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# Genetic and Biochemical Screening for Endocrine Disease: III. Costs and Logistics

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**Abstract. The cost of screening tests in endocrine disease can be determined in a number of ways, including the charge or billed cost, the production cost, or most appropriately the cost to achieve the intended aim of the test (cost-effectiveness). Cost-effectiveness analysis allows clinicians to determine whether an added benefit of a test comes at an acceptable cost. For example, analysis of the cost-effectiveness of routine thyroid function tests prior to surgery in elderly patients with nodular thyroid disease shows that the cost per life saved is only US $405, making the tests clearly cost-effective. Cost-effectiveness does not always equate with affordability, however, especially in developing countries. Thyroid function testing prior to surgery represents only 0.8% of the average household income in Australia and is therefore both cost-effective and affordable, whereas in Sri Lanka the same screening test represents up to 50% of the average monthly income. A survey of membership of the International Association of Endocrine Surgeons worldwide showed that molecular genetic screening for endocrine disease is readily available in 67% of institutions, with all of those having facilities for the rearrangement during transfection (*RET*) proto-oncogene testing, and lesser numbers having access to the *Menin* gene, the von Hippel-Lindau syndrome (*VHL*) gene, or linkage analysis for familial pheochromocytoma. The median cost of screening for the *RET* proto-oncogene was $290 (range $100–3000). Cost-effectiveness analysis of molecular genetic screening for MEN-II syndrome demonstrates that the cost per life saved is only $5175. This compares favorably with reliance on screening based on annual pentagastrin testing, where the cost per life saved is as high as $76,315. Molecular genetic screening for endocrine disease (e.g., the MEN-II syndrome) is not only cost-effective but the therapy required (total thyroidectomy) is both acceptable and well tolerated.**

There are many ways to determine the actual "cost" of a screening test [1]. The commonest method for calculating how much a screening test costs is to consider the "billed cost," or the charge for performing the test. The billed cost of a screening test is important from the payer's or insurance company's perspective but may not represent the real or actual cost of the test [2]. An alternative is to consider the "production cost," which represents the cost to the laboratory of performing the test. The production cost of a screening test is important from the provider's perspective as the production costs of many tests performed in academic medical center laboratories often exceeds the billed cost by a considerable amount, especially if all the capital and infrastructure costs are included in the production cost. Even that figure, however, may not represent the real "cost" of a screening test. It is probably more important to consider what it costs to achieve the intended aim of performing the screening test in the first place. If, for example, the aim of the screening test is to detect a genetic disease and allow a therapeutic intervention that reduces morbidity, the real "cost" of the test represents the total cost of saving a life (i.e., the "cost-benefit" of the test). The cost-benefit of a screening test is important from the societal perspective.

"Cost-benefit" is a term derived from the financial sector, where all the outcomes are valued in monetary terms. It has been somewhat modified in the medical context to the concept of "cost-effectiveness," where the outcomes are considered not just from the financial perspective but from the benefit that may be accrued to an individual or a society [1, 3]. A test or intervention is said to be cost-effective if: (1) it costs less and is at least as effective as alternative tests; (2) it costs more but is more effective with the added benefit considered to be worth the extra cost; (3) it costs less and is less effective, but the alternative is not worth the added cost. The second scenario is the commonest faced in clinical practice, where a new test or procedure is introduced that costs more but is said to provide a significantly better outcome. Cost-effectiveness analysis aims to determine whether the added benefit comes at an acceptable cost [4].

Cost-effectiveness analysis is based on the principles of decision analysis. Decision analysis is a systematic quantitative approach for assessing the relative value of one or more decision options and allows clinicians to make decisions on how to manage individual patients [5, 6]. The basis of decision analysis is the decision tree (Fig. 1). A decision between competing tests or interventions is made—the decision node (e.g., whether to immunize against measles). One or more chance occurrences may then take place—the chance node (e.g., exposure to the measles virus). There then follow a number of outcomes (e.g., death from measles infection). The probability of each chance occurrence at the chance node and each subsequent outcome are then determined on the basis of a review of the literature or from available

