



Economic Evaluation of Recombinant Human Thyroid Stimulating Hormone Stimulation vs. Thyroid Hormone Withdrawal Prior to Radioiodine Ablation for Thyroid Cancer: The Korean Perspective

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Background: Previous studies have suggested that recombinant human thyroid stimulating hormone (rhTSH) stimulation is an acceptable alternative to thyroid hormone withdrawal (THW) when radioiodine remnant ablation is planned for thyroid cancer treatment, based on superior short-term quality of life with non-inferior remnant ablation efficacy. This study evaluated the cost-effectiveness of radioiodine remnant ablation using rhTSH, compared with the traditional preparation method which renders patients hypothyroid by THW, in Korean perspective.

Methods: This economic evaluation considered the costs and benefits to the Korean public healthcare system. Clinical experts were surveyed regarding the current practice of radioiodine ablation in Korea and their responses helped inform assumptions used in a cost effectiveness model. Markov modelling with 17 weekly cycles was used to assess the incremental costs per quality-adjusted life year (QALY) associated with rhTSH. Clinical inputs were based on a multi-center, randomized controlled trial comparing remnant ablation success after rhTSH preparation with THW. The additional costs associated with rhTSH were considered relative to the clinical benefits and cost offsets.

Results: The additional benefits of rhTSH (0.036 QALY) are achieved with an additional cost of Korean won ₩961,105, equating to cost per QALY of ₩26,697,361. Sensitivity analyses had only a modest impact upon cost-effectiveness, with one-way sensitivity results of approximately ₩33,000,000/QALY.

Conclusion: The use of rhTSH is a cost-effective alternative to endogenous hypothyroid stimulation prior to radioiodine ablation for patients who have undergone thyroidectomy in Korea.

Keywords: Cost-effectiveness; Hypothyroid; Thyrotropin alfa; Thyroid neoplasms; Radioiodine; Ablation

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INTRODUCTION

Total or near-total thyroidectomy followed by ^{131}I radioiodine ablation constitutes the initial treatment for differentiated thyroid cancer (DTC) [1,2]. The aim of radioiodine ablation is to facilitate detection of recurrent disease and to decrease the risk of recurrence by destroying remnant thyroid tissue [2]. For ablation to be successful, patients must have elevated levels of thyroid stimulating hormone (TSH). Traditionally, endogenous stimulation by thyroid hormone withdrawal (THW) has been used to elevate serum TSH, which can take 3 to 8 weeks after thyroidectomy. Although hypothyroidism by THW elevates serum TSH levels suitable for radioiodine uptake, it is commonly associated with a negative impact on quality of life in DTC patients [3-6]. Symptoms of induced hypothyroidism by THW may be severe and can prevent some patients from performing usual daily activities. Also, there is considerable evidence suggesting endogenous stimulation results in greater work absenteeism [4,7].

An alternative to rendering the patients hypothyroid is exogenous stimulation of TSH using recombinant human thyroid stimulating hormone (rhTSH; Thyrogen, Genzyme Transgenics Corp., Cambridge, MA, USA). This allows patients to continue thyroid hormone replacement with thyroxine (T4) after thyroidectomy and therefore renders the patients euthyroid. Recent randomized prospective studies have reported that rhTSH was as effective as THW for successful ablation in low-dose and high-dose radioiodine ablation [8,9]. Furthermore, some studies indicate considerable quality of life benefits with exogenous stimulation using rhTSH [10]. However, exogenous stimulation with rhTSH is more costly than endogenous stimulation. Therefore, economic evaluation is necessary whether the use of rhTSH is cost effective alternative to THW to offset the incremental cost.

METHODS

Economic model structure

The economic model is based on an analysis published by Mernagh et al. [11] that was previously modified for the Swedish market, and that supported reimbursement. The present economic model takes a healthcare system perspective, capturing only those costs and outcomes that directly impact the Korean public healthcare system.

This economic evaluation was undertaken to assess the incremental benefits gained from rhTSH in the course of abla-

tion, in the context of costs relative to patient benefit. The benefits were expressed in units of quality-adjusted life years (QALYs) using “utility weights” from 0 (death) to 1 (perfect health), a standard method in health economics.

The model utilized a Markov chain structure to simulate the costs and outcomes of low to intermediate risk thyroid cancer patients requiring 100 mCi of radioiodine ablation. The model consisted of two arms: one with exogenous stimulation with rhTSH, the other with endogenous stimulation. A Markov model is a well-accepted method of economic evaluation for following patients as they move between different health states.

