NPV
Haugen (1999)[a]	≥ 2 ng/mL	rhTSH	86% **	95%	89%	98%	70%
	≥ 2 ng/mL	on-THT	43%	96%	57%	97%	37%

Abbreviations: Tg, thyroglobulin; rhTSH, recombinant human thyroid-stimulating hormone; THT, thyroid hormone therapy; PPV, positive predictive value; NPV, negative predictive value; WBS, whole body scanning.
**Denotes a significant difference between rhTSH-stimulated WBS and serum Tg versus on-THT ($p < 0.01$) (method 10 of Newcombe (1998)).

The analysis of serum Tg measurements taken while patients are receiving THT demonstrates a significantly lower sensitivity ($p < 0.001$) compared with rhTSH-stimulated WBS and serum Tg testing. It should be noted that these values were not derived from a subpopulation of patients in whom THT withdrawal was medically contraindicated, but from all patients enrolled in the Haugen (1999) study. Therefore, the level to which these results can be generalised is uncertain. Nevertheless, the diagnostic accuracy of rhTSH-stimulated WBS and serum Tg is likely to be considerably better than the on-THT serum Tg test alone.

Summary of diagnostic accuracy

The use of rhTSH instead of THT withdrawal would result in a reduction in diagnostic accuracy. In particular, it appears that the sensitivity of this diagnostic procedure is somewhat lower than THT withdrawal. In practice, this would result in 13 per cent[7] of patients with disease being misclassified as disease-negative. However, in a slow-progressing disease such as thyroid cancer, this may not be considered critical. These patients are likely to be detected at their next follow-up, assuming they continue to comply with their scheduled diagnostic assessments. The disadvantage of poorer accuracy needs to be weighed up against the improvement in quality of life (and hence compliance) that results from avoidance of hypothyroidism caused by THT withdrawal. This is considered in the next section.

The use of serum Tg testing alone significantly decreases the diagnostic accuracy of both rhTSH and THT withdrawal.

The ability to stimulate iodine uptake using rhTSH means that patients for whom THT withdrawal is contraindicated can now undergo a rhTSH-stimulated WBS and Tg testing, rather than being limited to on-THT serum Tg testing. This represents a considerable improvement in diagnostic accuracy for this group of patients.

[7] Sensitivity of THT withdrawal – sensitivity of rhTSH (Table 9)

Quality of life data

Table 14 summarises the quality of life (QOL) data collected in the comparative trials of rhTSH. In addition, the results of the SF-36 survey were mapped to utility values using the SF-6D index method of Brazier *et al* (1998).

Table 14 Summary of quality of life data collected for rhTSH

Study publication	SF-36	Billewicz	POMS	SF-6D
Haugen (1999)	✓	✓	x	Derived
Ladenson (1997)	x	✓	✓	x

Abbreviation: POMS, short form Profile of Mood Scale.

It is important to remember that the treatment phases were not blinded to either patient or the investigators conducting the questionnaire. This introduces the potential for bias, particularly with subjective QOL instruments.

SF-36

The SF-36 is a multipurpose self-administered survey of general health status validated for international use. The SF-36 questionnaire is a generic QOL instrument that measures the following eight health concepts: physical functioning; role-physical; bodily pain; general health; vitality; social functioning; role-emotional; and mental health. The SF-36 survey also provides a summary of physical and mental health measures, as well as a self-evaluation of the change in overall health during the past year.

Patients were assessed for QOL at the following three time points (Haugen *et al* 1999):

- while on THT prior to receiving rhTSH (but due for follow-up monitoring)
- after rhTSH, before the rhTSH phase scan, while on THT
- during THT withdrawal, on the day of ^{131}I administration with TSH $\geq$ 25 mU/L

Table 15 summarises the QOL changes measured by SF-36 in the Haugen (1999) study.

Table 15 SF-36 – quality of life

SF-36 QOL concept	Baseline	rhTSH phase (change from baseline)	THT withdrawal phase (change from baseline)	THT withdrawal phase (change from rhTSH phase)
Physical functioning	84.5	1.8*	–24.2**	–26.1**
Role-physical	85.7	–3.2	–48.9**	–45.7**
Bodily pain	82.2	0.1	–14.1**	–14.0**
General health	58.5	–2.0**	–3.2**	–1.1
Vitality	55.6	3.1	2.6	–0.6
Social functioning	47.3	–1.1	0.3	1.4
Role-emotional	88.6	–4.0*	–43.8**	–39.7**
Mental health	63.2	1.0	0.3	–0.7

Abbreviations: THT, thyroid hormone therapy; QOL, quality of life.
* = significant difference ($p < 0.05$) in favour of the rhTSH phase (Wilcoxon signed rank test).
** = significant difference ($p < 0.01$) in favour of the rhTSH phase (Wilcoxon signed rank test).

Three QOL domains (physical functioning; general health; role-emotional) showed a small but significant change in score from baseline when patients were treated with rhTSH. Five domains (physical functioning; role-physical; bodily pain; general health; and role-emotional) showed significant reductions in the THT withdrawal phase scores when compared to baseline scores. When a comparison was made between the rhTSH phase and the THT withdrawal phase, it was found that four of the eight QOL domains were significantly reduced in patients undergoing THT withdrawal. The magnitude of these changes was considerable.

Billewicz scale

The Billewicz scale is used to measure the presence or absence of hypothyroid signs or symptoms. It is an observer-rated scale developed to serve as a diagnostic index for identifying clinical hypothyroidism specifically. Patients were assessed for symptoms of hypothyroidism at the following three time points (Haugen *et al* 1999):

- while on THT prior to receiving rhTSH (but due for follow-up monitoring)
- after rhTSH, before the rhTSH phase scan, while on THT
- during THT withdrawal, before the hypothyroid phase scans.

Table 16 summarises the presence of hypothyroid signs or symptoms measured by the Billewicz scale in the Haugen (1999) and Ladenson (1997) studies.

Table 16 Billewicz scale – presence of hypothyroid signs and symptoms

Billewicz sign or symptom	Haugen (1999)			Ladenson (1997)		
	Baseline n/N (%)	rhTSH phase n/N (%)	THT withdrawal phase n/N (%)	Baseline n/N (%)	rhTSH phase n/N (%)	THT withdrawal phase n/N (%)
Diminished sweating	2/115 (1.7%)	3/115 (2.6%)	26/115* (22.6%)	3/144 (2.1%)	6/144 (4.2%)	42/144* (29.2%)
Dry skin	27/115 (23.5%)	19/115 (16.5%)	61/115* (53.0%)	23/144 (16.0%)	19/144 (13.2%)	74/144* (51.4%)
Cold intolerance	14/115 (12.1%)	15/115 (13.0%)	81/115* (70.4%)	15/144 (10.4%)	13/144 (9.0%)	88/144* (61.1%)
Weight increase	9/115 (7.8%)	7/115 (6.1%)	58/115* (50.4%)	21/144 (14.6%)	13/144 (9.0%)	89/144* (61.8%)
Constipation	9/115 (7.8%)	8/115 (7.0%)	44/115* (38.3%)	9/144 (6.25%)	14/144 (9.7%)	50/144* (34.7%)
Hoarseness	14/115 (12.1)	14/115 (12.2%)	52/115* (45.2%)	17/144 (11.8%)	11/144 (7.6%)	79/144* (54.9%)
Paraesthesia	10/115 (8.7%)	12/115 (10.4%)	38/115* (33.0%)	13/144 (9.0%)	8/144 (5.6%)	48/144* (33.3%)
Deafness	9/115 (7.8%)	8/115 (7.0%)	12/115 (10.4%)	6/144 (4.2%)	3/144 (2.1%)	18/144* (12.5%)
Slow movements	2/115 (1.7%)	2/115 (1.7%)	59/115* (51.3%)	4/144 (2.8%)	8/144 (5.6%)	98/144* (68.1%)
Coarse skin	4/115 (3.5%)	3/115 (2.6%)	30/115* (26.1%)	3/144 (2.1%)	3/144 (2.1%)	39/144* (27.1%)
Cold skin	1/115 (0.9%)	4/115 (3.5%)	60/115* (52.2%)	4/144 (2.8%)	5/144 (3.4%)	62/144* (43.1%)
Periorbital puffiness	2/115 (1.7%)	1/115 (2.6%)	87/115* (75.7%)	7/144 (4.9%)	9/144 (6.3%)	84/144* (58.3%)
Slowing of anklejerk	0/92 (0.0%)	1/92 (1.1%)	48/92* (52.2%)	0/143 (0.0%)	4/143 (2.8%)	83/143* (58.0)
Decrease in pulse rate	7/115 (6.1%)	6/115 (5.3%)	52/115* (45.6%)	10/144 (6.9%)	9/144 (6.3%)	69/144* (47.9%)

Abbreviation: THT, thyroid hormone therapy.
* = significant difference between rhTSH phase and THT withdrawal phase ($p < 0.05$) in favour of the rhTSH phase (method 10 of Newcombe (1998) for calculating confidence intervals of the change for paired dichotomous outcomes).

The results show that patients have a lower incidence of hypothyroid signs and symptoms in the rhTSH phase of the studies than in the THT withdrawal phase. These differences were statistically significant for all 14 signs and symptoms of hypothyroidism in the Ladenson (1997) study and for all except deafness in the Haugen (1999) study.

Short form Profile of Mood Scale (POMS)

POMS is a self-administered scale which assesses the following six mood states: tension-anxiety; depression-dejection; anger-hostility; confusion-bewilderment; vigour-activity; and fatigue-inertia. Patients were assessed using POMS at the following three time points (Ladenson et al. 1997):

- while on THT prior to receiving rhTSH (but due for follow-up monitoring)
- after rhTSH, before the rhTSH phase scan, while on THT
- during THT withdrawal, before the hypothyroid phase scans.

Table 17 summarises the results of the POMS assessment reported in the Ladenson (1997) study.

Table 17 Short form Profile of Mood Scale

Mood states	Baseline mean (SD)	rhTSH mean (SD)	Hypothyroidism mean (SD)
Fatigue	4.52 (4.27)	5.86 (8.15)	14.28 (10.41)**
Vigour	11.93 (5.41)	11.63 (9.01)	9.88 (13.41)**
Depression	2.28 (4.15)	4.00 (11.97)	11.26 (18.28)**
Anger	2.22 (3.27)	3.54 (10.32)	10.05 (16.02)**
Tension	4.51 (3.88)	5.11 (9.01)	10.77 (13.37)**
Confusion	2.23 (2.43)	3.37 (7.92)	8.75 (11.23)**

Abbreviation: SD, standard deviation.
** = significant difference ($p < 0.01$) in favour of the rhTSH phase.

When a comparison was made between the rhTSH phase and the THT withdrawal phase, it was found that all six mood state domains were significantly worse in patients undergoing THT withdrawal ($p < 0.01$). The magnitude of these changes was considerable.

Utility data

Utility values were derived from QOL data using the method described by Brazier *et al* (1998). In summary, a preference-based single index (SF-6D) was derived from the SF-36 health survey conducted in the Haugen (1999) study. Utilities were derived on the basis of individual patient data. Only the patients, who were evaluable, with no Tg antibodies and no missing data, were considered in these analyses. Paired t-tests were performed and the results were bootstrapped[8] to assess the significance of the differences in mean utilities between the three periods. The results of this analysis are shown in **Table 18.**

[8]Repeated sampling with replacement from an observed data sample which is used to estimate the distribution around the mean utility values.

Table 18 Utility values

Phase	Mean	Standard deviation	Minimum	Median	Maximum
Primary assessment (successfully ablated patients)					
Pre-treatment	0.801	0.114	0.473	0.840	1.000
rhTSH[a]	0.795	0.119	0.389	0.825	1.000
THT withdrawal[bc]	0.652	0.144	0.353	0.650	0.940
Secondary assessment (all patients)					
Pre-treatment	0.802	0.110	0.473	0.842	1.000
rhTSH[a]	0.797	0.114	0.389	0.834	1.000
THT withdrawal[bc]	0.666	0.140	0.353	0.653	0.940

Abbreviation: THT, thyroid hormone therapy.

[a]Differences between mean utility values during pre-treatment and rhTSH were not significant .

[b]Differences between mean utility values during pre-treatment and THT withdrawal were significant ($p < 0.001$) and favoured pre-treatment phase.

[c]Differences between mean utility values during rhTSH and THT withdrawal were significant ($p < 0.001$) and favoured rhTSH.

The results show that there was no statistically significant difference between the mean utility values in the pre-treatment and rhTSH phases of the study. Utility values were significantly lower in the THT withdrawal phase than in the pre-treatment or rhTSH phase of the study ($p < 0.001$). The hypothyroidism experienced during THT withdrawal has considerable impact upon the health utility of an individual (0.66 on a scale where 1.0 = perfect health and 0 = death).

Summary of quality of life data

In summary, QOL evidence comes from open-labelled trials where the order of the diagnostic interventions was neither balanced nor randomised. Nevertheless, the results of the SF-36 survey indicated a poorer general QOL during THT withdrawal than during rhTSH administration. Scores for four domains (physical functioning; role-physical; bodily pain; and role-emotional) showed significant and large differences between the THT withdrawal phase and the rhTSH phase. The results of the hypothyroid-specific Billewicz scale show that patients have a lower incidence of hypothyroid signs and symptoms in the rhTSH phase of the studies than in the THT withdrawal phase.