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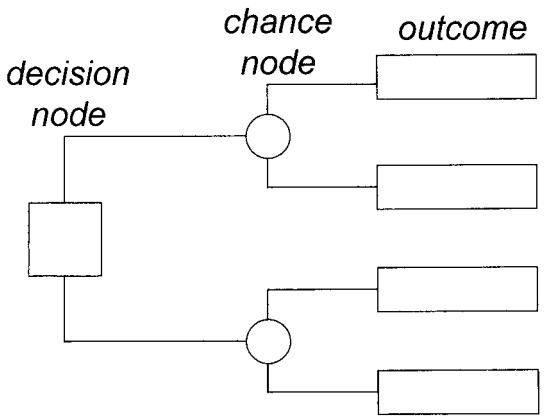


**Fig. 1.** Construction of a decision tree demonstrating decision node, chance node, and outcome.

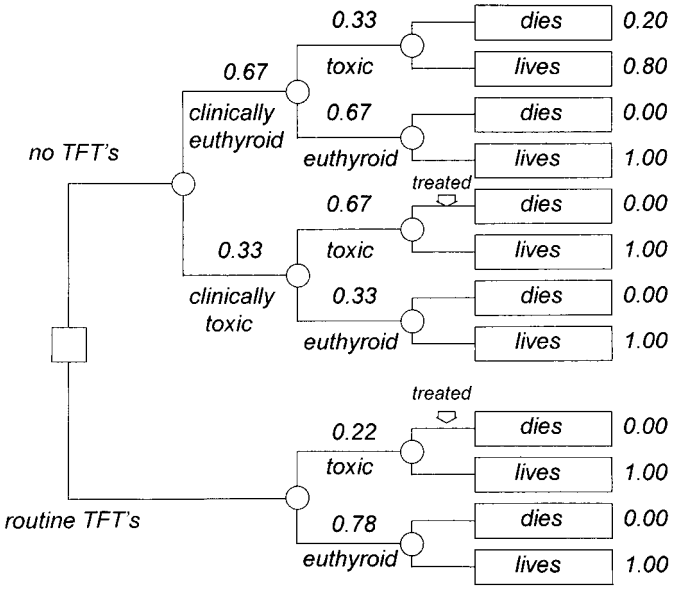


**Fig. 2.** Decision tree for the use of routine thyroid function tests (TFT's) prior to thyroid surgery in elderly patients. Numbers in the figure represent the probabilities of either the chance or the outcome.

data. The overall risk can be calculated for each arm of the decision tree by folding back and averaging the probabilities and the added benefit (e.g., lives saved by immunization) obtained by subtracting the two individual risks [1]. Cost-effectiveness can be calculated by determining the total cost of all the tests or interventions divided by added benefit; for example, the cost-effectiveness of routine measles vaccination is around US $73,000 per life saved [7].

### Cost-effectiveness of Basic Endocrine Screening Tests

An example of a simple use of cost-effectiveness analysis to determine the effectiveness of endocrine screening tests is shown in Figure 2, which examines the use of routine thyroid function tests prior to thyroid surgery in elderly patients. The question asked is whether routine thyroid function testing prior to surgery in elderly patients is cost-effective for preventing unexpected operative or anesthetic deaths directly associated with thyrotoxicosis. A number of basic assumptions must be made including the following (determined in this case from our own thyroid surgery database): that 22% of patients over age 65 years with nodular goiter have biochemical thyrotoxicosis and that operative mortality such as cardiac arrhythmias or thyrotoxic storm for elderly patients with untreated thyrotoxicosis is 20%. It is also assumed that clinical acumen is correct when diagnosing only two-thirds of cases of biochemical thyrotoxicosis in elderly patients, although the analysis is later tested with increasing degrees of clinical accuracy up to 95%. Calculation of the probabilities in the decision tree demonstrates that the probability of death from thyrotoxicosis-associated complications, if routine thyroid function testing is not carried out prior to surgery, is 0.044 (i.e., 44 deaths per 1000 procedures). If routine thyroid function testing is performed prior to surgery, all patients with biochemical thyrotoxicosis will have been treated; so, in theory, the risk of dying from thyrotoxic complications is zero. Thus 44 lives per 1000 procedures will have been saved by the routine use of thyroid function tests in elderly patients. Because 890 extra tests will have been performed (1000 tests in the "routine" arm versus 110 tests performed selectively for patients suspected of being thyrotoxic in the other arm), the cost of saving those 44 lives is $17,800 ($20 per thyroid function test), or $405 per life saved. This is clearly a highly cost-effective procedure if compared, for example, to routine measles vaccination. Sensitivity analysis, in which a range of assumptions is tested, provides a measure of how robust the cost-effectiveness analysis really is. Table 1 shows a sensitivity analysis for increasing accuracy in detecting thyrotoxicosis or reducing operative mortality. Even at the extremes of the range of assumptions the analysis is robust, and the use of routine thyroid function testing in this situation clearly remains cost-effective.