The model was run for 17 one-week cycles. This 17-week duration is a departure from a previous version by Mernagh et al. [11], which followed patients over the course of a lifetime and suggested the theoretical advantage of a reduction in secondary malignancies because of faster clearance of radioiodine from the body. The 17-week evaluation enables all immediate and downstream quality of life benefits offered by rhTSH to be adequately captured. That is, the avoidance of hypothyroidism and the more rapid recovery to full health are captured. Furthermore, as all differences in costs and quality of life are already captured, the model ceases at this point. The relatively short duration of the model is reflective of the short-term nature of the quality of life gains offered, which is in itself, reflective of the short-term morbidity caused by hypothyroidism. Half-cycle correction is not employed as patients are not able to move between health states in either the first or final stages of the model.

The model only relates to low- to intermediate-risk radioiodine ablation in thyroid cancer patients similar to those in the pivotal randomized controlled study [10], and does not include patients with stage IV or distant metastases.

There are key assumptions in the economic evaluation, as follows: (1) the model assumes equal efficacy of ablation (100%) in both arms; this assumption is based on the pivotal clinical trial by Pacini et al. [10]; (2) It was assumed that exogenously-stimulated patients are ablated 1 week following thyroidectomy, while endogenously stimulated patients are ablated at various points in time, often more than 4 weeks after the thyroidectomy; the latter is based on a survey conducted among Korean clinicians describing their current practice; (3) the model applies quality of life results observed over time in each arm of the pivotal clinical trial (SF-6D results, reported by Schroeder et al. [12]); (4) patients are released from the radio-protective ward earlier when prepared for ablation via exogenous stimulation, based on findings by Borget et al. [13] and

Pacini et al. [10]; and (5) the cost of radioactive waste disposal has not been independently estimated. Instead, it is assumed to have been captured in the fees for ablation and/or radio-protective ward stay.

In Korea, patients are eligible for a one-time reimbursement for rhTSH if they meet one the following criteria: (1) have experienced a serious adverse event due to T4 withdrawal in previous treatment; (2) are over 65 years old; (3) have cardiac or pulmonary dysfunction; (4) have hypopituitarism; (5) show evidence of fast-growing cancer; or (6) underwent a total or near total thyroidectomy for remnant ablation. The last criterion was added in the revised Korea reimbursement system [14].

Economic model variables

The estimation of a number of the variables used to populate the economic model relied upon the results of a treatment survey conducted among clinical experts currently practicing endocrinology, nuclear medicine, and surgery in Korea (Appendix 1).

The objective of the survey was to establish the current practice of radioiodine ablation (100 mCi) of well-DTC, in Korean patients who are endogenously-stimulated prior to ablation. Optum Australia developed the survey questionnaire and conducted the data analysis. The survey itself was administered by a local representative of Genzyme, based in Korea. The survey consisted of twelve questions, eleven of which related to endogenously-stimulated patients and one related to the administration of rhTSH. Though the majority of questions were framed to generate a quantitative response, qualitative answers were appropriate in some cases. The survey was conducted via face-to-face interviews with six experts based in endocrinology, nuclear medicine or surgical departments around Korea. Each clinical expert was presented with the survey during a meeting with a Genzyme representative. A note describing the purpose and rationale behind each question was also provided

to the interviewer.

In general, the survey was well understood by all of the clinical experts, which was reflected by the consistency of the answers given. The six experts treated a total of approximately 2,000 newly diagnosed thyroid cancer patients with radioiodine ablation each year. Standard protocol dictates that patients undergo approximately 4 weeks of levothyroxine withdrawal prior to radioiodine ablation. All six clinicians indicated that 100% of their patients would commence T4 replacement therapy directly after thyroidectomy, to be withdrawn at a later time. The aim of this question was to assess the extent of potential supply constraints in terms of radio-ablation facilities in the Korean healthcare system. The indication that all thyroidectomy patients would commence T4 immediately after surgery suggests that this may be a substantial issue in Korea. However, the duration of T4 replacement therapy prior to withdrawal was not defined in the responses to the treatment survey. Since the availability of radio-ablation facilities is independent of the choice of pre-ablative treatment, it would affect both arms in the model equally. As such, this pre-ablative T4 supplementation period is assumed to occur prior to the beginning of the modelled evaluation; and thus, it does not impact the duration or outcomes of the evaluation itself. The majority of respondents also indicated that patients undergoing endogenous hypothyroid stimulation are not completely withdrawn from thyroid hormone replacement therapy. Rather, patients transition from T4 to a 2-week treatment of triiodothyronine (T3) therapy, followed by complete withdrawal. After transition to T3 therapy, the majority of patients are ablated within 4 weeks. All patients were ablated within 6 weeks.

