



Molecular Analysis of the Indeterminate Thyroid Nodule: A Rapid Progression from Past to Future

Aaron Ross Chidakel*

Division of Endocrinology, Diabetes and Metabolism, NYU Langone Medical Center, New York, 10016, USA

*Corresponding author: Aaron Ross Chidakel, Division of Endocrinology, Diabetes and Metabolism, Preston R. Tisch Center for Men's Health, NYU Langone Medical Center, New York, 10016, USA, Tel: 646-754-2000; E-mail: Aaron.Chidakel@nyumc.org

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Editorial

Thyroid nodules, or growths in the thyroid gland, have presented a diagnostic dilemma for a number of years. Whereas the great majority of thyroid nodules are benign and do not require intervention, for the minority of nodules which are malignant, early intervention is key to decreasing cancer-related morbidity and mortality. Fine-needle aspiration (FNA) of thyroid nodules has been the mainstay for detecting the presence of cancer in thyroid nodules for many years. However, FNA is not a perfect diagnostic tool, and indeterminate cytology diagnoses remain a diagnostic challenge [1]. It was not long ago that surgery was required in order to assess whether indeterminate cytology was indicative of a malignant tumor or a benign thyroid nodule. Furthermore, variation in the interpretation of cytopathologic samples can occur between pathologists and across institutions, thereby complicating management decisions. This led to unnecessary surgeries, with potential complications which could have otherwise been avoided. Recently, molecular tests have become available with increasing accuracy for ruling in and ruling out malignancy [2]. The Afirma analysis, a microarray-based test launched in 2011, was the first gene classifier analysis which was commercially available for testing of cytologically indeterminate thyroid nodules. As such, it was demonstrated to reduce the number of unnecessary surgeries by 50 percent [3]. However, while it was marketed as a highly accurate rule-out test for malignancy in thyroid nodules with indeterminate cytology, its shortcoming was in its lower ability in adequately ruling in thyroid malignancy [4]. Recently, newer tests have become available, with improvements on both the positive and negative values in differentiating malignancy from benign thyroid nodules. ThyroSeq v2 is a multigene test that is based on the targeted DNA and RNA next-generation sequencing analysis of 56 genes (i.e. point mutations and small insertions/deletions in 14 genes and 42 types of gene fusions) and expression levels of 16 genes. Next-generation sequencing offers high sensitivity of detection and ability to quantify the proportion of cells carrying a given mutation. In addition to providing information

regarding whether a thyroid nodule is malignant, ThyroSeq and other tests based on the detection of mutations may provide further information regarding the nature of the thyroid cancer and may help determine how aggressive the cancer may potentially be. These tests may therefore be able to help guide the extent of surgery [5]. Although the newest generation of molecular testing has high sensitivity and specificity and provides greater input on the nature of thyroid malignancy, several limitations still exist. These challenges include the recent introduction of the histopathological diagnosis "Non-Invasive Follicular Thyroid neoplasm with Papillary-like nuclear features", the correlation of genetic mutations within both benign and malignant pathologic diagnoses, the lack of follow-up of molecular marker negative nodules, and the cost-effectiveness of molecular markers [6]. Future improvements in the field of molecular markers will likely address these issues and will lead to improvements in our ability to distinguish benign from malignant thyroid nodules and to help guide future surgeries in a more precise and effective manner.

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