**Table 1.** Sensitivity analysis of the cost-effectiveness of routine thyroid function testing in elderly patients undergoing surgery for nodular goiter.

| Factor (%) | Operative mortality (%) | Cost per life saved ($) |
|---|---|---|
| Increasing clinical accuracy | | |
| 67 | 20 | 405 |
| 80 | 20 | 661 |
| 95 | 20 | 2664 |
| Reducing operative mortality | | |
| 67 | 20 | 405 |
| 67 | 10 | 811 |
| 67 | 5 | 1622 |

The same is not necessarily true for other routine preoperative endocrine screening tests. For example, a similar cost-effectiveness analysis can be undertaken to examine the use of routine preoperative measurement of serum calcitonin to detect a medullary thyroid carcinoma (MTC) within a nodular goiter. Such an analysis demonstrates the cost per life saved to be approximately $1.5 million. Clearly such a screening test, although clinically effective for detecting medullary thyroid carcinoma, is not cost-effective.

### Affordability versus Cost-effectiveness: World Perspective

Cost-effectiveness still requires a a value judgment as to whether the added benefit comes at an acceptable cost. Often such judgments are made within the context of affluent or technologically advanced countries and may not be applicable to developing countries because, although still "cost-effective," the tests are simply not affordable. It is interesting, for example, to compare the above scenario in a relatively affluent country such as Australia, where the average monthly household income is approximately $3000, to a developing country such as Sri Lanka where the average monthly household income may be as low as $40. In Australia a single thyroid function test ($20) represents 0.8% of a household's monthly income, whereas it is 50% of a household's monthly income in Sri Lanka. Likewise, in Australia the cost-effectiveness of saving one life ($405) by performing routine thyroid function tests in elderly patients represents 1.2% of a household's annual income compared to 95% of that income in Sri Lanka. What is cost-effective may not be affordable, especially in the scenario of a Sri Lankan family being asked to give up 50% of its monthly income for a single endocrine screening test. In such countries alternatives such as clinical diagnostic indices have often been developed to cope with unaffordable screening tests [8].

### Molecular Genetic Screening for Endocrine Disease

Controversy about genetic screening programs relates not so much to diagnostic uncertainty but to the nature of the therapy required following the diagnosis of a genetic disorder (e.g., the need for total colectomy for familial adenomatosis polyposis coli [9, 10] or for prophylactic bilateral mastectomy for hereditary breast cancer [11]. Molecular genetic screening for endocrine disease is somewhat different, however. If we consider screening for multiple endocrine neoplasia type II (MEN-II) syndrome, for example, the therapy required (total thyroidectomy) is well tolerated with no significant impact on the quality of life except for the need for medication. In addition, the other manifestations of MEN-II occur at a later age and involve different screening strategies. MEN-II is thus an ideal disease with which to consider the cost-effectiveness of screening programs for endocrine disease [12].

### Survey of International Association of Endocrine Surgeons (IAES) Membership

To obtain a broader worldwide perspective of the costs and logistics of molecular genetic screening for endocrine screening, a survey was carried out among all members of the IAES. A total of 240 survey forms were sent out, with 123 replies received. Of those responding, 83 (67%) indicated that molecular genetic screening was readily available within their institution. The specific tests stated to be available included *RET* proto-oncogene testing ($n$ = 81), testing for the *Menin* gene ($n$ = 29), testing for the *VHL* gene ($n$ = 32), and linkage analysis for hereditary pheochromocytoma ($n$ = 31). There were 44 responses where the cost of molecular genetic screening tests was known. The range of costs was $100 to $3000 (median $290, mean $472). Fourteen respondents indicated that the test was free of charge in their institution, and 65 respondents were unaware of the cost of the test. Further questions included whether pentagastrin testing was still performed in the institution (to which 54 responded "yes"), and whether all cases of apparently sporadic MTC were screened for *RET* mutations (to which 63 responded "yes").