The QOL data from the SF-36 survey were used to derive health utility values. The resultant utility for the temporary health state of hypothyroidism is 0.650, compared with 0.825 for patients receiving rhTSH. These utility values summarise the QOL advantage of rhTSH relative to THT withdrawal, although it is important to remember that this benefit is transient (up to 12 weeks) and infrequent[9].

[9] Expert opinion has estimated that, on average, Australian routine monitoring occurs at six months, one year, three years and five years after initial treatment. If patients subsequently test positive and require further treatment, they then recommence monitoring at the beginning of this schedule.

What are the economic considerations?

It is a requirement of the MSAC terms of reference that the economic implications of the new health technology are considered. This is particularly important when a new technology offers health benefits at an additional cost, as is so often the case. An economic evaluation helps to determine whether the additional cost represents value for money. To assess the value for money of a new health intervention, it is necessary to express the incremental cost associated with the new treatment relative to the incremental health benefit gained. When this information is available, an incremental cost-effectiveness ratio (ICER) can be calculated:

$$\text{ICER} = \frac{\text{Cost}_{\text{new technology}} - \text{Cost}_{\text{comparator}}}{\text{Effectiveness}_{\text{new technology}} - \text{Effectiveness}_{\text{comparator}}}$$

In cases where a new technology offers inferior or equal health benefits at a higher cost, it clearly does not provide value for money.

When determining the incremental cost of the new technology, several factors should be considered: the costs of the treatment itself; the costs of any downstream management including secondary to misdiagnosis or non-compliance; treatment costs for any adverse reactions; and also any cost savings achieved. With respect to incremental effectiveness, there are several possible ways of expressing the effectiveness of the treatment. The effectiveness may be expressed as a measured intermediate health outcome (eg, mmHg reduction in blood pressure) or as an end-stage outcome (eg, life-year gained). Alternatively, the effectiveness may be expressed as quality-adjusted life-years gained, a measure that incorporates both the quality and the quantity of life-years gained (a cost utility analysis).

Approach of the economic evaluation

The cost-effectiveness of rhTSH as an alternative to the standard THT withdrawal method in the detection of thyroid cancer was assessed using a decision-analytic model. The model followed patients to determine the costs and health outcomes according to which procedure they underwent prior to the diagnostic scan. Due to the nature of the diagnostic procedure, a Markov model was invoked – allowing a series of events to unfold over time. In this instance, events were modelled over a 5-year period. For the primary assessment, this period begins after the patient has undergone initial thyroid cancer treatment and has subsequently tested negative after going through the standard THT withdrawal diagnostic testing procedure.

The model incorporates four important aspects of using rhTSH relative to standard THT withdrawal in this group of patients:

- the differences in intensity and cost of resource use between the two procedures

- the poorer diagnostic sensitivity of rhTSH and the effect this has on the diagnosis and treatment of patients with thyroid cancer

- the improvement in quality of life associated with the use of rhTSH compared with THT withdrawal

- the effect of rhTSH in improving compliance and reducing the number of patients who discontinue regular monitoring for cancer recurrence

The sensitivity of the rhTSH scan will affect the way patients are classified following a scan. The reduced sensitivity of diagnostic testing using rhTSH will inevitably result in more patients being misclassified. Consequently, patients requiring treatment may be incorrectly classified as cancer-free (false-negatives). Such misdiagnosis has the potential to influence health outcomes as well as costs. It should be noted, however, that due to the slow-progressing nature of thyroid cancer, the dangers and the effects on health states associated with a failure to treat are not as great as they may be with other diseases.

It should also be noted that although the difference in sensitivity between rhTSH and THT withdrawal was statistically significant, the difference in specificity was not. Therefore, the impact of the comparative accuracy of the two testing modalities on cost-effectiveness was investigated through sensitivity analyses (ie, assuming equal sensitivity and specificity for rhTSH and THT withdrawal) (**Table 24**).

The effectiveness of the current standard THT withdrawal method is limited by poor patient compliance rates, due to the hypothyroidism associated with withdrawing from hormone therapy. One potential benefit of the introduction of rhTSH is improved effectiveness of thyroid cancer monitoring through increased compliance rates. However, this is associated with increased total health care costs, primarily due to the high cost of rhTSH compared with the current THT withdrawal method.

As indicated above, Markov modelling allows the model to unfold over time, capturing events as they occur. A cycle length of 1.5 months has been selected. This is equal to the length of the THT withdrawal period and is the shortest period of interest within the diagnostic procedure. Each single progression through to a terminal node (those indicated with a triangle) therefore represents the passing of 1.5 months. It must be noted, however, that there are a number of tunnel states (eg, 'Treatment + 6-month scan: false-positive'). Such points in the model loop into themselves until the desired length of time has passed – in this case a period of 7.5 months (allowing for a 1.5-month period of withdrawal and scan following a 6-month wait after treatment). The model continues to unfold until 40 cycles (5 years) have taken place, at which time it terminates.

The two arms of the model, the THT withdrawal arm and the rhTSH arm, appear in **Figures 2** and **3**, respectively.

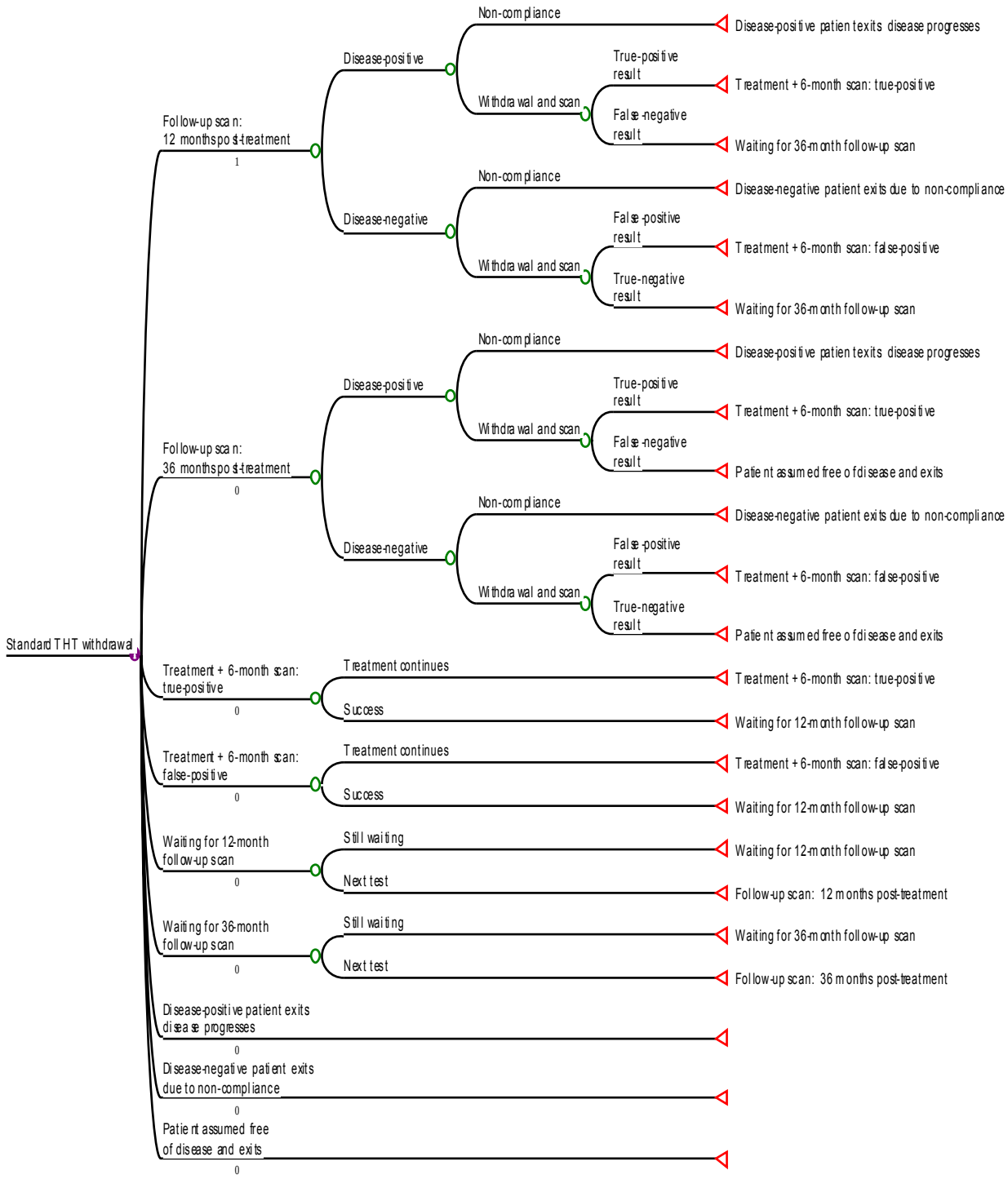

Figure 2 THT withdrawal arm of the modelled economic evaluation

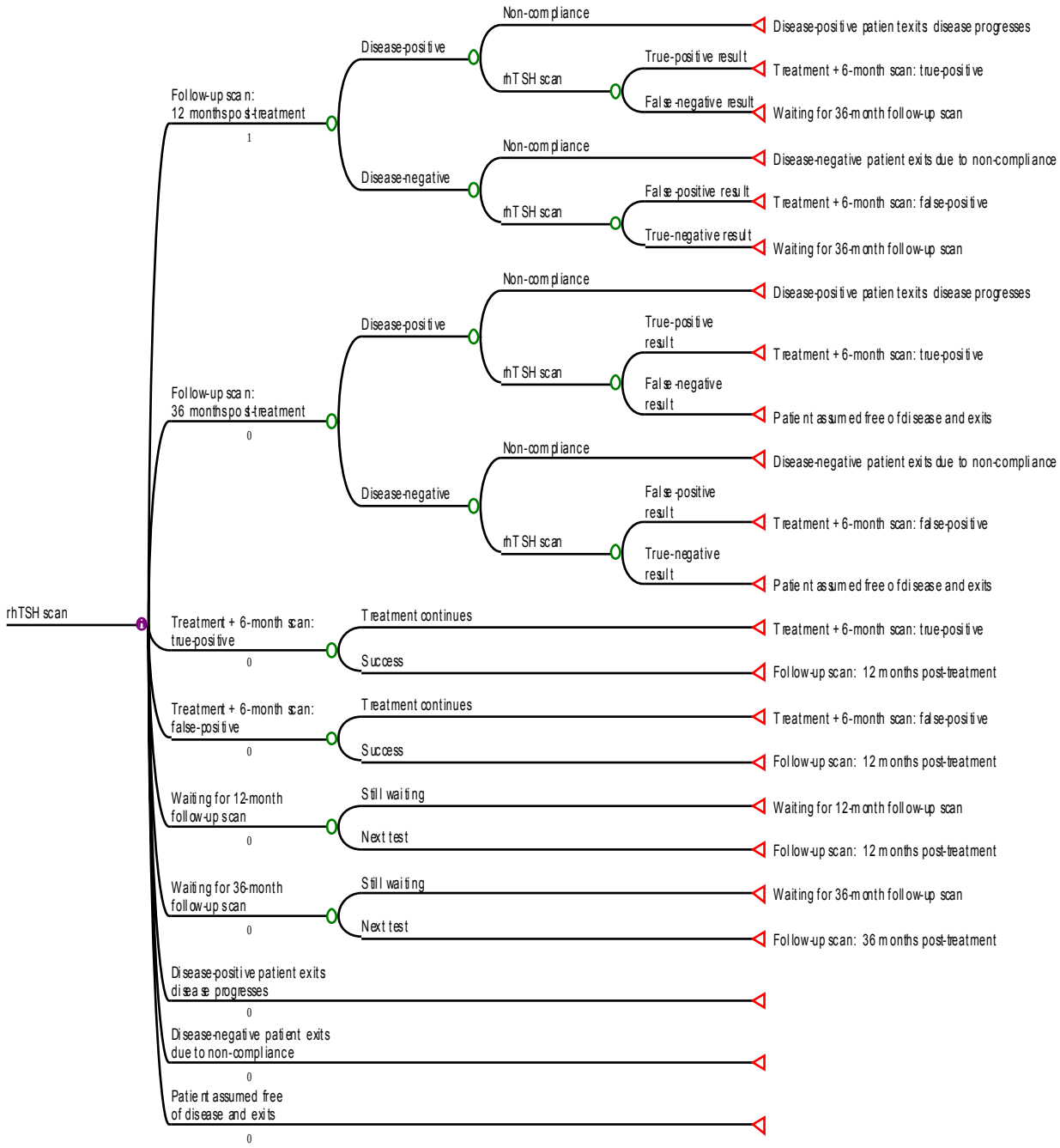

Figure 3 rhTSH arm of the modelled economic evaluation

Cost inputs

The component costs applied to the modelled economic evaluation are presented in **Table 19**. The main cost incurred is the cost of rhTSH (in the rhTSH arm only; assumed to be Thyrogen™) at $1953 per patient per diagnostic follow-up. The additional cost associated with these patients remaining on THT (assumed to be T_4), rather than withdrawing, is negligible as the cost of THT is small. Furthermore, 50 per cent of the

THT withdrawal patients receive 4 weeks of T_3 as a substitute. The cost of each WBS scan and Tg test is identical in each arm. The cost of radioiodine ablation treatment (ie, as a result of either a true-positive or false-positive test) is considerable.