Clinical inputs

Four distinct health states in each of the two arms are incorporated into the economic model (Table 1). A schematic of the

Table 1. Duration of Health States Applied to the Economic Model

Health state	Exogenously-stimulated (rhTSH)	Endogenously-stimulated (hypothyroid)
Pre-ablation	1 week	Between 2 and 7 weeks (refer to Table 2)
Ablation	1 week	1 week
Initial post-ablation period	4 weeks	4 weeks
Second post-ablation period	4 weeks	4 weeks
Patient recovered (well state)	Remainder of the model (7 weeks per patient)	Remainder of the model (average 3.6 weeks per patient) ^a

rhTSH, recombinant human thyroid stimulating hormone.

^aAlthough the average duration of this health state was 3.6 weeks, the model was still run for 17 weeks. This ensures consistency with Memagh et al. [11] and similarly ensures that all patients reach the ‘well’ health state, and remain there for at least one full cycle (1 week).

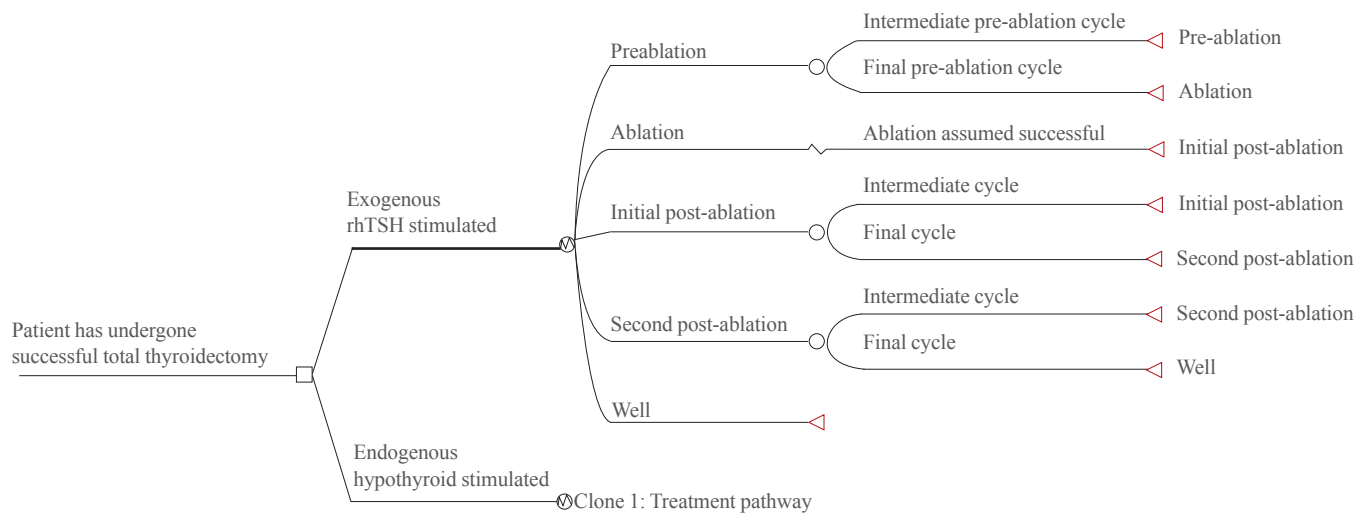


Fig. 1. Simplified schematic of the structure of the Korean adaptation of economic model. rhTSH, recombinant human thyroid stimulating hormone.