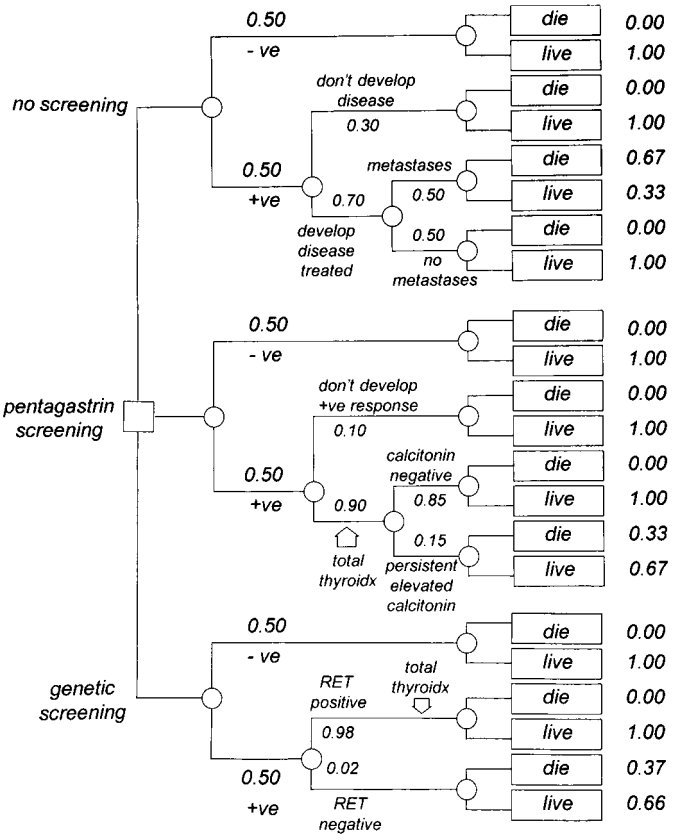


**Fig. 3.** Decision tree for preoperative screening of MEN-II families comparing no screening versus pentagastrin screening versus molecular genetic screening. Numbers in the figure represent the probabilities of either the chance or outcome. +ve: positive; −ve: negative; thyroidx: thyroidectomy.

### Cost-effectiveness of Molecular Genetic Screening for MEN-II

The causative gene for MEN-II was identified by two independent groups in 1993 [13, 14]. This discovery has enabled the identification of gene carriers among family members of MEN-II families and the potential to treat the disease surgically before clinical presentation [15]. To determine the cost-effectiveness of molecular genetic screening for MEN-II, it is necessary to start with a number of assumptions, including: (1) among gene carriers in an MEN-II family, 70% develop clinical disease during their lifetime [16]; (2) of those same gene carriers, 90% demonstrate a positive response to pentagastrin testing if tested regularly [12]; (3) if MTC is not detected until clinical presentation, 50% of patients have metastases by the time of presentation [17, 18]; (4) if MTC (or C-cell hyperplasia) is detected by pentagastrin testing, only 15% of patients have persistent disease after total thyroidectomy [19]; (5) the overall mortality from MTC for patients who present with clinical disease is 33% [20]; (6) the mortality for patients who present with nodal metastases is 66% [21].

Based on these assumptions, a decision analysis tree (Fig. 3) can

**Table 2.** Cost-effectiveness in terms of cost per life saved for pentagastrin testing vs. no testing or for genetic screening vs. no testing.

| Testing | Cost per test ($) | Risk of dying | Cost per life saved ($) |
|---|---|---|---|
| None | 0 | 117/1000 | 0 |
| Pentagastrin | 7250 | 22/1000 | 76,315 |
| Genetic screening | 500 | 3/1000 | 5,175 |

be constructed comparing three decision options: no screening for individuals of a known MEN-II family versus screening with pentagastrin testing versus molecular genetic screening. Clearly, the situation is more complex, as many centers continue to perform pentagastrin testing even after molecular genetic screening has been completed; but it is reasonable to analyze the options separately to compare true cost-effectiveness. Looking initially at the first option (i.e., if no screening program of any sort is undertaken), 50% of family members do not have the disease and clearly do not die of MTC. Of the 50% gene-affected family members, 30% still do not develop clinical disease and thus also do not die of MTC, whereas of the remaining subjects 67% of those who present with metastases eventually die of MTC. Calculation of the probabilities on each arm gives an overall risk of dying of 0.117; that is, of 1000 members of an MEN-II family, 117 eventually die of the disease.

