Interpace Diagnostics®
Resolving Diagnostic Uncertainty

Executive Summary

ThyGeNEXT® (mutation panel) + ThyraMIR®v2 (miRNA Risk Classifier)

Interpace Diagnostics, Inc. (Parsippany, NJ) offers a multi-platform testing option for thyroid nodules that includes the ThyGeNEXT® expanded mutation panel (formerly ThyGenX®), in combination with the ThyraMIR®v2 microRNA risk classifier, to help inform clinical management decisions.

When a thyroid nodule is identified, a patient typically undergoes an FNA (fine-needle aspiration) procedure to help determine if the nodule is benign or malignant. During the FNA procedure, cells are collected and slides are made for microscopic evaluation. In most cases a pathologist can examine the slide to determine if the sample is benign or malignant. However, in approximately 10%–30%[1] of cases, a clear determination cannot be made and an indeterminate cytology diagnosis is rendered.

The risk of malignancy (ROM) associated with an indeterminate cytology diagnosis is 6%–30% for AUS/FLUS (B-III), 10%–40% for FN/SFN (B-IV), and 45%–75% for SMC (B-V).[2] The unique combination testing approach with ThyGeNEXT + ThyraMIRv2 provides highly accurate risk stratification of indeterminate thyroid nodules. Prior to the advent of molecular testing, patients with an indeterminate cytology diagnosis (Bethesda III, IV, or V) were typically sent for surgery, often resulting in unnecessary surgeries for benign thyroid nodules.

Over the past decade, molecular testing has gained wide acceptance as a useful tool for providing reliable diagnostic information and reducing unnecessary surgeries. In addition to informing clinical decisions regarding the need for, or extent of, surgery, molecular testing now includes prognostic markers and can be used to identify appropriate therapeutic treatment options or the potential for treatment failures. There is mounting data that reveals the negative impact that mutations such as *BRAF* V600E and *TERT* have on I-131 avidity.[3] Therefore, knowing the mutation status can help direct patient management.

Additional insights into the measurement of molecular test performance have also been highlighted in recent years. It has been well established that the underlying cancer prevalence of a study population directly impacts the performance of any molecular test. There are numerous published studies and guidelines that discuss this important nuance to understanding the true performance of any molecular test. If the cancer prevalence of a study population is low, then the NPV (negative predictive value) is expected to be higher; if the cancer prevalence is high then the NPV is expected to be lowered. The inverse holds true for PPV (positive predictive value). An ideal molecular test is one that can provide both a high NPV (rule-out malignancy) and a high PPV (rule-in malignancy).

The markers within the expanded mutation panel (ThyGeNEXT) include the most common mutations/fusions associated with thyroid malignancies (*BRAF* V600E, *RET/PTC1*, *RET/PTC2*, *RAS*, *TERT,* and others).[4] There are thousands of published studies on these mutations and their relevance to thyroid malignancies.

Interpace Diagnostics' goal was to create a diagnostic test that could accurately assess the risk of malignancy of indeterminate thyroid nodules, thereby providing physicians and patients with actionable information. Interpace regularly receives input and guidance from experts in the field of Endocrinology, Pathology, and Thyroid Surgery.

ThyGeNEXT +ThyraMIRv2 provides the highest PPV and NPV of any commercially available test, offering physicians and patients the benefit of being able to both "Rule In" or "Rule Out" cancer with a high degree of accuracy. The use of ThyGeNEXT + ThyraMIRv2 in indeterminate samples can significantly reduce the number of unnecessary surgeries.[5]

Published clinical utility data for ThyGeNEXT® + ThyraMIR® has shown that mutation panels alone do not sufficiently risk-stratify thyroid nodules. The use of microRNA classification complements cytology and mutation analysis with the capacity to better differentiate nodules at high risk of malignancy.[6,7] The ThyraMIR miRNA classifier provides additional risk information, especially when no mutations or an isolated *RAS*-like mutation is found with ThyGeNEXT.[8]

There are numerous published studies on Interpace's multi-platform test approach, including analytical and clinical validation of this testing for indeterminate thyroid nodules, as well as for the diagnosis of Medullary Thyroid Carcinoma.[6-10] Most recently, the clinical validation study by Finkelstein et al (n=197) revealed a test performance of 99% NPV at negative threshold and a 96% PPV at positive threshold[11]. In addition, the use of ThyraMIRv2 in conjunction with ThyGeNEXT led to a 52% reduction in the Moderate-Risk group, helping to limit false positives and negatives. There was 100% accuracy for the samples that were reclassified by ThyraMIRv2 vs ThyraMIRv1. This large, blinded, multi-center, retrospective study utilized the gold standard of unanimous histopathology consensus to overcome any potential inter-observer variability.

Clinical practice guidelines support the use of molecular testing when the cytology diagnosis is indeterminate (B-III and B-IV).[12,13] In addition, "the 2022 NCCN Panel recommends molecular testing to help inform decisions regarding systemic therapy and to determine eligibility for clinical trials."[11] The ThyGeNEXT mutation panel includes many known potential therapeutic targets, including variants or fusions of the following genes: *BRAF, AKT, ALK, HRAS, KRAS, NRAS, NTRK, PPARG, PTEN,* and *RET*.

ThyGeNEXT and ThyraMIRv2 offer physicians and patients a valuable tool to provide highly accurate risk assessment for indeterminate thyroid nodules. In addition, this testing is very convenient and, unlike other testing options, never requires any special shipping or refrigeration. The testing can be performed on a fresh FNA specimen or using a diagnostic cytology slide with just >80 follicular cells. In addition, Interpace captures a high-resolution digital image of all slides prior to testing and stores these images for their clients.

These tests have been shown to be cost-effective[5] and can eliminate the need for repeat FNA biopsies to collect the sample for molecular testing, saving money for both the patient and the health system and sparing the patient lost time and the anxiety of a second procedure. Lastly, both ThyGeNEXT and ThyraMIRv2 are covered by Medicare and most managed care plans.

References

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