Table 2. Distribution of Time Spent between Thyroidectomy and Ablation in the Endogenously-Stimulated Patient Group

Duration of time between thyroidectomy and ablation	Proportion of patients as estimated by the expert opinion survey, %	Transition probability used in the model of a patient in the pre-ablation state moving to the ablation state, % ^a
Less than 3 weeks ^b	0	0
3 weeks	0.3	0.3
4 weeks	72.42	72.64
5 weeks	13.64	50.00
6 weeks	13.64	100
Greater than 6 weeks ^c	0	100

^aCalculated by dividing the proportion of patients in any given interval by the proportion of patients remaining in the pre-ablation health state (e.g., probability at 5 weeks = $13.64\% / [1 - 72.42\% - 0.30\% - 0.00\%] = 50.00\%$); ^bAssumed to be 2 weeks for all patients; ^cAssumed to be 7 weeks for all patients.

model is depicted in Fig. 1. The interval between thyroidectomy and ablation for endogenously-stimulated patients was determined via the clinician survey described above. As patients can only undergo ablation once TSH levels have naturally elevated to a suitable level, it is intuitive that the interval will vary from patient to patient. As a consequence, the model enables patients to move from pre-ablation to ablation according to a set of probabilities. The clinician survey was used to derive these probabilities, which are presented in Table 2. Note that the results of the survey generate an expected mean duration of approximately 4.4 weeks (standard deviation ± 1.12 weeks).

With respect to exogenously-stimulated patients, radioiodine ablation was assumed to take place closer to the time of total thyroidectomy (which occurs prior to the beginning of the model).

This assumption is consistent with previous iterations of the economic model, and was a consequence of discussions with clinicians who indicated that ablation would occur earlier, presumably because: (1) patients would no longer need to wait several weeks for their TSH levels to be suitably elevated and (2) the clinical aim is to ablate any cancer remnants as soon as possible to reduce the risk of metastases. One week is required; however, to allow adequate time for recovery from thyroidectomy.

The results of the survey were also used to inform the duration of time spent in the radioprotective ward following ablation for endogenously-stimulated patients. As with the time between thyroidectomy and ablation, these results varied from patient to patient. The weighted average proportion of patients, and the overall average expected duration in a radioprotective

Table 3. Duration of Time Spent It the Radioprotective Ward for Endogenously-Stimulated (Recombinant Human Thyroid Stimulating Hormone) Patients

Duration	Proportion of patients, %	Expected duration, days
Less than 1 day	0	-
2 days	5.70	-
3 days	91.30	-
4 days	3.00	-
5 days	0	-
Average expected duration	-	2.97

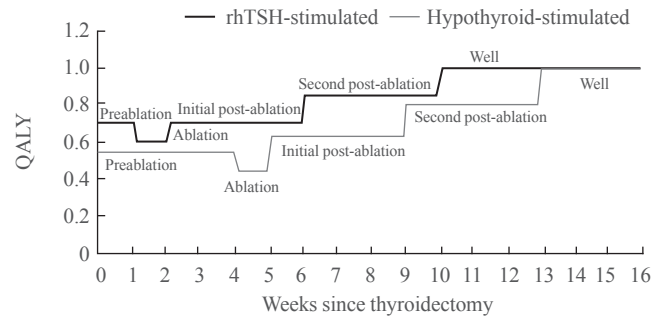


Fig. 2. Quality-adjusted life year (QALY) weights as used in the economic model. rhTSH, recombinant human thyroid stimulating hormone.

Table 4. Unit Costs Incorporated into the Economic Evaluation

Resource	Unit cost, ₩	Source
Ablative dose of radioiodine (I^{131}) to treat thyroid cancer (post-thyroidectomy)	387,890	Korean Health Insurance Review Agency (HIRA)
Whole body scan using radioiodine	113,680	HIRA
One day of hospitalization (inpatient) for patients receiving radioiodine ablation	216,550	HIRA
Visit to specialist (radiation oncologist)	17,400	HIRA
Visit to practice nurse	1,290	HIRA
Thyroid stimulating hormone quantification test	19,750	HIRA
Serum thyroglobulin count	17,200	HIRA
Thyroglobulin antibody test	14,870	HIRA
Weekly T4 drug cost	306	HIRA, based on 125 µg daily dose at ₩35/100 µg
Weekly T3 drug cost	966	HIRA, based on 60 µg daily dose at ₩46/20 µg
Recombinant human thyroid stimulating hormone (2-vial kit of Thyrogen)	1,219,000	Genzyme

T4, thyroxine; T3, triiodothyronine.

ward, is presented in Table 3.

The utility weights applied to the economic model were based upon the SF-36 data collected during the randomized controlled trial in the ablation setting [10]. SF-36 results are widely reported in the literature, consistently showing a significant impairment in quality of life with induced hypothyroidism [12,15]. These data were transformed to SF-6D QALY weights based on the method outlined by Brazier et al. [16]. Fig. 2 presents a summary of the utility weights associated with each of the health states.