Table 19 Component costs used in the model

	rhTSH arm	THT withdrawal arm
rhTSH (Thyrogen™) per diagnostic follow-up	$1953	–
Radioiodine ablation (per course)	$395.40	$395.40
Tg antibody test	$34.10	$34.10
T_3 (per week)	–	$18.33[a]
T_4 (per week)	$0.32[b]	$0.32[c]
Serum Tg test	$24.00	$24.00
Hospital stay/day	$410.17	$410.17
Whole body scan	$490.85	$490.85

Abbreviations: THT, thyroid hormone therapy; Tg, thyroglobulin; T_3, liothyronine sodium; T_4, thyroxine sodium.
[a]Those patients receiving T_3 for 4-weeks would incur $73.33.
[b]Those patients receiving T_4 for 6 weeks would incur a cost of $1.92.
[c]Those patients receiving T4 for 2 weeks would incur a cost of $0.64.

Health outcome inputs

This modelled economic evaluation uses a cost-utility approach. Outcomes are expressed as quality-adjusted life-years (QALYs). Health utilities are values that represent the strength of a person's preference for a specific health state (based on the relative desirability of different health states). Health states are valued on a scale from 1.0 (perfect health) to 0 (death). The advantage of a modelled cost-utility approach in this assessment is that it allows for simultaneous accounting of: the poor health state during the temporary period of hypothyroidism, the somewhat poorer diagnostic performance of rhTSH-stimulated testing and the lower compliance inherent with THT withdrawal.

The health utilities that differ between diagnostic arms were derived from the SF-36 data reported in the primary evidence (Haugen *et al* 1999). Individual patient data were converted to the utility index SF-6D according to the method of Brazier *et al* (1998) (for detail see **Table 18**). Utility values were not available for other health states and were estimated in conjunction with clinical opinion, using the known utilities as anchor points. All unknown utilities were common to both arms. All utility values used in the model are presented in **Table 20**. Utilities applied to the first diagnostic follow-up in the secondary assessment were derived from all patients in the Haugen (1999) study, so differ slightly from those used in the primary assessment, which related to patients with proof of initial successful ablation (**Table 35)**

Table 20 Utilities associated with the various health states

Health state	Utility	Source
A patient for whom diagnostic testing is imminent[a]	0.840	Derived from SF-36 survey (Haugen *et al* 1999)
A patient in the THT withdrawal stage[a]	0.650	Derived from SF-36 survey (Haugen *et al* 1999)
A patient who is currently receiving rhTSH[a]	0.825	Derived from SF-36 survey (Haugen *et al* 1999)
A patient who still intends to take part in regular monitoring, is still taking THT medication and is at risk of recurrence	0.850	Assumption
A patient who has had three negative tests, is no longer being monitored, but still taking THT medication and at risk of recurrence	0.880	Assumption
A patient who is asymptomatic, no longer being tested, but still taking THT medication and at risk of recurrence	0.860	Assumption
A patients who has symptomatic disease (often metastatic)	0.550	Assumption
A patient who is dead	0.00	Convention
An average of patients who are disease-positive but have exited the program due to non-compliance	0.650	Weighted average of patients who have – asymptomatic disease (50%) – symptomatic disease (40%) – died (10%) over the duration of the model
An average of patients who are disease-negative but have exited the program due to non-compliance	0.856	Weighted average of patients who have – disease-negative or asymptomatic disease (99%) – symptomatic disease (0.8%) – died (0.2%) over the duration of the model

Abbreviation: THT, thyroid hormone therapy.
[a]Health utilities for these health states were derived from the primary assessment (successfully ablated patients) (**Table 18**).

Other health outcome variables influencing the model are presented in **Table 21.** There is some uncertainty regarding both the diagnostic accuracy of rhTSH relative to THT withdrawal, and the proportion of disease-positive patients included in the cohort of patients presenting after one negative diagnostic follow-up result (the primary assessment). These inputs are tested in a sensitivity analyses.

Table 21 Other health outcome inputs

	rhTSH	THT withdrawal
Proportion of false-negatives	13%	0%
Proportion of false-positives	5%	0%
Proportion of disease-positive patients entering the model	20%	20%
Average radioiodine treatment courses required to ablate a true-positive patient successfully	1.5	1.5
Average radioiodine treatment courses required to ablate a false-positive patient successfully[a]	1	1

Abbreviation: THT, thyroid hormone therapy.
[a]As the patient is being treated for a disease they do not have, they will be 'cured' after the first treatment.

Costs and utilities are discounted at a rate of 5% per annum. Other assumptions applied to the model are presented in **Appendix J.**

Results of the modelled evaluation (primary assessment)

Incremental costs

The primary assessment model requires that all patients entering the model have already had a negative result at their previous diagnostic follow-up. Compared with the standard THT withdrawal procedure, the use of rhTSH in diagnostic follow-up for thyroid cancer results in an average cost per patient of $6761.10 over the 5-year period of the model. This reflects an average of 3.27 diagnostic follow-up tests and 0.758 treatment courses (excluding the initial thyroidectomy/radioiodine ablation treatment and first diagnostic follow-up). In contrast, the comparable average cost of THT withdrawal is $2308.90, reflecting an average of 2.12 diagnostic follow-up tests and 0.488 treatments. This equates to an incremental cost of $4452.20 per patient over the 5-year period of the model.

The difference in the number of diagnostic follow-up tests between the two diagnostic arms occurs primarily as a result of the improved compliance to rhTSH, because patients are not rendered hypothyroid. A second factor contributing to the increased number of diagnostic follow-up tests and treatments is the lower accuracy of rhTSH. In particular, the presence of false-positive results means that some patients receive unnecessary treatment. This has the added effect of requiring the patient to re-enter the model as a newly treated patient, thus incurring more frequent diagnostic tests.

It is not only the increased frequency of diagnostic follow-up testing that adds to the cost of rhTSH, but also the increased frequency of ablative treatment secondary to positive diagnostic results. This increase is driven by both increased compliance and reduced accuracy of scanning with rhTSH.

The unit cost of rhTSH *per se* (in this case Thyrogen™) is a major contributor to the incremental cost of rhTSH over THT withdrawal. **Figure 4** shows the total costs incurred in the 5-year model for the various components.

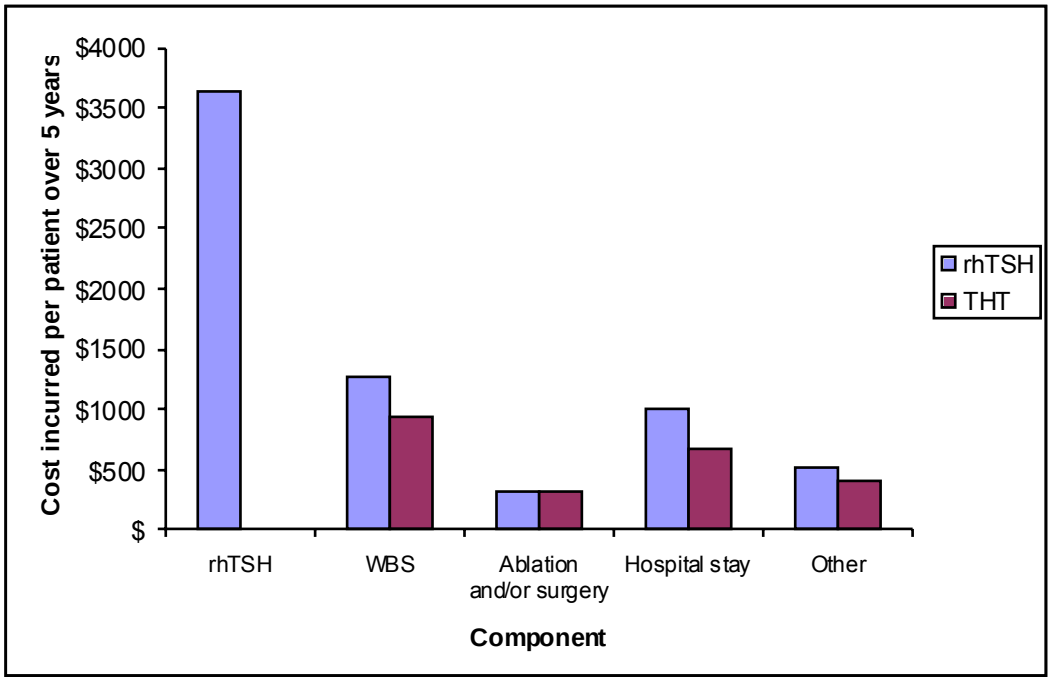

Figure 4 Total costs incurred in the 5-year model for the various components

Incremental outcomes

With regard to outcomes, rhTSH is associated with better quality of life for patients because they do not need to withdraw from thyroid hormones for diagnostic purposes and, therefore, do not become hypothyroid as a result. The use of rhTSH in diagnostic testing for thyroid cancer results in an average of 3.809 QALYs for the period of the model. [For comparison, 5 years of perfect health would be equivalent to 5.0 QALYs.] It is important to note that this includes 0.76 hypothyroid periods because patients using rhTSH for diagnostic use are currently required to use THT withdrawal for therapeutic use if they return a positive result[10].

In contrast, the average QALYs for patients in the THT withdrawal arm is 3.722, reflecting an average of 1.79 hypothyroid periods. The resultant incremental improvement in utility is 0.087. This is a small incremental difference in health utility, a consequence of improved utility occurring for an average of just six weeks per diagnostic follow-up period. The improved utility is not a permanent state and, once this is taken into account relative to the length of the period between diagnostic follow-ups, the difference in average utility between the THT withdrawal patients and rhTSH patients is quite small.

[10]rhTSH (Thyrogen™) is not currently registered for therapeutic use in Australia.

Table 22 Average per patient costs and outcomes resulting from the modelled evaluation (5-year time frame)

	rhTSH	Withdrawal	Incremental
Average cost	$6761.10	$2308.90	$4452.20
Average QALYs	3.809	3.722	0.087
Average number of scans	3.27	2.12	1.15
Average number of false-positives	0.1	0	0.1
Average number of false-negatives	0.07	0	0.07
Average number of treatments	0.758	0.488	0.270
Incremental cost-effectiveness (cost per QALY)			**$51,344.42[a]**

Abbreviation: QALY, quality-adjusted life-year.
[a]Incremental cost-effectiveness = Incremental cost/Incremental effectiveness. Incremental effectiveness is measured as incremental QALYs.

Incremental cost-effectiveness

The incremental cost-effectiveness in this case is expressed as a cost utility (cost per QALY). With significantly increased costs and a marginal improvement in average utility, the incremental cost-effectiveness of rhTSH in diagnostic scanning is $51,344.42 per QALY. This compares unfavourably with many other healthcare interventions (**Table 23**) and should be considered as only moderately cost-effective relative to standard THT withdrawal.

Table 23 Cost per QALY of other healthcare interventions

Therapy	Incremental cost per QALY (A$)	Source
Intensive care of infants (birth weight 500–999g)	$5360	(VICSG 1997)[a]
Childhood immunisation against Hib disease	$6930	(McIntyre *et al* 1994)
Cochlear implant for children	$5070–11,100	(Carter and Haily 1999)
Mammography screening	$16,355	(Hall *et al* 1992)
Cochlear implant for profoundly deaf adults	$11,790–38,150	(Carter and Haily 1999)
Raloxifene versus hormone replacement therapy for the prevention of hip fractures in osteoporotic women	$30,217	(Davey *et al* 2000)
Hospital dialysis	$57,053	(George *et al* 1998)

Abbreviations: QALY, quality-adjusted life-year; VICSG, Victorian Infant Collaborative Study Group.

Sensitivity analysis of the modelled evaluation

A number of variables in the model were derived with a degree of uncertainty. Consequently, different values have been ascribed to these variables in the sensitivity analysis in order to determine whether the initial values had a significant effect on the overall result. The variables considered in the sensitivity analysis were as follows.

- The compliance rate associated with the standard THT withdrawal method.
- The accuracy of the rhTSH and THT withdrawal (both sensitivity and specificity).

- The temporary health utility for a patient undergoing THT withdrawal.
- The proportion of disease-positive patients entering the model (for the primary assessment, patients enter the model subsequent to one negative diagnostic follow-up).
- The cost of rhTSH (Thyrogen™).
- The discount rate.
- The magnitude of all costs.
- Several simultaneous combinations of the above.

The specific adjustments made to the base case, and the resultant changes in the cost-utility ratio are presented in **Table 24**.