The introduction of pentagastrin screening reduces this mortality significantly, with 90% detected by screening and able to undergo total thyroidectomy at the time of diagnosis. The sensitivity of testing in younger individuals is markedly reduced, contributing to the fact that a small percentage of the group (15%) still have a persistently elevated serum calcitonin level, and some of those individuals still die of MTC [19]. The overall risk of dying in this group is 0.022. Molecular genetic screening further reduces the risk of dying from MTC, although not absolutely. On the assumption that 2% of family members who are gene carriers do not have an identifiable *RET* mutation, there are still a low number of deaths in this group when those individuals eventually present clinically [12], although the overall risk of dying is small (0.003). If, as has been claimed by some centers, genetic testing has the potential to identify 100% of gene carriers [22], this risk is of course reduced to zero.

The cost of molecular genetic testing is modest indeed. Based on the above survey data and assuming that the test is performed twice for every family member, the cost per screen is $580 (2 × $290). The cost of pentagastrin testing is more difficult to calculate. A single screening test costs approximately $500: $320 for the calcitonin analysis, $130 for the test performance, and $50 for the pentagastrin [12]. For potential gene carriers, the test is ideally performed annually in at-risk family members up to 30 years of age. An average of four tests are performed in this group, at an average overall cost of $2000. Because 50% of at-risk individuals are not in fact gene carriers, their testing would continue to be performed annually for about 25 years at a cost of 25 × $500 = $12,500 [23]. The average cost of screening all members of a family is thus approximately $7250 per individual. This is clearly more costly than molecular genetic screening, as it must be repeated annually, whereas genetic screening is a once-off test. Table 2 compares the cost and cost-effectiveness of the three options. Pentagastrin testing alone is cost-effective at $76,315 per life saved, a cost comparable to that for routine measles vaccination. Molecular genetic screening, when compared with pentagastrin screening fulfills all the criteria of an ideal cost-effective test, being both more effective in terms of lives saved and significantly less expensive. The cost-effectiveness of molecular genetic screening compared to no screening is only $5175 per life saved.

## Conclusions

Molecular genetic screening has now moved out of academic centers into commercial laboratories and is widely accepted in clinical practice. It is anticipated that the DNA diagnostic market will exceed $1 billion by 1998, and of that figure $340 million will be for genetic screening for cancer and $65 million for diagnostic tests for genetic disease [24].

A study in our own unit [25] has shown that *RET* proto-oncogene screening for MEN-II is well accepted by clinicians. Our own unit is the only laboratory offering *RET* proto-oncogene testing for all described mutations in Australasia at present. A survey was undertaken of all clinicians to whom results had been provided, and 26 MEN-II families comprising 164 individuals were identified in Australasia. Of the 56 *RET*-positive individuals who had been identified, 52 had already undergone total thyroidectomy. Of the four who had not undergone surgery, two were too young (3 and 4 years), one already had advanced metastatic MTC, and one declined surgery, preferring to pursue a sporting career. Of the 108 *RET*-negative individuals identified, none has continued to undergo biochemical screening with pentagastrin testing.

There is clearly an increasing need to be aware of the cost-benefit of molecular genetic testing. Fortunately, genetic screening for endocrine disease such as MEN-II, at a cost per life saved of just over $5000, is clearly cost-effective when compared to many other screening programs. It must be remembered, however, that although cost-effective affordability is still a major consideration for such programs in developing countries. For example, the cost of such a screening program for MEN-II in Sri Lanka would represent a sum seven times the annual average household income per life saved.

In addition to being cost-effective, the therapy required as a result of such screening programs (total thyroidectomy) is acceptable and well tolerated. There are few complications when performed in expert hands, and the patient then requires nothing more than lifelong thyroxine therapy.

