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Advancements in molecular diagnostic tests for indeterminate thyroid nodule cytologies

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Abstract

Thyroid nodules are a common clinical challenge, with approximately 5-7% of the adult population exhibiting palpable nodules. While the majority of these nodules are benign, a subset presents as indeterminate on Fine-Needle Aspiration Cytology (FNAC), posing a diagnostic dilemma. Molecular diagnostic tests have emerged as promising tools to aid in the management of patients with indeterminate thyroid nodules. This article provides a comprehensive overview of the advancements in molecular diagnostic tests for indeterminate thyroid nodule cytologies, focusing on their mechanisms, performance, clinical implications, and challenges.

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Introduction

Molecular diagnostic tests for indeterminate thyroid nodules utilize various techniques, including somatic mutation analysis, gene expression evaluation, microRNA (miRNA) profiling, and Next-Generation Sequencing (NGS). These tests aim to provide additional information beyond traditional cytology to guide clinical decision-making.

ThyroSeq test

The ThyroSeq Test (Version 3) utilizes targeted next-generation sequencing analysis of 112 cancer-related genes to identify point mutations, gene fusions, copy number alterations, or abnormal gene expression in thyroid nodules [1]. Validation studies have reported a sensitivity of 94% and a specificity of 82%, with a negative predictive value of 97% and a positive predictive value of 66% [2]. This molecular diagnostic test has the potential to eliminate the need for diagnostic surgery in up to 61% of patients with indeterminate nodules, offering a valuable tool in improving diagnostic outcomes and sparing patients from unnecessary procedures.

Afirma genomic sequencing classifier

The Afirma Genomic Sequencing Classifier utilizes RNA sequencing and comprises 12 classifiers composed of 10,196 genes to analyze thyroid nodules. It has been reported to have a specificity of 68% and a positive predictive value of 47%, with a sensitivity of 91% and a negative predictive value of 96% [2]. This molecular diagnostic tool is expected to reduce the frequency of diagnostic surgeries by aiding in the identification of benign nodules, thus sparing patients from unnecessary procedures [3]. Thus, the ThyroSeq and Afirma assays reported positive and negative predictive values that make them suitable for use in both rule-in and rule-out testing.

ThyroPrint and combination assays

ThyroPrint is a gene expression classifier that relies on the interrogation of 10 microRNAs (miRNAs) for assessing thyroid nodules. It has demonstrated strong performance, boasting a sensitivity of 96%, specificity of 87%, and positive and negative predictive values of 78% and 98%, respectively [4]. The Combination Assay integrates miRNA classification (ThyraMIR) with

next-generation sequencing mutation analysis (ThyGeNEXT). While it has reported a positive predictive value of 74% and a negative predictive value of 94%, it is important to note that it is yet to undergo independent validation [5].

ThyroSPEC molecular test

ThyroSPEC is a cost-efficient mutation detection panel that utilizes matrix-assisted laser desorption/ionization–time of flight mass spectrometry. It is designed to detect the most prevalent 117 point mutations and 23 gene fusions associated with thyroid cancer [6]. Notably, ThyroSPEC analyzes residual liquid material or FNAC material from a representative FNAC glass slide smear obtained after routine FNAC procedures, offering a practical and convenient approach to molecular testing in thyroid nodules.

Challenges and considerations

Despite their potential, molecular diagnostic tests face challenges, including the need for additional FNAC material, high cost, and limited validation studies outside the United States. Variability in the prevalence of biomarkers in benign lesions underscores the importance of cautious interpretation and further characterization of these markers.

Clinical implications and cost-effectiveness

The clinical utility and cost-effectiveness of molecular diagnostic tests depend on various factors, including healthcare setting, test cost, risk of malignancy, and test performance characteristics. Large patient cohort studies are essential to evaluate the impact of these tests on clinical decision-making and healthcare costs.

Future perspectives

Future research should focus on independent validation studies, long-term outcome assessments, and the integration of molecular and histological data for accurate classification of thyroid tumors. Additionally, efforts to enhance the accessibility and affordability of molecular diagnostic tests are warranted to benefit patients worldwide.

Conclusion

Molecular diagnostic tests represent a significant advancement in the management of indeterminate thyroid nodules, offering improved risk stratification and personalized treatment decisions. Despite current challenges, ongoing research and clinical experience are expected to refine these tests and optimize their clinical utility, ultimately improving patient outcomes in thyroid nodule management.

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