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# Cost-Effectiveness of Using a Molecular Diagnostic Test to Improve Preoperative Diagnosis of Thyroid Cancer

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ABSTRACT

**Objective:** Fine-needle aspiration biopsy (FNAB) is a safe and inexpensive diagnostic procedure for evaluating thyroid nodules.Up to 25% of the results from an FNAB, however, may not be diagnostic or may be indeterminate, leading to a subsequent diagnostic thyroid surgery. A new molecularly based diagnostic test could potentially reduce indeterminate cytological results and, with high accuracy, provide a definitive diagnosis for cancer in thyroid nodules. The aim of the study was to estimate the cost-effectiveness of utilizing a molecular diagnostic (DX) test as an adjunct to FNAB, compared with NoDX, to improve the preoperative diagnosis of thyroid nodules. **Methods:** We constructed a patient-level simulation model to estimate the clinical and economic outcomes of using a DX test compared with current practice (NoDX) for the diagnosis of thyroid nodules. By using a cost-effectiveness framework, we measured incremental clinical benefits in terms of quality-adjusted life-years and incremental costs over a 10-year time horizon. **Results:** Assuming 95% sensitivity and specificity of the Dx test when used as an adjunct to FNAB, the utilization of the DX test resulted in a gain of 0.046 quality-adjusted life-years (95% confidence interval 0.019–0.078) and a saving of $1087 (95% confidence interval $691–$1533) in direct costs per patient. If the cost of the Dx test is less than $1087 per test, we expect to save quality-adjusted life-years and reduce costs when it is utilized. Sensitivity of the DX test, compared with specificity, had a larger influence on the overall outcomes.

*Keywords:* cost-effectiveness, gene expression, molecular diagnostic test, thyroid cancer, fine needle aspiration biopsy, The Bethesta System for Reporting Thyroid Cytopathology (TBSRTC).



## Introduction

Thyroid nodules are common, affecting from 4% to 7% in the general population [1]. Fortunately, only a small proportion of these nodules (approximately 5%) are cancerous [1,2]. Fine-needle aspiration biopsy (FNAB) is currently the standard of practice for evaluating thyroid nodules due to its low cost, low complication rate, and availability [3]. The introduction of FNAB in the early 1980s has resulted in significant economic savings and improved patient outcomes by reducing the number of diagnostic thyroid operations required and improving the detection rate of thyroid cancer [4].

A major drawback of FNAB of thyroid nodules is the large number of indeterminate or suspicious cancer diagnoses in that often the lesions cannot definitively be classified as benign or malignant following FNAB. Clinical decision making following an indeterminate cytological result is challenging and may lead to either overtreatment or undertreatment of thyroid nodules. This diagnostic uncertainty is a consequence of not only the subjective nature of thyroid cytology but also the overlapping cytomorphologic characteristics of benign and malignant thyroid lesions. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is the result of a recent multidisciplinary effort to develop a uniform system for reporting thyroid FNAB cytological results and their clinical significance [5]. The Bethesda thyroid FNAB cytology reporting system is particularly helpful for providing a clear estimate of cancer risk and recommendations for the management of indeterminate cases (i.e., atypia of undetermined significance, follicular neoplasm, and suspicious cases). Even after following the currently recommended diagnostic algorithm, about half of the thyroid nodules operated on for an indeterminate diagnosis are eventually found to be benign [5,6]. Therefore, the development of a new diagnostic test that can serve as an adjunct to FNAB and reduce the number of unnecessary diagnostic thyroid operations would have significant clinical and economic value.

In the current study, we aimed to 1) evaluate the overall performance of FNAB in combination with the TBSRTC (current practice) in directing thyroid nodule surgical management and 2) estimate the cost-effectiveness of using a new molecular diagnostic (DX) test as an adjunct to FNAB compared with best current practice (FNAB in combination with the TBSRTC guidelines, hereafter referred to as NoDX). We performed the analyses in scenarios for only individuals with an indeterminate FNAB cytological diagnosis, as well as for all individuals who present with thyroid nodules (i.e., including nondiagnostic, benign, and malignant cases in the target population).