## Résumé

Les coûts des test de dépistage en matière de maladie endocrine peuvent être calculés de plusieurs façons, tenant compte des charges ou des coûts selon les factures, des coûts de production ou, encore plus approprié, des coûts nécessaires pour obtenir l'objectif affiché du test (coût efficacité)(CE). L'analyse du CE permet aux cliniciens de déterminer si tel ou tel bénéfice d'un test compense les coûts impliqués. Par exemple, l'analyse du CE des tests de la fonction thyroïdienne pré-opératoires chez le sujet âgé ayant un nodule de la thyroïde a montré que les coûts engendrés pour chaque vie sauvée était seulement de $405, ce qui est clairement coût efficace. Etre coût efficace, cependant, n'équivaut pas toujours à la possibilité de payer, surtout dans les pays en voie de développement. Les coûts des tests de fonction thyroïdienne pré-opératoires représentent seulement 0.8% du salaire moyen en

Australie, un prix qui est à la fois coût efficace et abordable, mais en Sri Lanka, ces mêmes tests de dépistage représentent environ 50% du salaire moyen mensuel. Une enquête mondiale des membres de l'International Association of Endocrine Surgery (IAES) a montré que le dépistage génétique était facilement disponible dans 67% des institutions, toutes ayant la possibilité de rechercher le remaniement par transfection proto-oncogène (RET) alors qu'un peu moins avaient la possibilité de rechercher le gène MEN 1, le gène du syndrome de von Hippel-Lindau (VHL) ou faire l'analyse de liaison pour le phéochromocytome familial. Le prix (médian) du dépistage par la recherche du remaniement par transfection proto-oncogène (RET) était de $290 (extrêmes $100 à $3,000). L'analyse du CE pour le dépistage génétique moléculaire des syndromes MEN2 démontre que le coût par vie sauvée est de $5,175. Ceci se compare bien avec le test de dépistage par dosage de la pentagastrine annuel où le coût par vie sauvée peut aller jusqu'à $76,315. Rechercher les maladies endocrines comme les syndromes MEN2 par la génétique moléculaire n'est pas seulement d'une coût-efficacité mais la thérapeutique nécessaire (thyroïdectomie totale) est à la fois acceptable et bien tolérée.

**Resumen**

El costo de las pruebas de tamizaje en las enfermedades endocrinas puede ser determinado por diversos métodos, los cuales incluyen análisis del cargo o costo de la cuenta, el costo de producción o, tal vez, lo más apropiado, el costo para lograr el propósito que se pretende con la realización de la prueba (costo-efectividad). El análisis de costo-efectividad permite al médico establecer si el beneficio adicional de una prueba implica un costo aceptable. Por ejemplo, el análisis del costo-efectividad de las pruebas rutinarias de función tiroidea practicadas con anterioridad a la cirugía en pacientes de edad avanzada en enfermedad nodular de la glándula tiroides demuestra que el costo por cada vida que se salve es de sólo $405, cifr a que es claramente costo-efectiva. Sin embargo, el costo-efectividad no siempre quiere decir capacidad de pago, especialmente en los países en vía de desarrollo. El costo de las pruebas preoperatorias de función tiroidea representan apenas el 0.8% del promedio del ingreso de una familia en Australia, lo cual indica que son costo-efectivas y costeables, en tanto que en Sri Lanka el costo de las mismas pruebas representa el 50% del ingreso mensual. Una investigación realizada a nivel mundial entre los miembros de la IAES (International Association for Endocrine Surgery) señaló que las pruebas de tamizaje genético para enfermedades endocrinas son fácilmente asequibles en 67% de las instituciones, que todas ellas poseen la capacidad de realizar la prueba de reordenación por transfección del proto-oncogen RET y que sólo algunas poseen acceso a las pruebas para el gen MENIM, el gen del Síndrome de Von Hippel-Lindau (VHL) o el análisis de ligación para feocromocitoma familiar. El costo promedio de las pruebas para el proto-oncogen RET fue de $290, con un rango entre $100 y $3000. El análisis del tamizaje genético molecular para NEM-2 demuestra que el costo por cada vida que se salve es de apenas $5.175. Esto se compara favorablemente con la conducta de tamizaje basado en pruebas anuales con pentagastrina, donde el costo por cada vida que se salve llega hasta $76.315. El tamizaje genético molecular para enfermedades endocrinas tales como los síndromes NEM-2 no sólo es costo-efectivo, sino que el tratamiento requerido (tiroidectomía total) es de alta aceptación y bien tolerado.

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