Table 24 Results of the sensitivity analyses

Variable and values	Marginal cost per QALY
Baseline case	**$51,344.42**
Compliance for THT withdrawal arm = 80%	
THT withdrawal sens = 100% , spec = 100% ; rhTSH sens = 87% , spec = 95%	
Health utility of THT withdrawal = 0.65	
Proportion of disease positive patients = 20%	
Cost of rhTSH = $1953	
5% discount rate	
Altered compliance of THT withdrawal	
1. 60%	$39,322.52
2. 100%	$107,937.69
Altered accuracy	
3. THT withdrawal sens = 98% , spec = 81% ; rhTSH sens = 86% , spec = 65% [a]	$133,702.32
4. THT withdrawal sens = 100% , spec = 100% ; rhTSH sens = 100% , spec = 100%	$48,890.25
Altered health utility for THT withdrawal	
5. 0.506 (–1 SD)	$41,162.93
6. 0.794 (+1 SD)	$68.217.84
Proportion of disease-positive patients	
7. 10%	$62,523.96
8. 30%	$46,148.55
Altered cost of rhTSH	
9. $1000	$30,829.44
Altered discount rate	
10. 0% discount rate	$49,693.98
11. 10% discount rate	$52,946.42
Altered costs	
12. Decrease all costs by 50%	$25,672.21
13. Increase all costs by 50%	$77,016.63
Combined sensitivity	
3 and 7	$222,826.38
3 and 8	$99,649.40
4 and 7	$52,788.96
4 and 8	$48,428.07

Abbreviations: THT, thyroid hormone therapy; QALY, quality-adjusted life-year.
[a]Adjusted for an imperfect standard using the method of Valenstein (1990).

The effectiveness of THT withdrawal is limited by the deterrent effect hypothyroidism has on compliance to follow-up diagnostic testing. However, the exact extent of non-compliance is uncertain. While the base case assumed a compliance rate in the THT arm of 80%, the sensitivity analysis investigated the effect of both 60% and 100%. With poorer compliance, the cost of scanning patients is reduced, but the disease-positive, non-complying patients do incur costs as a result of disease progression. They also have poor health utility for the same reason.

Consequently, if compliance rates are actually lower than has been assumed in the modelled evaluation, rhTSH becomes more cost-effective for use in diagnostic scanning. On the other hand, if the compliance rate in the THT withdrawal arm is actually higher than is assumed in the modelled evaluation, the cost-effectiveness of rhTSH is reduced. The results are shown in **Table 24**.

Figure 5 illustrates the cost per QALY of rhTSH over a range of compliance rates in the THT withdrawal arm.

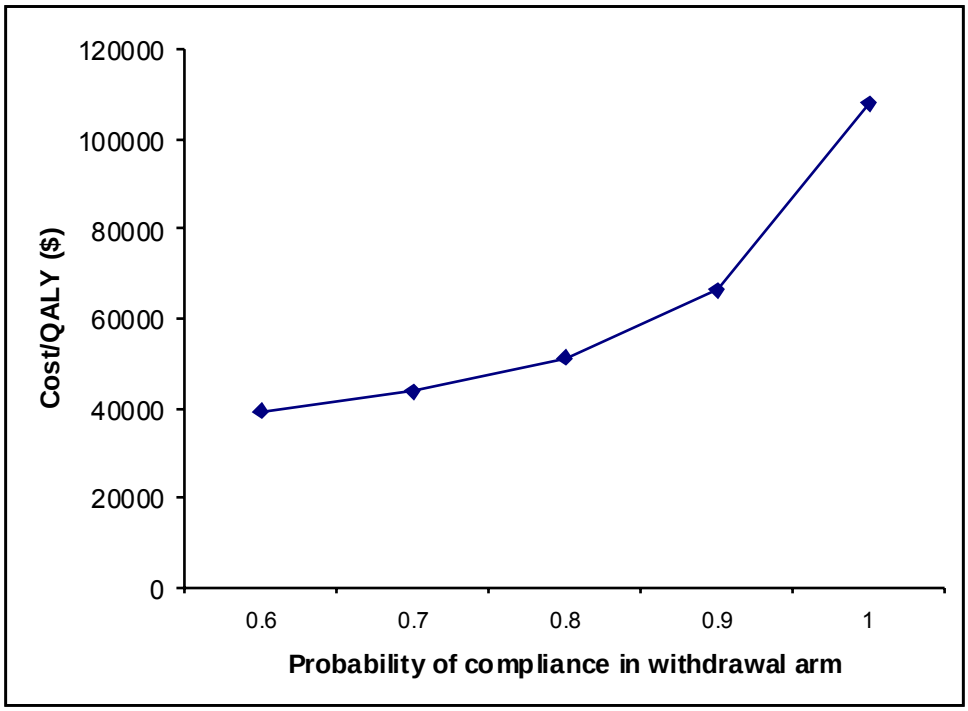

Figure 5 Cost-effectiveness of rhTSH with alterations in compliance in the THT withdrawal arm

The probabilities of reaching an accurate diagnosis using rhTSH have been obtained from the published literature (Haugen *et al* 1999), with a 13% chance of a false-negative and an 5% chance of a false-positive as the baseline case (ie, sensitivity = 87%, specificity = 95%). The accuracy of the THT withdrawal scan has been assumed to be perfect, in the absence of reliable data on which to base a better estimate. Because such an assumption may be viewed as unrealistic, two sensitivity analyses have been undertaken. The first applies the adjusted sensitivity and specificity values for rhTSH (86% and 65%, respectively) when assuming a sensitivity and specificity of THT withdrawal of 98% and 81%, respectively. The second sensitivity analysis assumes rhTSH returns perfectly accurate results.

The reduction in the marginal cost of rhTSH results from costs falling in the rhTSH arm as a result of a reduction in wasted resources. As the accuracy of scans using rhTSH improves, less unnecessary treatment is given and fewer patients receive additional scans before disease is detected following false-negative results. Consequently, with more efficient resource use, the marginal cost falls.

In terms of effectiveness, the average utility of patients in the rhTSH arm improves because fewer patients go through unnecessary treatment (and the withdrawal associated with the treatment) and fewer go through an extra withdrawal before the disease is successfully detected. However, it is apparent that while the lower diagnostic accuracy is important, it is not the main driver of the high base-case cost-effectiveness ratio. Even with perfect accuracy, the cost-effectiveness ratio remains at $48,890.

The ability to avoid a period of hypothyroidism prior to follow-up diagnostic testing is the clinical advantage offered by rhTSH. Therefore, it is important to test the impact of the health utility assigned to the hypothyroid health state. This value was derived from a trial in which patients and administrators were not blinded to the diagnostic intervention taking place. Furthermore, the order of the diagnostic interventions was not randomised or balanced. Therefore, it is possible that the subjective SF-36 scores on which the health utilities are based are affected by bias. The sensitivity analyses tested an increase and a decrease of one standard deviation in the THT withdrawal utility value. The results are shown in **Table 24**.

An unusual feature of the model is its specificity to the cohort of patients who have already returned a negative result in their first post-treatment diagnostic follow-up. Limiting the model to this cohort has the effect of reducing the proportion of disease-positive patients entering the model. To test the effect of this specification on the model, this proportion was altered. The results are displayed in **Table 24** and **Figure 6**.

Increasing the proportion of disease-positive patients increases the average cost of both rhTSH and THT withdrawal, because more patients require further treatment before progressing to less frequent scanning. Their longer presence in the model adds considerably to the overall costs. However, the difference between the costs in the two arms decreases. The increased probability of disease-positive patients also reduces the average utility of patients in both arms, as they remain in the model for longer. However, the utility of those in the THT withdrawal arm falls to a greater extent due to the poor utility associated with withdrawal. Because the change in the incremental effectiveness (the denominator of the cost-effectiveness ratio) increases more than the change in the incremental cost (the numerator), the overall effect of increasing the proportion of disease-positive patients is to decrease the cost-effectiveness ratio.

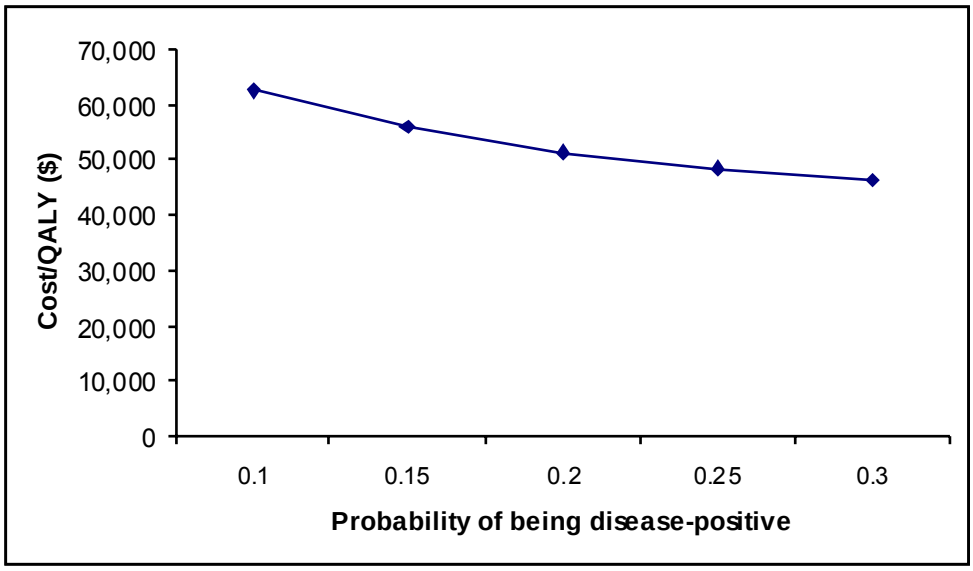

Figure 6 **Cost-effectiveness of rhTSH with alterations in the proportion of disease-positive patients entering the model**

It is also possible to test the impact of the cost of rhTSH *per se* upon the cost-effectiveness. Applying an rhTSH cost of $1000, for example, results in a cost of $30,829 per QALY. **Figure 7** shows the cost per QALY for a range of rhTSH costs. It is clear that the cost of rhTSH is a major determinant of the cost effectiveness ratio.

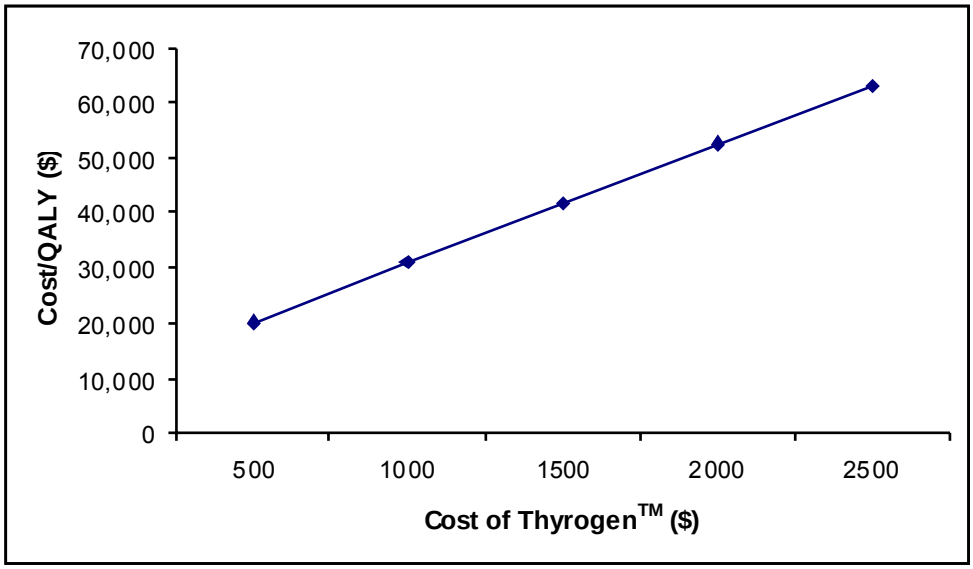

Figure 7 **Cost-effectiveness of rhTSH with alterations in the cost of rhTSH**

Several combined sensitivity analyses were conducted. This allowed for the situation where model inputs are altered simultaneously. The results are presented in **Table 24**.

Results of the modelled economic evaluation (secondary assessment)

The cost effectiveness of rhTSH from the time of the initial post-treatment was investigated using a second decision analytical model. The model and the results are presented in **Appendix K**.

Summary

A decision-analytic modelled evaluation was used to determine the costs and effectiveness of the use of rhTSH in follow-up diagnostic scanning for thyroid cancer, compared with the current method of THT withdrawal prior to scanning. The model was designed to capture the effects of the differences in costs between the two procedures, the poorer diagnostic accuracy of rhTSH scans, the improved quality of life associated with the proposed scanning method, and the effect of rhTSH in improving compliance rates.

The model was not only able to measure the incremental cost-effectiveness of the use of rhTSH, but was also capable of illustrating the extra resource use in terms of additional scans and treatment courses. Due to the lower accuracy of diagnostic testing when rhTSH is used, resource wastage occurs because of false-positive and false-negative results. However, more disease-positive patients are appropriately treated due to increased compliance in the rhTSH arm.

The average increase in utility associated with rhTSH is marginal because the period of lowest utility associated with THT withdrawal is only 6 weeks in duration for every scan (with intervals of up to 2 years between follow-up diagnostic testing). This, in addition to the extra costs incurred by less efficient use of resources, means that the cost-effectiveness ratio for rhTSH scanning is relatively high compared with the current method of withdrawing patients from THT. In fact, the cost per QALY of $51,344.42 in the baseline scenario lies marginally outside the range that is normally considered reasonably cost-effective for publicly funded health care intervention.