Economic inputs

The economic inputs used in the model are presented in Table 4. All unit costs are presented in South Korean won (₩). The costs applied to each arm of the economic model are presented in Table 5. The main difference between the two treatment groups is the presence of rhTSH and its administration (2×

nurse visits for injections) as a cost in the exogenously-stimulated arm only. Other differences include a lower expected cost of both time spent in the radioprotective ward in the exogenously-stimulated (rhTSH) arm and the cost of 2 weeks of T3 therapy in the endogenously-stimulated arm (THW) during the pre-ablation health state. Four of the six respondents to the Korean treatment survey indicated that for endogenously-stimulated patients, TSH quantification would be performed once, after 4 weeks of T4 withdrawal. If the patient’s TSH level had not reached the desired value for ablation, it would not be measured again. This is reflected in the ablation timeframes given in the treatment survey, which showed >99% of patients will be ablated between 4 and 6 weeks following T4 withdrawal, with the majority undergoing ablation at week 4 (72%). Based on these data, the model assumes that patients in the endogenously-stimulated arm of the model receive one TSH quantification test in the pre-ablation health state. The clinician surveys

Table 5. Costs Applied to Each Treatment Arm

	Unit cost, ₩	Total cost per health state (₩), exogenous stimulated (rhTSH) arm	Total cost per health state (₩), endogenous stimulated (hypothyroid) arm
Pre-ablation			
T4 therapy (daily cost)	44	306	(-)
TSH testing (including TSH measurement, thyroglobulin count and antigen test)	51,820	51,820	51,820
2×Specialist visits	17,400	34,800	34,800
1×Nurse visit (first rhTSH administration)	1,290	1,290	(-)
1×Nurse visit (second rhTSH administration)	1,290	1,290	(-)
T3 therapy (daily cost)	138	(-)	1,932
1×Specialist visit for hypothyroidism symptom management	17,400	(-)	261
rhTSH (Thyrogen)	1,219,000	1,219,000	(-)
Ablation			
Ablative dose of radioiodine (100 mCi)	387,890	387,890	387,890
T4 therapy (daily cost)	44	306	(-)
Hospital stay (1.85 days vs. 2.97 days)	216,550	400,617	643,153
2×Specialist visits	17,400	17,400	34,800
Whole body scan using radioiodine	113,680	113,680	113,680
Post-ablation			
T4 therapy (daily cost)	44	2,450	2,450
Hospital day	17,400	17,400	17,400
Well			
T4 therapy (daily cost)	44	2,144	1,102
Total cost over the duration of the model	-	2,250,393	1,289,288

rhTSH, recombinant human thyroid stimulating hormone; T4, thyroxine; T3, triiodothyronine.

Table 6. Base Case Analysis

Parameter	Exogenously-stimulated (rhTSH)	Endogenously-stimulated (hypothyroid)	Incremental difference
Cost per patient over the course of the model, ₩	2,250,393	1,289,288	961,105
QALYs per patient over the course of the model	0.281	0.245	0.036
ICER, ₩/QALY	-	-	26,697,361

rhTSH, recombinant human thyroid stimulating hormone; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

also reveal that a small proportion (1% to 2%) of endogenous-stimulated patients would seek additional treatment from a specialist for treatment of symptoms related to hypothyroidism. A rate of 1.5% was applied to the model to capture the cost of these additional specialist visits.

RESULTS

Base case analysis

The results of the economic model are presented in Table 6. The cost of rhTSH in this radioiodine ablation setting (₩2,250,393) is higher than endogenous stimulation of TSH (₩1,289,288). The use of rhTSH is also associated with an improved health-

Table 7. Sensitivity Analysis

Model	Incremental cost, ₩	Incremental QALY	ICER, ₩/QUALY
Inclusion of indirect costs (i.e., loss of productivity)	848,173	0.036	23,560,361
Assume no difference in the time spent in the radioprotective ward (i.e., 2.97 days in both arms)	1,220,736	0.036	33,909,333
Increasing the duration of the pre-ablation health state in the exogenously-stimulated arm to 2 weeks (base case: 1 week)	977,424	0.030	32,580,800
Reducing the incremental utility difference in the pre-ablation health state by 50% (i.e., increasing the utility of hypothyroidism from 0.548–0.631)	977,118	0.029	33,693,724

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

related quality of life, as illustrated by an increase in QALY terms (0.036).