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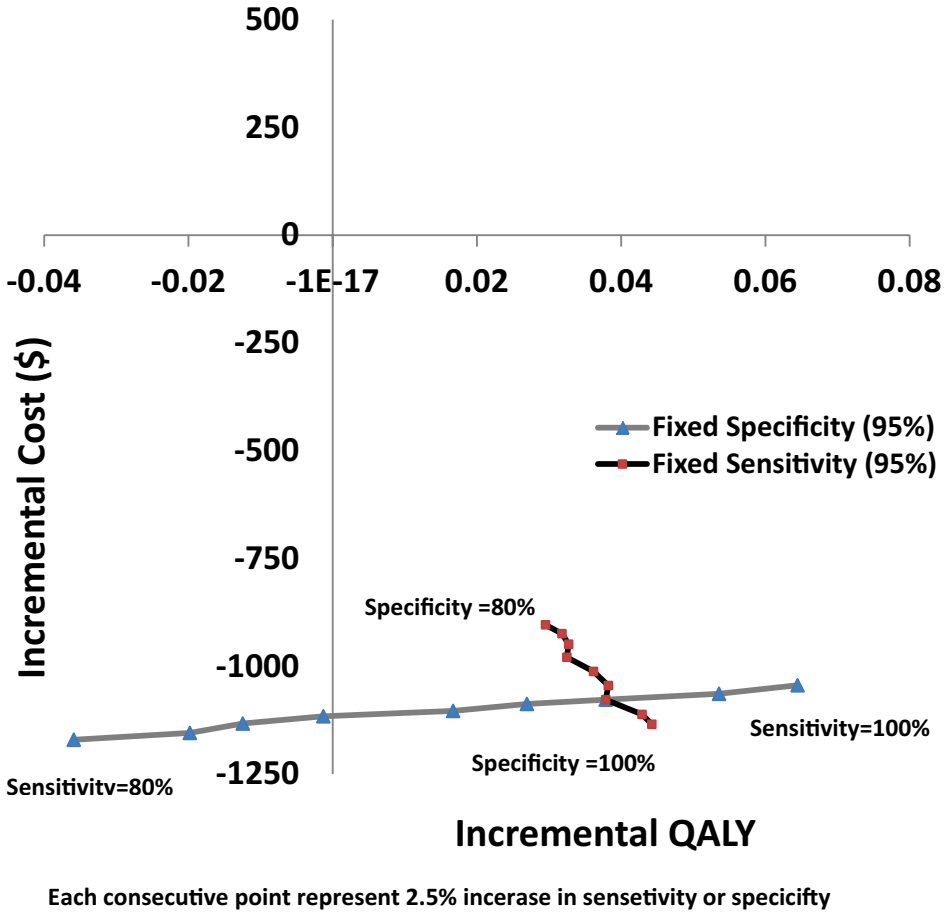


**Fig. 1 – Incremental cost and effectiveness for different sensitivity and specificity of DX test. DX, diagnostic; QALY, quality-adjusted life-year.**

## Methods

### *Model design*

We developed a patient-level discrete event simulation model by using Arena, Version 13.0 (Rockwell Software, Inc., Milwaukee, WI), to calculate the incremental cost-effectiveness of using the DX test in conjunction with FNAB relative to current practice (NoDX) in two simulated cohorts of 10,000 patients with an initial indeterminate FNAB cytological diagnosis. In a patient-level model, one hypothetical patient is created and assigned to the NoDX arm and an identical clone is created and assigned to the DX arm (see Figure 1 available in the Appendix in Supplemental Material found at http://dx.doi.org/10.1016/j.jval.2012.06.017). The model was run over a 10-year time horizon, and results were determined from the societal perspective. Depending on the subsequent diagnostic results in each arm, patients underwent either a total thyroidectomy or hemithyroidectomy, or alternatively were followed clinically, in accordance with the TBSRTC. In particular, we simulated the number of malignant cases across diagnostic categories, and then by comparing the final cytology and histology, each patient was classified as a true-positive, false-positive, true-negative, or false-negative cancer case. The incidence of major morbidity following surgery (i.e., permanent hypoparathyroidism and/or recurrent laryngeal nerve injury [RLNI]) and cancer recurrence was included in the model as was cancer-related mortality.

We needed to explicitly simulate the results of sequential test outcomes for each patient to calculate the overall number of false positives and false negatives in our simulation. We also modeled the time as a continuous variable (rather than using fixed cycles). As such, we used discrete event simulation, which offers the capacity to develop continuous time, patient-level simulations with great flexibility for doing first-order and second-order sensitivity analyses [7,8].

### *Data sources and assumptions*

In the simulation, following the TBSRTC classification of a nodule, there were six possible cytologic outcomes subsequent to an FNAB [5]: 1) nondiagnostic or unsatisfactory, 2) benign, 3) atypia or follicular lesion of undetermined significance, 4) follicular neoplasm, 5) suspicious for malignancy, or 6) malignant. We defined an indeterminate cytological result as an FNAB diagnosis being atypia or follicular lesion of undetermined significance, follicular neoplasm, or suspicious for malignancy. Furthermore, on the basis of review of the literature, we utilized the proportion of patients in each category, and the probabilities of malignancy for each category, to inform the progression through the model (Table 1) [5]. The possible pathways in the model were designed on the basis of proposed management recommendations for each cytological diagnostic category [5].

Unlike the NoDx test arm, the diagnostic results in the DX test arm were confined to two possible diagnoses: benign or malignant. The overall prevalence of malignancy was assumed to be equal in the two arms of the model. Therefore, for a given sensi-