It is important to bear in mind the degree of uncertainty surrounding a number of variables within the model. In particular, there is uncertainty regarding the compliance rate for the current scanning procedure. Furthermore, the assumption of perfect accuracy in that test is likely to be unrealistic. Consequently, sensitivity analyses have been undertaken, illustrating that the cost-effectiveness ratio can change markedly with changes in these variables. For example, a modest reduction in the proposed cost of rhTSH would improve the value for money of this technology.

Financial impact

To estimate the total financial impact of reimbursement of rhTSH, it is necessary to multiply the costs incurred per diagnostic presentation by the number of these follow-up presentations. In doing this, an upper and lower bound are applied for the estimated number of presentations. The lower bound (945) is the number of scans per year minus the number of new patients each year, based on the assumption that new patients will undergo THT withdrawal for their initial post-treatment scan and that all scans that follow will be conducted using rhTSH WBS. The upper bound (2526) is the current number of scans per year. This assumes that all scans are replaced with rhTSH WBS – contrary to the indication. **Table 25** indicates the average cost per presentation per year derived from the modelled economic evaluation.

Table 25 Estimated total financial cost of rhTSH and THT withdrawal

	rhTSH	THT withdrawal	Incremental
Number of diagnostic follow-up presentations	945–2526	945–2526[b]	-
Modelled average cost of diagnostic presentations[a]	$1352.22	$461.78	$890.44
Total cost per annum	$1,277,848–3,415,708	$436,382–1,166,456	$841,466–2,249,251

Abbreviation: THT, thyroid hormone therapy.
[a]Includes all costs incurred within the model (diagnostic costs and treatment costs, such as completion thyroidectomy).
[b]These figures represent the number of THT withdrawal scans that would be replaced by those using rhTSH and, therefore, represent a cost saving.

These estimates exclude those patients who currently are undergoing diagnostic follow-up with on-THT serum Tg testing alone (ie, those for whom THT withdrawal is contraindicated). The magnitude of this patient cohort is unknown. If this cohort represents an additional 250 patients who could potentially undergo rhTSH WBS and Tg for diagnostic follow-up, the upper estimate of total rhTSH cost would increase to $3,753,763.

It should be noted that, so far, 100% market penetration for the low and high market potential estimates has been assumed. If 50% market penetration is assumed instead, this reduces the incremental financial impact to $421,187–1,124,626 or, if the 250 patients for whom THT withdrawal is contraindicated are included, $421,187–1,281,901.

In summary, as the total number of patients requiring diagnostic follow-up is small, the total financial cost of rhTSH is modest.

Conclusions

Recombinant human TSH is indicated for use with serum Tg testing and whole body radioiodine scanning undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer. This assessment focused primarily on the cohort of post-thyroidectomy patients who have already had one negative follow-up using the current THT withdrawal method.

Safety

In general, the adverse events associated with the use of rhTSH appear to be mild in nature. The most commonly reported adverse events associated with rhTSH use are headache and nausea. However, there are also individual case studies that report serious adverse events thought to result from the swelling of metastases after rhTSH administration. To reduce the incidence of these severe adverse events, pre-treatment with corticosteroids may be considered prior to the administration of rhTSH in patients with metastatic disease in confined spaces. The adverse events associated with rhTSH administration should be considered in the context of adverse events associated with hypothyroidism secondary to THT withdrawal.

Effectiveness

Evidence regarding the diagnostic accuracy of rhTSH relative to THT withdrawal was obtained from two studies classified as level 2 evidence. When used with concurrent serum Tg testing and WBS, the diagnostic accuracy of rhTSH was lower than that of THT withdrawal. In particular, the ability to detect a disease- or remnant-positive patient (sensitivity) was reduced.

An important finding of this assessment was the poor diagnostic accuracy of rhTSH-stimulated serum Tg testing alone, when compared with using rhTSH concurrently with WBS and serum Tg testing. This reinforces the practice of including both WBS *and* serum testing in the periodic follow-up of thyroid cancer patients.

This assessment focused primarily on the cohort of patients who had already had one negative follow-up using the current THT withdrawal method. However, the effectiveness results were found to be generalisable to the broader population of patients that includes those presenting for their first diagnostic follow-up.

In the group of patients for whom THT withdrawal is medically contraindicated, rhTSH-stimulated WBS together with serum Tg testing provides a considerable improvement in diagnostic accuracy, relative to on-THT serum Tg testing.

The disadvantage of poorer accuracy needs to be considered in the context of the improvement in quality of life (and hence compliance) that results from avoidance of the short (up to 12 weeks) and infrequent periods of hypothyroidism caused by THT withdrawal.

Cost-effectiveness

The diagnostic use of rhTSH results in significantly increased cost and only a marginal improvement in average utility, relative to THT withdrawal. The incremental cost-utility ratio does not compare favourably with other health care interventions. However, this result is highly sensitive to the proposed cost of rhTSH *per se*. Furthermore, the value for money of rhTSH is somewhat improved if indirect costs are included (**Appendix L**).

When the population using rhTSH is broadened to include patients who have not already had a negative follow-up using THT withdrawal, rhTSH becomes considerably less cost-effective.

The total population for whom the diagnostic use of rhTSH is indicated is small. For this reason, the total financial impact of public reimbursement is likely to be modest.

Recommendation

MSAC recommended that on the strength of evidence pertaining to the diagnostic use of recombinant thyroid-stimulating hormone in well-differentiated thyroid cancer, public funding should be supported for this procedure only in patients in whom THT withdrawal is medically contraindicated. In addition, on the basis of the current evidence, both rhTSH-stimulated whole body scanning and serum Tg testing should be undertaken concurrently. MSAC recommends that public funding for rhTSH should not be supported in patients who are able to tolerate THT withdrawal, on the basis of lower diagnostic sensitivity and a high cost-effectiveness ratio.

The Minister for Health and Ageing accepted this recommendation on 16 October 2002.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or affiliation
Dr Stephen Blamey (Chair)	General surgery
Professor Bruce Barraclough	General surgery
Professor Syd Bell	Pathology
Dr Paul Craft	Clinical epidemiology and oncology
Professor Ian Fraser	Reproductive medicine
Associate Professor Jane Hall	Health economics
Dr Terri Jackson	Health economics
Ms Rebecca James	Consumer health issues
Professor Brendon Kearney	Health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Associate Professor Richard King	Internal medicine
Dr Ray Kirk	Health research
Dr Michael Kitchener	Nuclear medicine
Mr Lou McCallum	Consumer health issues
Emeritus Professor Peter Phelan	Paediatrics

Dr Ewa Piejko	General practice
Dr David Robinson	Plastic surgery
Professor John Simes	Clinical epidemiology and clinical trials
Professor Richard Smallwood	Chief Medical Officer, Commonwealth Department of Health and Ageing
Professor Bryant Stokes	Neurological surgery, representing the Australian Health Ministers' Advisory Council
Associate Professor Ken Thomson	Radiology
Dr Douglas Travis	Urology

Appendix B Supporting committee

Supporting committee for MSAC application 1043
Recombinant human thyroid-stimulating hormone as a diagnostic agent for well-differentiated thyroid cancer

Mr Stephen Blamey (Chair) BSc, MBBS, FACS, FRACS General Surgeon Monash Medical Centre, Melbourne	Chair of MSAC
Professor Bruce Barraclough MBBS, FRACS, DDU, FACS General Surgeon Royal North Shore Hospital, Sydney	MSAC Member
Dr Michael Kitchener MBBS, FRACP Nuclear Medicine Specialist, Adelaide	MSAC Member
Dr Roger Allison MBBS, FRCR, DMRT, DObstRCOG Radiation Oncologist Royal Brisbane Hospital	nominated by the Royal Australian and New Zealand College of Radiologists
Professor Leigh Delbridge BMedSc, MBBS, FRACS, MD Surgeon Royal North Shore Hospital, Sydney	nominated by the Royal Australasian College of Surgeons
Dr Bruce Robinson MBBS, MSc Endocrinologist Royal North Shore Hospital, Sydney	nominated by the Endocrine Society
Dr Monica Rossleigh MBBS, FRACP, MD Nuclear Medicine Specialist Royal Prince of Wales Hospital, Sydney	nominated by the Australia and New Zealand Association of Physicians in Nuclear Medicine
Ms Catherine Thompson RN, Grad Dip Geront (Mon) Consumer Representative	Nominated by the Consumers' Health Forum

Appendix C Studies included in the review

Table 26 Characteristics of studies included in the effectiveness review

Study	Location/ date	Population	QS	Age (years)/ gender (M/F)	Study focus	Protocol	Reference test
Haugen	US, multicentre/ (1999)	Patients with differentiated thyroid cancer 62% Papillary 17% Follicular	9	Age (mean = 44±15) Gender (43/74)	To compare the effects of two different dosing regimens of rhTSH with THT withdrawal	Prospective, evaluator-blinded[a], with sequential diagnostic measurements	Concordance with THT withdrawal WBS and/or serum Tg
Ladenson	US, multicentre/ (1997)	Patients with differentiated thyroid cancer 88% Papillary 9% Follicular	9	Age (mean = 44)	To evaluate the efficacy and side effects of rhTSH administration as compared with THT withdrawal	Prospective, evaluator-blinded, with sequential diagnostic measurements	Concordance with THT withdrawal WBS
Mazzaferri and Kloos	US/ (2002)	Patients with differentiated thyroid cancer 71% Papillary 9% Follicular	2	Age (median = 36.3) Gender (19/88)	To evaluate the utility of rhTSH-stimulated serum Tg on patients with undetectable or low on-THT serum Tg values	Retrospective, with a combination of variable reference standards	Variable
Pacini	Italy/ (2001)	Patients with differentiated thyroid cancer 92% Papillary 8% Follicular	9	Age (mean = 39.4±13.1) Gender (21/72)	To evaluate the utility of rhTSH-stimulated serum Tg on patients with undetectable on-THT serum Tg values	Prospective, with sequential diagnostic measurements	THT withdrawal WBS and serum Tg
Robbins	US, single centre/ (2001)	Patients with differentiated thyroid cancer 87% Papillary 8% Follicular	0	Age (mean = 44.2–45.6) Gender (110/179)	To evaluate the efficacy of rhTSH when compared to THT withdrawal	Retrospective, parallel cohort	Composite of all clinical information

Abbreviations: QS, quality score; WBS, radioiodine whole body scan; Tg, thyroglobulin; rhTSH, THT, thyroid hormone therapy.
[a]Based on the quality scoring system described in **Appendix F.**
[b]Only WBS was evaluator blinded, serum Tg was assessed unblinded.

Appendix D Literature search strategies

Medline search strategy

The search strategy used to identify relevant studies of rhTSH in Medline is presented in **Table 27**.

Table 27 rhTSH MEDLINE search strategy (1966 to April week 1 2002)

	Keyword/search history	Results
1	exp Thyroid neoplasms/	21,158
2	thyroid neoplasm$.mp.	20,634
3	exp thyroidectomy/ or thyroidectomy.mp.	11,443
4	thyroid cancer$.mp.	4543
5	differentiated thyroid.mp.	1676
6	thyroid remnant$.mp.	200
7	exp Neoplasm recurrence, local/	40,521
8	thyroid carcinoma$.mp.	6412
9	neoplasm recur$.mp.	40,553
10	exp Neoplasm, residual/	2057
11	residual neoplasm$.mp.	25
12	or/1–1	71,143
13	thyrogen.mp.	9
14	recombinant human thyrotropin.mp.	52
15	recombinant thyrotropin.mp.	17
16	recombinant human thyroid stimulating hormone.mp.	22
17	recombinant thyroid stimulating hormone.mp.	4
18	recombinant human TSH.mp.	68
19	recombinant TSH.mp.	57
20	exogenous human thyroid stimulating hormone.mp.	0
21	exogenous thyroid stimulating hormone.mp.	9
22	exogenous human tsh.mp.	2
23	exogenous tsh.mp.	84
24	exogenous human thyrotropin.mp.	0
25	exogenous thyrotropin.mp.	31
26	rhTSH.mp.	56
27	rTSH.mp.	46
28	thyrotropin alpha.mp.	30
29	thyrotropin alfa.mp.	4
30	exp Thyrotropin/du [Diagnostic Use]	361
31	194100-83-9.rn.	0
32	or/13–1	673
33	12 and 32	175
34	animal.sh.	3,247,184
35	human.sh.	7,520,555
36	34 not 35	2,541,206
37	33 not 36	170
38	limit 37 to yr=1980–2002	115

Embase search strategy

The search strategy used to identify relevant studies of rhTSH in Embase is presented in **Table 28**.