Sensitivity analyses

A number of sensitivity analyses were conducted to test the effect of altering key assumptions and to determine the key drivers of the model. Many of these tests are extreme scenarios. The results of the sensitivity analyses are presented in Table 7. The analyses suggested that difference in productivity was a major driver of the model results. These sensitivity analyses are discussed in greater detail below.

DISCUSSION

The present economic investigation indicates that the use of rhTSH in preparation for radioiodine remnant ablation has economic benefits in addition to health benefits, with an incremental cost-effectiveness ratio (ICER) of ₩26,697,361/QALY. New health care interventions are typically accepted if the ICER is below ₩30,000,000, and therefore the use of rhTSH represents cost-effective technology (i.e., the additional benefits to the patients and society are achieved for an acceptable net cost).

In addition to improved quality of life for patients, there is also a productivity benefit associated with rhTSH. A number of reports have indicated significantly reduced productivity and increased employment absenteeism in the hypothyroid state compared with the euthyroid state [3,4,7]. The sensitivity analysis performed in this economic evaluation takes a similar approach to Mernagh et al. [11], by basing the estimate of work days lost on data from Luster et al. [3]. Luster et al. [3] reported that German patients rendered hypothyroid in the diagnostic setting were absent from work for an average of 11 days. Another study by Borget et al. [7] reported that patients undergoing rhTSH preparation in a diagnostic setting take an average

of 3 days off work, compared to 11 days for the hypothyroid group. In a pivotal remnant ablation study, 15.6% of the subjects in the endogenous-stimulation arm reported markedly reduced daily productivity compared with 8.6% of subjects who received exogenously stimulation [17]. Therefore, the loss of work productivity in exogenously-stimulated patients was crudely estimated to be 50% of that of the endogenously-stimulated patients who withdrew from thyroid hormone, i.e., 50% of 11 days, or 5.5 days. It should be noted that, although the Luster et al. [3] data was sourced from patients undergoing diagnostic ¹³¹I scanning, they are assumed to be representative of pre-ablation use, because in both cases patients are rendered equally hypothyroid. Considering the number of days of work lost in the rhTSH arm is half of that experienced by patients in the endogenously-stimulated arm, the incremental cost difference between the two groups is reduced with the inclusion of indirect costs. The incremental utility difference is unchanged; therefore, the overall ICER is lower in this scenario, indicating that rhTSH is more cost-effective.

The most significant cost-offset included in this economic model is that associated with the shorter duration of time spent in the radioprotective ward following radioiodine ablation. The sensitivity analyses demonstrate the impact of the removal of this cost-offset on the overall cost-effectiveness. A number of studies have reported faster clearance of ¹³¹I from the body after radioiodine ablation when patients are prepared for ablation with rhTSH rather than endogenous stimulation [10,18–20]. Regardless of the measure used, the radiation clearance is approximately 35% faster with rhTSH-stimulation than with hypothyroid-stimulation. This is not unexpected given the impairment of renal function that is known to occur with hypothyroidism. Based on a study by Borget et al. [13], the model assumes that hospital discharge occurs 27 hours earlier for patients receiving rhTSH. However, if the advantage of less time

spent in the radioprotective ward is ignored entirely, rhTSH generated a modest increase in ICER of ₩33,909,333 per QALY. Even under these extreme assumptions, exogenous stimulation using rhTSH may be acceptable value for money.

The sensitivity analysis shows that increasing the period between surgery and ablation from 1 to 2 weeks for exogenously-stimulated patients with rhTSH has little impact on overall cost-effectiveness of rhTSH after reimbursement. That said, there is a practical advantage to the shorter duration of time between thyroidectomy and ablation prepared by exogenously-stimulated patients. By removing the requirement for TSH levels to naturally elevate over time, timing of ablation can be more flexible, resulting in fewer scheduling issues. This may free up hospital beds for other uses or for additional patients. However, this advantage is not captured in the present economic evaluation.

A sensitivity analysis also was conducted to test the impact of the utility differential between being rendered hypothyroid or not. The utility difference between the pre-ablation health states was reduced by 50% by increasing the utility associated with hypothyroidism from 0.548 to 0.631. The model showed that change in utility difference in the pre-ablation health state by 50% generated in ICER of ₩33,693,724 per QALY. However, the advantage of more rapid recovery to full health and other cost off-sets of rhTSH should be considered under these extreme situation.

