The Role of Genetic Markers in the Evaluation and Management of Thyroid Nodules

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KEYWORDS

• Thyroid nodules • Indeterminate cytology • Molecular markers • Genetic testing

KEY POINTS

- Genetic markers should only be used as an ancillary diagnostic tool for indeterminate thyroid nodules.
- Veracyte Afirma may improve the diagnostic accuracy for a subset of indeterminate cytologic diagnosis.
- Overall clinical, imaging, and cytopathologic evaluation in addition to patient preference should guide the management of indeterminate nodules.
- Further multicentered and independent validation studies are needed in order to prove the efficacy of commercially available genetic markers.

INTRODUCTION

Thyroid nodules are common, with increasing incidence, but only 5% to 15% of nodules are malignant. Fine-needle aspiration (FNA) with cytopathologic evaluation is the gold standard test for distinguishing benign from malignant nodules, but in about 20% of instances the test is indeterminate, often leading to diagnostic surgeries. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) classification defines indeterminate cytology as either (1) atypical cells of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) or (2) follicular neoplasm (FN)/suspicious for a follicular neoplasm (SFN). However, the final pathology in most diagnostic surgeries proves the nodule to be benign. The risk of malignancy in the final pathology for those cytology samples deemed indeterminate can vary from

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5% to 30%, depending on the category within the Bethesda classification. In contrast, FNAs that are read as suspicious for malignancy are associated with a 60% to 75% risk of malignancy, and a cytologic sample read as positive for malignancy has a 96% to 98% chance of being malignant on final pathology.[1,2] Furthermore, even within the cytologic categories, significant variability exists in the risk of malignancy between the institutions and pathologists.[3] Therefore, highly sensitive and specific diagnostic tools are essential for minimizing unnecessary diagnostic surgeries and 2-stage operations. In an effort to improve diagnostic accuracy, many existing and innovative diagnostic utilities are being actively investigated, including elastography, optical probes, serum biomarkers, and molecular tests. Among them, genetic markers have shown initial promise as a diagnostic tool that may complement standard clinical, radiologic, and FNA evaluation of thyroid nodules.

Thus far, genetic markers have been investigated at various stages of evaluation for management of thyroid nodules. Such efforts have led to a few commercially available gene-based diagnostic tools for indeterminate thyroid nodules. Because molecular testing is progressing rapidly with few publications available, readers should not use information provided here as rules or recommendations. Instead, this article is an educational launching point to further clinicians' knowledge of these state-of-the-art tests. Molecular testing in thyroid nodules is minimally invasive, and it may avoid the intervariability and intravariability often observed in cytologic or histopathologic analysis, potentially becoming the most important, cost-effective, and operator-independent diagnostic tool in the evaluation of a thyroid nodule; however, more research is needed. For the foreseeable future, the best evaluation of thyroid nodules will be achieved with a thorough physical examination, ultrasonography, and cytopathologic evaluation, coupled with the treating physician's experience and judgment. Molecular testing will supplement but not replace this comprehensive approach.

BACKGROUND

The role of commonly associated genetic mutations in thyroid cancer is being actively investigated. However, the role of genetic alterations in tumorigenesis, the clinicopathologic presentations, and their diagnostic or prognostic importance are yet to be fully defined. Thus far, no single molecular marker has shown clinically acceptable negative predictive values (NPVs) and positive predictive values (PPVs), allowing their use as a sole diagnostic tool in evaluating thyroid nodules. Nonetheless, modern high-throughput gene extraction, microarray profiling, and computational analysis have defined certain panels of genetic markers that are promising in the evaluation of thyroid nodules. Many surgical and basic science laboratories have been pioneers over the last decade by using large cohorts of patient needle aspirates, tissue, and blood samples from patients with a variety of thyroid disorders. Recent clinical studies, such as the Afirma Veracyte Trial, have validated the usefulness and efficacy of commercially available tests in diagnosis of indeterminate thyroid nodules. In addition, these studies have shown the importance of incorporation of molecular testing in the national guidelines, such as the National Comprehensive Cancer Network (NCCN). Since December of 2012, genetic testing has been poised to become a mainstream practice in the management of thyroid neoplasms.[4]

CURRENTLY AVAILABLE TECHNIQUES

The 2 most clinically promising types of molecular panels currently are (1) gene expression profiling tools that use the RNA expression profiles of thyroid FNA samples to try to rule out thyroid cancer by determining which nodules have a benign RNA