Table 28 rhTSH Embase search strategy (1980 to 2002 week 14)

	Keyword/search history	Results
1	exp Thyroid tumor/	13,669
2	thyroid neoplasm$.mp.	413
3	exp subtotal thyroidectomy/ or exp thyroidectomy/ or thyroidectomy.mp.	5672
4	thyroid cancer$.mp.	5424
5	thyroid carcinoma$.mp.	7222
6	differentiated thyroid.mp.	1550
7	thyroid remnant$.mp.	175
8	exp Recurrent cancer/	2383
9	neoplasm recur$.mp.	44
10	NEOPLASM, RESIDUAL.mp.	1
11	residual neoplasm$.mp.	24
12	or/1–11	19,953
13	thyrogen.mp.	31
14	recombinant human thyrotropin.mp.	52
15	recombinant thyrotropin.mp.	75
16	recombinant human thyroid stimulating hormone.mp.	20
17	recombinant thyroid stimulating hormone.mp.	4
18	recombinant human TSH.mp.	62
19	recombinant TSH.mp.	55
20	exogenous human thyroid stimulating hormone.mp.	0
21	exogenous thyroid stimulating hormone.mp.	6
22	exogenous human tsh.mp.	2
23	exogenous tsh.mp.	51
24	exogenous human thyrotropin.mp.	0
25	exogenous thyrotropin.mp.	16
26	rhTSH.mp.	49
27	rTSH.mp.	36
28	thyrotropin alpha.mp.	18
29	thyrotropin alfa.mp.	1
30	exp Thyrotropin/ad,ae,im,an,it,cb,iv,cm,pd,cr,pe,ct,pk,do,pr,dt,sc,dv	569
31	194100-83-9.rn.	45
32	or/13-31	812
33	12 and 32	163
34	animal.sh.	15,432
35	human.sh.	3,922,096
36	34 not 35	12,603
37	33 not 36	163

Appendix E List of citations and reasons for exclusion

1. Anonymous (1996), M.D. Anderson studies drug for thyroid cancer testing. *Oncology* 10: 820-829
   Reason for exclusion: news article

2. Achong DM, Tenorio LE (2001). I-123 uptake by mediastinal goiter after recombinant human thyroid-stimulating hormone administration. *Clinical Nuclear Medicine* 26: 817-819
   Reason for exclusion: wrong patient group

3. Ain KB, Taylor KD (1994). Somatostatin analogs affect proliferation of human thyroid carcinoma cell lines *in vitro*. *Journal of Clinical Endocrinology & Metabolism* 78: 1097-1102
   Reason for exclusion: non-human study

4. Antonicelli F, Omri B, Breton MF, Rothhut B, Russo-Marie F, Pavlovic-Hournac M, Haye B (1989). Identification of four lipocortin proteins and phosphorylation of lipocortin I by protein kinase C in cytosols of porcine thyroid cell cultures. *FEBS Letters* 258: 346-350
   Reason for exclusion: non-human study

5. Aslam SN, Daly RG (2001). Use of recombinant human thyrotropin in a complicated case of metastatic papillary thyroid carcinoma. *Endocrine Practice* 7: 99-101
   Reason for exclusion: wrong usage

6. Aust G, Scherbaum WA (1996). Expression of cytokines in the thyroid: Thyrocytes as potential cytokine producers. *Experimental & Clinical Endocrinology & Diabetes* 104: 64-67
   Reason for exclusion: review

7. Banu KS, Govindarajulu P, Aruldhas MM (2001). Testosterone and estradiol have specific differential modulatory effect on the proliferation of human thyroid papillary and follicular carcinoma cell lines independent of TSH action. *Endocrine Pathology* 12: 315-327
   Reason for exclusion: non-human study

8. Basaria S, Westra WH, Cooper DS (2001). Clinical case seminar: Ectopic lingual thyroid masquerading as thyroid cancer metastases. *Journal of Clinical Endocrinology & Metabolism* 86: 392-395
   Reason for exclusion: wrong patient group

9. Baskin HJ, Atwood TM, Holcomb LP (2000). Recombinant human thyrotropin stimulation of thyroglobulin in the follow-up of patients with stage I or II differentiated thyroid carcinoma. *Endocrine Practice* 6: 430-434
   Reason for exclusion: non-comparative study

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: review

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: wrong patient group

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Reason for exclusion: *in vitro* study

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Reason for exclusion: small sample size

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Reason for exclusion: non-comparative study

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Reason for exclusion: review

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Reason for exclusion: *in vitro* study

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: editorial

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: small sample size

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Reason for exclusion: review

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: *in vitro* study

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: non-human study

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Reason for exclusion: *in vitro* study

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Reason for exclusion: non-human study

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: review

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Reason for exclusion: *in vitro* study

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Reason for exclusion: small sample size

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Reason for exclusion: wrong usage

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Reason for exclusion: *in vitro* study

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Reason for exclusion: wrong usage

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Reason for exclusion: non-comparative study

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Reason for exclusion: wrong patient group

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Reason for exclusion: survey

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: small sample size

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Reason for exclusion: small sample size

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: review

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Reason for exclusion: note

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Reason for exclusion: review

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Reason for exclusion: wrong usage

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Reason for exclusion: wrong usage

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: wrong patient group

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Reason for exclusion: wrong usage

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Reason for exclusion: editorial

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Reason for exclusion: non-comparative study

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Reason for exclusion: letter

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: review

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: editorial

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: *in vitro* study

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Reason for exclusion: *in vitro* study

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: review

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: review

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: *in vitro* study

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: review

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: review

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Reason for exclusion: *in vitro* study

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Reason for exclusion: review

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Reason for exclusion: wrong patient group

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Reason for exclusion: non-comparative study

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: editorial

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Reason for exclusion: *in vitro* study

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: small sample size

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: non-human study

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Reason for exclusion: editorial

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Reason for exclusion: review

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Reason for exclusion: review

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Reason for exclusion: letter

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Reason for exclusion: review

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Reason for exclusion: non-human study

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Reason for exclusion: *in vitro* study

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Reason for exclusion: review

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Reason for exclusion: non-human study

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Reason for exclusion: not a rhTSH study

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Reason for exclusion: *in vitro* study

Appendix F Quality scoring

Table 29 Quality scoring scale for trials of rhTSH

Evaluation criteria	Quality score
Criteria for study validity	
A. Was the test compared with a valid reference measure?	
The test was compared to different reference measures	0
The test was compared consistently to an imperfect reference measure/s	1
The test was compared consistently to a near perfect reference measure/s	2
B. Were the test and the reference standard measured independently (blind) of each other?	
The test and reference standard were not measured independently of each other	0
The reference standard was measured independently of the test but not vice versa	1
The test was measured independently of the reference standard but not vice versa	2
The test was measured independently of the reference standard and the reference standard independently of the test	3
C. Was the choice of patients who were assessed by the reference standard independent of the test results (avoidance of verification bias)?	
No	0
Partially	1
Yes	2
D. Was the test performed independently of all other clinical information?	
No	0
Yes	1
E. Was the reference standard measured before any interventions were started with knowledge of test results (avoidance of treatment paradox)?	
No	0
Yes	1
Additional validity criteria for studies comparing tests	
F. Were tests (test, reference standard and comparator) compared in a valid design?	
Different tests done on different individuals, not randomly allocated	0
Different tests done on randomly allocated individuals	1
All tests performed on each individual	2
Criteria relevant to the applicability of the results	
G. The clinical problem	
Not representative of patient group reviewed (eg, a high/low percentage of patients with advanced disease)	0
Partially representative of patient group (eg, a high/low prevalence of positive patients)	1
Representative of patient group (eg, disease prevalence approximating the patient group in which the test will be used)	2
Highly representative of patient group (eg, disease prevalence and severity nearly identical to the patient group in which the test will be used)	3

Appendix G Study characteristics

Table 30 Characteristics of the five comparative trials included in the analysis of efficacy of the diagnostic use of rhTSH in thyroid cancer

Authors	N	Design	Appropriateness of patient population to indication under review	Appropriateness of scanning technique to Australian practice	Avoided patient selection bias [a]	Avoided verification bias[b]	Avoided measurement bias[c]	Avoided intervention bias[d]	Sensitivity and specificity
Haugen *et al* (1999)	229 (226)	Phase III, prospective, open-label trial with sequential diagnostic measurements Randomised to two dosing regimens Blinding: three blinded evaluators for ^{131}I scans Withdrawal rate: 1.3% Arms: 2; 2 × rhTSH 24 hours apart vs 3 × rhTSH 72 hours apart; rhTSH followed by THT withdrawal	142/229 (62.0%) papillary 40/229 (17.0%) papillary/follicular 39/229 (17%) follicular 8/229 (3%) Hurthle cell. 49/229 (21%) metastatic disease 83% previous radioiodine therapy Cancer stage 56% stage I 20% stage II 17% stage III 7% stage IV 49% of patients tested positive in one or both scans	Whole body: minimum 30 minutes or 140,000 counts Spot images: minimum 10–15 minutes or 60,000 counts for large field or 35,000 counts for small field	No	Yes	Reference = THT withdrawal scan. Three scan evaluators were blind to diagnostic technique (evaluated in 'pairs')	Yes	<u>Published results</u> Concordance Arm I: WBS Concordant = 101 (89%) Discordant = 12 (11%) rhTSH scan superior = 3 (3%) THT withdrawal scan superior = 9 (8%) <u>Evaluation results</u> Arm I (Primary analysis, successfully ablated patients): Sensitivity = 87% Specificity = 95% Accuracy = 89% PPV = 98% NPV = 74%

Authors	N	Design	Appropriateness of patient population to indication under review	Appropriateness of scanning technique to Australian practice	Avoided patient selection bias [a]	Avoided verification bias[b]	Avoided measurement bias[c]	Avoided intervention bias[d]	Sensitivity and specificity
Ladenson *et al* (1997)	152 (127)	Phase III; prospective, open-label trial with sequential diagnostic measurements, Blinding: three blinded evaluators for ^{131}I scans Withdrawal rate: 16.4% Arms: 1; rhTSH followed by THT withdrawal	Papillary = 112/127 (88%) Follicular = 12/127 (9%) Hurthle cell = 3/127 (2%) 39% had metastatic disease 77% had previous radioiodine therapy 49% of patients tested positive in one or both scans Sites of radioiodine concentrating tissue after most recent surgery No uptake = 3/127 (2.0%) Thyroid bed 75/127 (59.0%) Other cervical 34/127 (27.0%) Intrathoracic 10/127 (7.9%) Skeletal 5/127 (3.9%)	No details provided	No Large drop-out rate	Yes	Reference = THT withdrawal scan Three scan evaluators were blind to diagnostic technique (not clear if they were evaluated in 'pairs')	Yes	<u>Published results</u> *WBS alone:* Sensitivity = 69% Specificity = 96% Accuracy = 83% PPV = 93% NPV = 78% *Serum Tg alone:* Serum Tg only measured in 35 patients. Serum Tg measured at sub-optimal time point and in separate testing facilities *Tg & scan:* not reported <u>Evaluation results</u> (metastatic disease WBS alone class ≥2) Sensitivity = 60% Specificity = 95% Accuracy = 92% PPV = 46% NPV = 97%

Authors	N	Design	Appropriateness of patient population to indication under review	Appropriateness of scanning technique to Australian practice	Avoided patient selection bias [a]	Avoided verification bias[b]	Avoided measurement bias[c]	Avoided intervention bias[d]	Sensitivity and specificity
Mazzaferri and Kloos (2002)	107	Retrospective study with a combination of variable reference standards	Typical papillary carcinoma (71%), variant (9%), tall cell (2%), or Hurthle cell variant (1%). Papillary carcinomas; or typical follicular (11%) or Hurthle cell (6%) carcinoma 2 patients had distant metastases when thyroid cancer was initially diagnosed. Patients with papillary or follicular thyroid cancer who had undergone rhTSH testing were studied if, before rhTSH testing, they had been free of disease on the basis of clinical examination and had one or more undetectable or low serum Tg measurement taken while receiving thyroid hormone therapy. All had previously undergone Dx WBS and Rx WBS after initial ablation, chest X-ray.	Imaging was performed with 3.8–5.1 mCi (141–189 MBq) ^{131}I. Images were obtained using a Picker Prism XP camera. WBS with anterior and posterior views were performed at a scan speed of 5.23 cm/min	No	No. The reference standard varied between patients	No. rhTSH test results were used to determine follow up tests	No	<u>Published results/evaluation results</u> *rhTSH serum Tg* *(>2.0 ng/mL)* Sensitivity =100 % Specificity = 91% Accuracy = 92% PPV = 55% NPV = 87% *rhTSH WBS* Sensitivity = 27% Specificity = 91% Accuracy = 84% PPV = 25% NPV = 95%

Authors	N	Design	Appropriateness of patient population to indication under review	Appropriateness of scanning technique to Australian practice	Avoided patient selection bias [a]	Avoided verification bias[b]	Avoided measurement bias[c]	Avoided intervention bias[d]	Sensitivity and specificity
Pacini *et al*, (2001)	72	Prospective study with sequential diagnostic interventions (rhTSH and Tg, then THT withdrawal WBS and Tg)	Patients with well differentiated thyroid cancer (66 papillary and 6 follicular), previously treated with near-total thyroidectomy and 131-I thyroid ablation, scheduled for routine diagnostic WBS regardless of any clinical suspicion of metastatic disease. Admission criteria were: an undetectable (<1 ng/mL) serum Tg on T_4 suppressive therapy, and negative anti-Tg antibodies at the time of inclusion.	Scan speed was 10 cm/min, with a total count of at least 100,000 cpm. Imaging was performed 72 h after the administration of a 4 mCi tracer dose radioiodine.	Consecutive patients	All patients received the rhTSH Tg test and the THT withdrawal Tg and WBS	Reference standard serum Tg and WBS in hypothyroid patients. Not reported if WBS evaluation was blinded	Yes	Evaluation results *rhTSH Serum Tg (<1.0 ng/mL)* Sensitivity = 74% Specificity = 100% Accuracy = 85% PPV = 100% NPV = 73%