The current economic evaluation relates to the ablation setting and therefore differs from the models evaluating the use of rhTSH in the diagnostic setting. The amount of radioiodine transmitted to the patient in the ablation setting (3.7 GBq) is approximately 20-fold higher than the amount typically provided in a diagnostic setting (150 MBq), and therefore faster clearance of radioiodine with rhTSH is of greater importance in this ablation setting. However, the two settings are similar in terms of quality of life benefits of rhTSH, regardless of whether the setting is diagnostic testing or remnant ablation.

Recently, the national reimbursement criteria for using rhTSH was expanded as of October 2013 in Korea [14]. The revised reimbursement system allows patients who undergo total thyroidectomy to receive an one-time reimbursement for radioiodine ablation during their lifetime. Patients who have had serious adverse effects due to T4 withdrawal in previous radioiodine ablation are also eligible for reimbursement, per the previous criteria. After reimbursement, rhTSH may cost a patient as little as ₩58,695, compared to ₩1,219,000 before reimbursement. Therefore, the cost-effectiveness of rhTSH can be

maximized under the newly expanded Korean insurance reimbursement criteria.

In summary, the present analyses indicate that the therapeutic use of rhTSH is a cost-effective method of preparation for radioiodine ablation following thyroidectomy in Korea. This finding is consistent with analyses conducted in other international jurisdictions [11,21]. In the Korean context, rhTSH offers substantial quality of life benefits over conventional endogenous stimulation at a reduced health-related cost after reimbursement. These advantages are magnified when important societal costs such as loss of productivity are included in the analysis. Furthermore, the base case assumptions were shown to be largely robust to extreme manipulation during sensitivity analysis.

This economic evaluation does not capture any flow-on benefits associated with rhTSH use, such as more efficient use hospital resources, nor does the model incorporate any reduction in secondary cancers that could result from faster clearance of radioiodine. Regardless of these omissions, the use of rhTSH is a cost-effective alternative to endogenous hypothyroid stimulation prior to radioiodine ablation for patients who have undergone thyroidectomy in Korea. It is particularly cost-effective given the newly expanded Korean insurance reimbursement criteria.

CONFLICTS OF INTEREST

JHC is medical advisor in Genzyme Corporation. Genzyme Corporation funded the development of the economic model and the application of this model to the Korean setting.

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Appendix 1. Treatment Practice Survey

**Korean treatment practice survey:
Post-thyroidectomy radioiodine ablation for well-differentiated thyroid cancer**

(Time required to complete survey: ~10 minutes)

Purpose of questionnaire

This survey is being conducted by Genzyme AB, a Sanofi company.

The aim is to obtain clinical advice regarding the current practice of radioiodine ablation (100 mCi) of well-differentiated thyroid cancer in Korea, to inform assumptions used in a cost-effectiveness model.

The survey is being sent to endocrinologists, nuclear medicine physicians, and surgeons across Korea who oversee the post-thyroidectomy radioiodine-ablation of thyroid cancer remnants. All responses will be de-identified prior to analysis. The findings may be included within a reimbursement dossier and may also be reported within a peer-reviewed publication.

The information in this box will be used solely for administrative purposes only.

I, (print name)

Of (print address/hospital name)

.....

Phone number or email address **please complete** (for data queries only)

declare that I have completed the following survey to the best of my knowledge, and consent to the inclusion of the de-identified data within a modelled economic evaluation to be used in a reimbursement dossier and/or peer-reviewed publication.

.....
Signature

.....
Date

Please state if you have any conflicts of interest associated with the content of this questionnaire:

.....
.....
.....

Survey conducted by: XXX

XXX,

XXX

Contact: XXX

Please return **all pages** by **Fax to XXX** by **XXX, 2014**

- Start of survey -

In answering the following questions please consider all patients treated in your hospital/unit for well-differentiated, non-metastatic, thyroid cancer who receive I¹³¹ radioiodine ablation (100 mCi) following thyroidectomy. These questions only relate to patients undergoing endogenous stimulation by the with-holding or with-drawing of thyroid hormone therapy.