Authors	N	Design	Appropriateness of patient population to indication under review	Appropriateness of scanning technique to Australian practice	Avoided patient selection bias [a]	Avoided verification bias[b]	Avoided measurement bias[c]	Avoided intervention bias[d]	Sensitivity and specificity
Robbins *et al* (2001)	128 (rhTSH) and 161 (THT with-drawal)	Retrospective, open-label, parallel cohort study Not randomised (patient chose either rhTSH or THT withdrawal) Blinding: na Withdrawal: na Arms: 2; rhTSH vs THT withdrawal	rhTSH 87% papillary 8% follicular 23% had distant metastases within the first 3 months of cancer diagnosis 51% had evidence of metastatic thyroid cancer 37% had no evidence of disease 37% had thyroid bed uptake only 59% received ^{131}I treatments prior to study enrolment Cancer stage Stage I = 44% Stage II = 15% Stage III = 26% Stage IV = 16% THT withdrawal 81% papillary 7% follicular 18% had distant metastases within the first 3 months of cancer diagnosis	WBS 8 cm/minute 10 minute neck views	Yes, all subsequent patients in 1998–99 were included but bias introduced by allocation to parallel groups 1. Patients recruited in 1998 had to meet FDA criteria (ie, can't elevate endogenous TSH with THT withdrawal or intolerant to hypo-thyroidism	N/A to this design	Reference standard = clinical status, either metastatic (MET) or no evidence of disease (NED) MET criteria: 1. Suppressed Tg > 2 µg/mL with abnormal radiographic result 2. Suppressed Tg >10 µg/mL with prior metastatic disease 3. Low Tg but positive post-therapy scan 4. Positive PET scan Thyroid bed only (TB) patients were shown separately, and excluded from main analysis (15% and 40%)	Retrospective design increases likelihood of different interventions between arms. 11 patients excluded in whom clinical status could not be assigned	Published results[e] *rhTSH WBS* Sensitivity = 69% Specificity = 100% Accuracy = 83% PPV = 100% NPV = 71% *THT withdrawal WBS* Sensitivity = 80% Specificity = 93% Accuracy = 84% PPV = 96% NPV = 67% *rhTSH Tg (>2 ng/mL)* Sensitivity = 86% Specificity = 82% Accuracy = 84% PPV = 87% NPV = 80% *THT withdrawal Tg (>2 ng/mL)* Sensitivity = 79% Specificity = 89% Accuracy = 82% PPV = 95% NPV = 62%

Authors	N	Design	Appropriateness of patient population to indication under review	Appropriateness of scanning technique to Australian practice	Avoided patient selection bias [a]	Avoided verification bias[b]	Avoided measurement bias[c]	Avoided intervention bias[d]	Sensitivity and specificity
Robbins *et al* (2001) cont.			45% had evidence of metastatic thyroid cancer 17% had no evidence of disease 12% had thyroid bed uptake only 49% received ^{131}I treatments prior study enrolment Cancer stage Stage I = 45% Stage II = 16% Stage III = 23% Stage IV = 15%		2. Patients recruited in 1999 believed THT withdrawal better; may not have chosen rhTSH if not insured; may have presented already withdrawn; bias toward rhTSH if bad hypo–thyroidism symptoms or had already experienced previous THT withdrawal Exclusion of Thyroid bed only patients from analysis may bias results				*rhTSH WBS or Tg (>2 ng/mL)* Sensitivity = 98% Specificity = 82% Accuracy = 92% PPV = 89% NPV = 97% *THT withdrawal WBS or Tg (>2 ng/mL)* Sensitivity = 96% Specificity = 81% Accuracy = 92% PPV = 93% NPV = 88% Evaluation results[f] *rhTSH WBS* Sensitivity = 77% Specificity = 100% Accuracy = 85% PPV = 100% NPV = 71% *THT withdrawal WBS* Sensitivity = 89% Specificity = 93% Accuracy = 90% PPV = 98% NPV = 65%

Authors	N	Design	Appropriateness of patient population to indication under review	Appropriateness of scanning technique to Australian practice	Avoided patient selection bias [a]	Avoided verification bias[b]	Avoided measurement bias[c]	Avoided intervention bias[d]	Sensitivity and specificity
Robbins *et al* (2001) cont.									*rhTSH Tg (>2 ng/mL)* Sensitivity = 76% Specificity = 82% Accuracy = 78% PPV = 88% NPV = 67% *THT withdrawal Tg (>2 ng/mL)* Sensitivity = 70% Specificity = 89% Accuracy = 92% PPV = 97% NPV = 39% *rhTSH WBS or Tg (>2 ng/mL)* Sensitivity = 99% Specificity = 82% Accuracy = 93% PPV = 90% NPV = 97% *THT withdrawal WBS or Tg (>2 ng/mL)* Sensitivity = 98% Specificity = 81% Accuracy = 95% PPV = 96% NPV = 88%

Abbreviations: FDA, Food and Drugs Administration; PET, positron emission tomography; PPV, positive predictive value; NPV, negative predictive value; Tg, thyroglobulin; THT, thyroid hormone therapy; DxWBS, diagnostic whole body scanning; RxWBS, therapeutic whole body scanning; WBS, whole body scanning.

[a] Consecutive attendees.

[b] ie, did all patients get both tests irrespective of results?

[c] Valid reference standard? Test and reference standard measured independently of each other? Independent of other clinical information?

[d] Any intervention that could have impacted on either the test or reference standard results.

[e] Excluding patients with thyroid bed uptake

[f] Including patients with thyroid bed uptake

Appendix H Radioiodine uptake classification system

Table 31 Radioiodine WBS uptake classification system

Description	Class	Criteria
No uptake	0	No evidence of post-thyroidectomy thyroid remnant, well differentiated thyroid cancer within the thyroid bed, or metastases
Uptake limited to thyroid bed	1	Evidence of well-differentiated thyroid cancer or persistent remnant limited to the thyroid bed
Uptake outside the thyroid bed but limited to the neck region (exclusive of class 1)	2	Evidence of well-differentiated thyroid cancer – local metastases
Uptake evident	2A	Solitary focus of uptake
Uptake evident	2B	Multiple foci of uptake
Uptake in the chest	3	Evidence of distant metastases
	3A	Uptake in mediastinum but not in the lungs
	3B	Nodular foci of uptake in the lungs
	3C	Diffuse uptake in the lungs
	3D	Any combination of 3A, 3B and/or 3C
Uptake outside of the neck and chest areas	4	Evidence of distant metastases
	4A	Solitary focus in the skeleton
	4B	More than one focus in the skeleton
	4C	One or more foci of uptake in the liver tissue
	4D	One or more foci of uptake in the brain tissue
	4E	Any combination of 4A or 4B with 4C or 4D

Appendix I rhTSH and WBS in the detection of metastatic disease

Secondary evaluation: use of rhTSH in conjunction with WBS alone to detect metastatic disease

Evidence relating to the effectiveness of rhTSH use for the detection of metastatic disease by radioiodine WBS alone was available from two studies (Haugen *et al* 1999) (**Table 32**) (Ladenson *et al* 1997). As noted previously, the assessment of radioiodine WBS was performed in a blinded fashion in both of these studies. Therefore, the radioiodine WBS assessments for both studies were classified as level 2 evidence.

Table 32 rhTSH/THT withdrawal effectiveness in the detection of metastatic disease by WBS

Trial	WBS metastatic disease positive definition	Testing mode	Sensitivity	Specificity	Accuracy	PPV	NPV
Haugen (1999)	Class ≥ 2	rhTSH	80% **	100%	98%	100%	98%
	Class ≥ 2	THT withdrawal	100%	100%	100%	100%	100%
Ladenson (1997)	Class ≥ 2	rhTSH	60% *	95% *	92%	46%	97%
	Class ≥ 2	THT withdrawal	100%	100%	100%	100%	100%

Abbreviations: THT, thyroid hormone therapy; WBS whole body radioiodine scan; PPV, positive predictive value; NPV, negative predictive value

*Denotes a significant difference between rhTSH and THT withdrawal ($p < 0.05$) (method 10 of Newcombe (1998)).

**Denotes a significant difference between rhTSH and THT withdrawal ($p < 0.01$) (method 10 of Newcombe (1998)).

When WBS is used alone to detect metastatic disease, and a patient with metastatic disease is defined as one with a WBS class of ≥ 2, the sensitivity of rhTSH was in the range 60–80 per cent, and the specificity was 95–100 per cent.

Appendix J Assumptions in the modelled economic evaluation

Tables 33 and **34** present the assumptions used in the primary assessment economic model.

Table 33 General assumptions incorporated into the model

Assumption	Rationale/source
The model terminates after 5 years	This assumption simply serves to limit an otherwise infinite process. Expert opinion agreed that a 5-year period would be likely to capture most of the costs and effectiveness of the diagnostic procedure
A patient exits after three consecutive negative results	Assumption. A patient with three consecutive negative results has a low probability of recurrence
A patient with a true-positive result is successfully treated with an average of 1.5 treatment courses	Expert opinion
A patient with a false-positive result is successfully treated with one treatment course	As the patient is being treated for a disease they do not have, they will be cured after the first treatment
There is perfect compliance with the first post-treatment scan	Patients have not yet had confirmation of the success of initial treatment and therefore perfect compliance is assumed *(only applies to secondary assessment model)*
A patient in the rhTSH arm who requires treatment, must undergo THT withdrawal prior to therapeutic use	rhTSH is not currently indicated for therapeutic use in Australia
Costs and utilities are discounted at 5% pa	Convention

Abbreviation: THT, thyroid hormone therapy.

Table 34 Assumptions regarding costs incorporated into the model

Assumption	Rationale/source
100% of patients receive a Tg antibody test with a serum Tg test	Best practice
A patient in the THT withdrawal arm of the model receives a TSH measurement an average of 1.1 times per withdrawal	Expert opinion
100% of patients comply with testing in the rhTSH arm of the model	Hypothyroidism is avoided
80% of patients comply with testing in the THT withdrawal arm of the model	Expert opinion. Patients choose not to comply due to hypothyroidism. This assumption is tested in the sensitivity analysis
10% of true-positive patients receive a completion thyroidectomy as part of their follow-up treatment, when they test positive again	A proportion of those facing a second course of treatment before continuing on through the model will require further surgery, as initial surgery was incomplete
50% of patients undertake T_3 replacement therapy	Expert opinion
95% of disease-negative patients in the rhTSH arm receive a true-negative result	Haugen *et al* (1999)
87% of disease-positive patients in the rhTSH arm receive a true-positive result	Haugen *et al* (1999)
The accuracy of the diagnostic procedure in the THT withdrawal arm is perfect	Assumption. This is discussed in the clinical section of this submission. An adjusted accuracy is tested in the sensitivity analysis
The entire 50% of patients not undertaking T_3 replacement therapy remain on T_4 for 2 weeks into the 6-week 'withdrawal' period	Expert opinion
Those remaining on T_4 for the additional 2 weeks receive 100 mg/day of T_4	MIMS 2002 (maintenance dose 100–150 mg/day)
Of those disease-positive patients who do not comply with further testing, an average of 50% remain in a state of having asymptomatic disease, 40% progress to symptomatic disease (usually metastatic) and 10% die, over the 5-year modelled period	Assumption
Of those disease-negative patients who do not comply with further testing, an average of 98% remain disease-negative, 1% relapse into having asymptomatic disease, 0.8% move to symptomatic disease and 0.2% die, over the 5-year modelled period	Assumption
Those patients who exit after three consecutive negative scans do not relapse within the 5-year duration of the model	Assumption

Abbreviations: THT, thyroid hormone therapy; Tg, thyroglobulin; T_3, liothyronine sodium; T_4, thyroxine sodium; TSH, thyroid-stimulating hormone.

Appendix K Secondary modelled economic evaluation

A secondary modelled economic evaluation has been undertaken (**Figures 8** and **9**) which has a number of differences from the model appearing in the main body of the submission. The major difference is that this model includes the first post-treatment diagnostic follow-up test, so patients no longer enter the model only after one negative diagnostic follow-up result.

The second difference is that patients in the rhTSH arm are assumed to be receiving rhTSH for all diagnostic follow-ups, including the first post-treatment follow-up. The only time at which a patient in the rhTSH arm will undergo THT withdrawal is for treatment[11] itself. Another modification made in the secondary model is that the probability of a patient being disease-or remnant-positive is higher in the initial post-treatment scan. The probability is assumed to be 0.5. A further difference is that the secondary model assumes perfect compliance in both arms at the time of the first follow-up test. At subsequent follow-up tests, the compliance in the THT withdrawal arm reduces, in the same manner as it did in the primary model.

Finally, different utilities have been used for patients receiving their initial post-treatment follow-up. These utilities were derived from all patients in Haugen et al (1999) (see **Table 18**). However, once a patient moves beyond this initial follow-up, the utilities revert to those used in the primary economic evaluation. Refer to **Table 35** for the altered utilities and **Table 20** for the utilities reverted to after the initial follow-up.