<p>1. How many newly diagnosed patients with well-differentiated thyroid cancer undergo I¹³¹ radioiodine ablation (100 mCi) following thyroidectomy in your hospital/unit each year? <i>(This question allows us to weight the responses by the number of patients treated by each group.)</i></p>	<p>_____ per year</p>
<p>2. With respect to patients having their initial post-thyroidectomy radioiodine ablation: What proportion of patients are <u>withheld from T4 replacement therapy immediately after thyroidectomy</u> in preparation for scheduled radio-ablation? What proportion of patients would commence T4 therapy after their thyroidectomy, to be <u>withdrawn from T4 at a later time</u> (i.e., start T4 after surgery, to be withdrawn sometime in future for radioiodine ablation)</p>	<p>T4 withheld after surgery: _____ % T4 withdrawn at later time: _____ % <i>(TOTAL MUST = 100%)</i></p>
<p>3. What TSH level must be attained before radio-ablation is performed?</p>	<p><input type="checkbox"/> >25 mU/L <input type="checkbox"/> >30 mU/L <input type="checkbox"/> Other: _____ mU/L <input type="checkbox"/> TSH not measured, wait a set time period instead. If so, how long? _____ weeks</p>
<p>4. How many weeks after starting withholding/withdrawal is the patient's TSH level <u>first</u> measured?</p>	<p>_____ weeks</p>
<p>5. If the patient's TSH level has not reached the required value for ablation when first tested, is it measured again? If yes, how many weeks later?</p>	<p>Yes <input type="checkbox"/> No <input type="checkbox"/> _____ weeks</p>
<p>6. Following the start of T4 withdrawal, what proportion of patients are ablated within the following timeframes in practice. <i>NB. Please complete all fields a) to f) below, indicating "0%" if necessary. Ensure the sum of a) to f) equals 100%.</i> Time from <u>start of T4 withdrawal</u> to <u>day of ablation</u> is: a) < 3 weeks b) 3 weeks c) 4 weeks d) 5 weeks e) 6 weeks f) > 6 weeks _____ % _____ % _____ % _____ % _____ % _____ % <i>(TOTAL MUST = 100%)</i></p>	

<p>7. Other than time required to reach target TSH, list <u>other factors</u> that influence the delay between surgery & ablation:</p> <p>_____</p> <p>_____</p>	
<p>8. What proportion of radioiodine <u>ablation</u> patients take T3 (liothyronine sodium) during the period between their thyroidectomy and radio-ablation?</p> <p>On average, for how many weeks would T3 be taken by patients?</p>	<p>_____ %</p> <p>_____ weeks</p>
<p>9. Over the period in which patients are receiving no T4 replacement therapy, some patients may seek treatment or reassurance due to symptoms of hypothyroidism.</p> <p>What percentage of patients visit their primary care physician for this reason?</p> <p>What percentage of patients visit their specialist for this reason?</p>	<p>_____ %</p> <p>_____ %</p>
<p>10. With respect to the ablative dose of I¹³¹ (100 mCi)</p> <p>Do Korean, provincial or hospital guidelines exist that govern the time to discharge from hospital after radioiodine ablation?</p> <p>In your unit, is the patient's external radiation routinely measured after radioiodine ablation?</p> <p>If so, does this measure influence when the patient is discharged from hospital?</p> <p>Do you have radioprotective facilities for patient isolation?</p>	<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Yes <input type="checkbox"/> No <input type="checkbox"/></p>
<p>11. Following ablation with I¹³¹ (100 mCi), what proportion of patients are released from hospital within the following timeframes:</p> <p><i>Please complete all fields a) to e) below, indicating "0%" if necessary. Ensure the sum a) to e) equals 100%.</i></p> <p>Time from <u>day of ablation</u> to <u>release from hospital</u> is:</p> <p>a) Within 1 day b) 2 days c) 3 days d) 4 days e) 5 days</p> <p>_____ % _____ % _____ % _____ % _____ %</p> <p>TOTAL MUST = 100%</p>	
<p>12. If patients are to receive Thyrogen[®], what health professionals would be involved in the administration of Thyrogen[®] (administration is by intramuscular injection)?</p> <p><i>Please tick one box</i></p> <p>a practice nurse alone <input type="checkbox"/> a GP alone <input type="checkbox"/> a specialist alone <input type="checkbox"/> a practice nurse & a specialist <input type="checkbox"/></p> <p>a practice nurse & a GP <input type="checkbox"/></p>	

- End of survey -

- Thank you for your cooperation -