Table 35 Utilities of patients in first post-treatment diagnostic scan

Health state	Utility	Rationale/source
A patient in the pre-treatment (baseline) stage	0.842	Derived from SF-36 survey
A patient in the withdrawal stage	0.653	Derived from SF-36 survey
Those patients who are currently receiving rhTSH treatment	0.834	Derived from SF-36 survey

[a]Health utilities for these health states were derived from the secondary assessment (all patients) (**Table 18**).

The secondary modelled economic evaluation produced a cost-effectiveness ratio that was 'dominated' by the current method of THT withdrawal. This means that despite using a decision-analytic model that incorporates all the health outcome advantages of rhTSH, it was shown to have worse effectiveness than THT withdrawal, while also having a higher cost. This was driven by poor results in terms of both cost and effectiveness in the rhTSH arm of the model. Furthermore, even when the sensitivity and specificity of rhTSH and THT withdrawal were assumed to be equal (100 per cent), the cost-effectiveness ratio of the model remained 'dominated' by THT withdrawal.

[11]rhTSH is not currently registered for therapeutic use in Australia.

The costs increase in both arms of the model because an additional diagnostic follow-up test occurs at the start of the model. Moreover, the increased probability of being disease-positive adds even more cost, as there is a greater likelihood of a patient requiring further treatment than there is in the primary evaluation. The added fact that rhTSH can lead to false results and, therefore, unnecessary treatment/follow-up tests, means that the cost in the rhTSH arm increases by a greater amount. Consequently, the incremental cost increases significantly.

In terms of effectiveness, there is a reduction in the health utility values in both arms of the model due to the presence of the additional diagnostic follow-up and the increased likelihood of additional treatment. However, the poorer accuracy of rhTSH and the consequential increase in treatment lowers the utility value of the rhTSH arm to such an extent that it falls below that of the THT withdrawal arm. Furthermore, in the THT withdrawal arm at the first follow-up test, there is no disease progression secondary to non-compliance, because non-compliance was not applied until the second follow-up test. Together, these factors cause the incremental effectiveness to become negative.

Because rhTSH is both more costly and less effective than THT withdrawal in the secondary model, it is said to be 'dominated' by the THT withdrawal arm. Consequently, it should not be recommended for use in patients at such an early stage of diagnostic scanning.

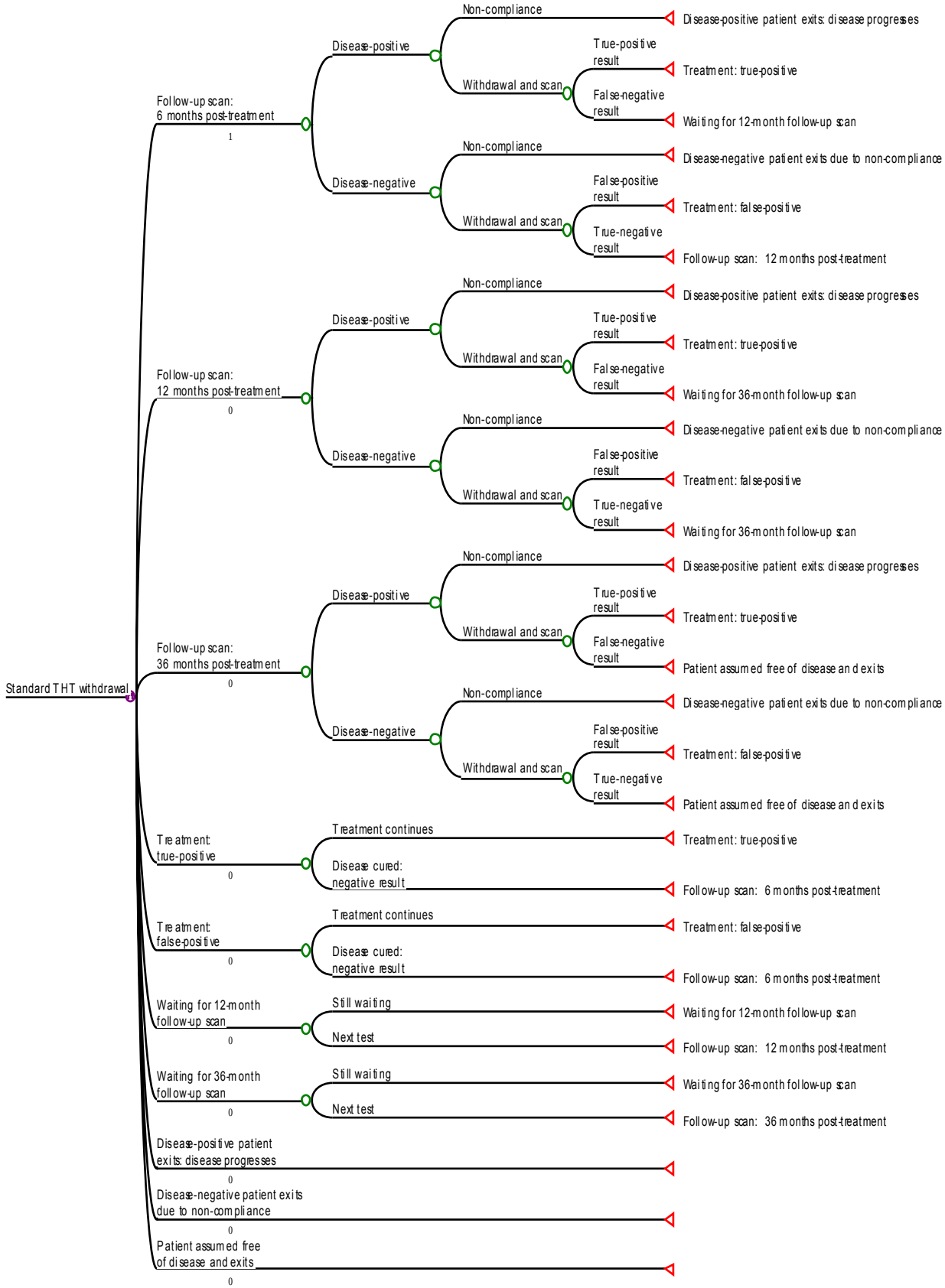

Figure 8 THT withdrawal arm of the secondary modelled economic evaluation

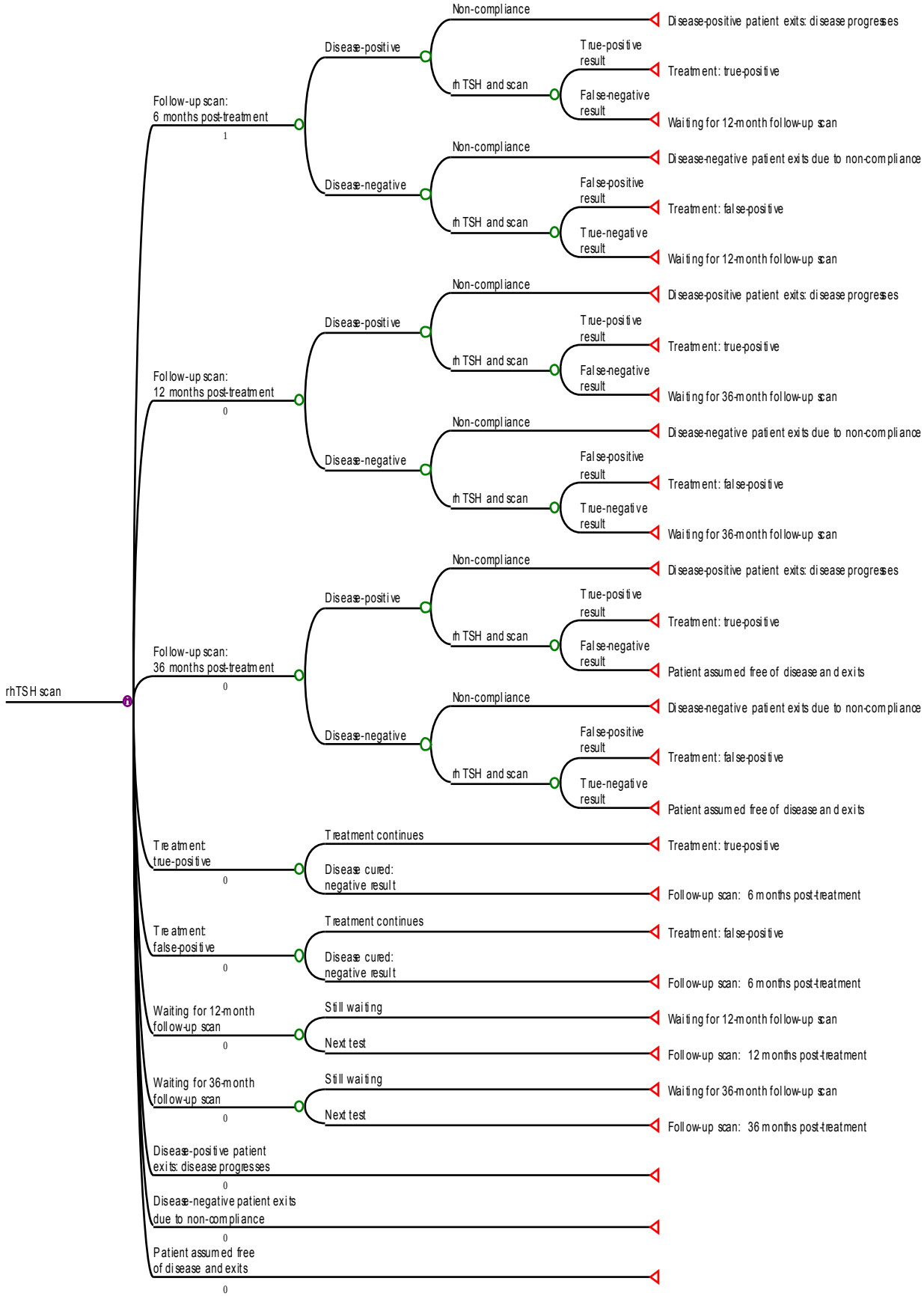

Figure 9 rhTSH arm of the secondary modelled economic evaluation

Appendix L Indirect cost analysis

In addition to the direct costs of diagnostic scanning, it is useful to consider the potential ramifications of cost-offsets arising from lost productivity. Productivity losses are likely to occur within the economy because some patients are unable to carry out their ordinary tasks of employment when withdrawing from THT. Evidence from the literature (Nijhuis *et al* 1999) indicates that 59% of productive time is lost over the duration of withdrawal. This equates to 3.54 weeks out of the total 6-week withdrawal period.

In order to determine the exact level of productive loss, the characteristics of the patient population must be taken into account. As the vast majority of thyroid cancer victims are of working age, it is reasonable to assume that their employment characteristics are similar to the rest of the population. That is, a normal labour force participation rate (ABS 2002b) is assumed. It is then necessary to weight average weekly earnings (ABS 2002a) to take account of the skewness of the patient population toward females.

In calculating the indirect costs, the 'friction cost method' is adopted. This method recognises that not all work days lost are productive work days, and assumes that 80% of all work days are productive (Brouwer and Koopmanschap 1988).

The components of the calculation are itemised in **Table 36.**

Table 36 Components of indirect costs

Weeks of work lost	3.54	
Productive work weeks lost	2.832	A
Proportion of female patients	74.38%	
Female average total weekly earnings	$541.70	
Weighted female weekly earnings	$402.93	B
Proportion of male patients	25.62%	
Male average total weekly earnings	$821.80	
Weighted male weekly earnings	$210.52	C
Participation rate	63.60%	D
Productive loss per patient	**$1104.92**	**= (B + C) × A × D**

This productive loss per patient can be considered as an additional cost associated with each withdrawal scan, whether it be in the withdrawal arm or the first post-treatment scan in the rhTSH arm. The indirect cost does not apply when using rhTSH, because the patient is not rendered hypothyroid in these circumstances.

Adding the productive loss per patient into the costs contained in the model reduces the marginal cost from $51,344.42 to $34,035.58. This results in an improvement in the incremental cost-effectiveness of rhTSH, at $17,308.84 per QALY.

Abbreviations

AIHW	Australian Institute of Health and Welfare
DOR	Diagnostic odds ratio
EU	European Union
FDA	Food and Drug Administration
^{131}I	Radioiodine
MSAC	Medical Services Advisory Committee
M-TAG	Medical Technology Assessment Group Pty Ltd
NHMRC	National Health and Medical Research Council
NPV	Negative predictive values
PBS	Pharmaceutical Benefits Schedule
POMS	Short form Profile of Mood Scale
PPV	Positive predictive values
QALYs	Quality-adjusted life-years
QOL	Quality of life
rhTSH	Recombinant human thyroid-stimulating hormone
RPBS	Repatriation Pharmaceutical Benefits Schedule
T_3	Liothyronine sodium
T_4	Thyroxine sodium
Tg	Thyroglobulin
TGA	Therapeutic Goods Administration
THT withdrawal	Periodic thyroid hormone therapy withdrawal
TSH	Thyroid-stimulating hormone
WBS	Radioiodine whole body scanning

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