Interpace Diagnostics®
Resolving Diagnostic Uncertainty

Executive Summary

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

Interpace Diagnostics, Inc. (Parsippany, NJ) offers a unique, multi-platform testing option for thyroid nodules that includes the ThyGeNEXT® expanded mutation panel (formerly ThyGenX®) in combination with the ThyraMIR® microRNA classifier. Interpace Diagnostics is the only company using a microRNA classifier to provide further risk classification for indeterminate thyroid nodules. microRNAs (miRNAs) are small non-coding RNAs that regulate gene expression. By disrupting protein synthesis, miRNAs regulate cellular processes such as survival, proliferation, migration, and death.

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 then 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® + ThyraMIR® is particularly useful at assessing the risk of malignancy in 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 ten years, molecular testing has gained wide acceptance as a useful tool for providing reliable diagnostic information and reducing unnecessary surgeries. In addition to informing the clinical decisions regarding the need for or extent of surgery, molecular testing now includes prognostic markers and can also be used to identify appropriate therapeutic treatment options. There is mounting data that also reveals the negative impact that some 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 high and 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 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). There are thousands of published studies on these mutations and their relevance to thyroid malignancies.

Interpace Diagnostics' goal was to create a multi-platform testing service that would be able to provide physicians and patients with actionable information while maintaining both a high PPV and a high NPV. Interpace regularly receives input and guidance from experts in the field of Endocrinology, Pathology, and Thyroid Surgery.

ThyGeNEXT® along with ThyraMIR® provides the highest PPV and a comparably high NPV to other marketed tests, 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® + ThyraMIR® in indeterminate samples can significantly reduce the number of unnecessary surgeries.

Published 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.[4,5] The ThyraMIR® miRNA Classifier provides additional risk information, especially when no mutations are found or weak driver mutations are found with ThyGeNEXT®.

There are numerous published studies on Interpace's multi-platform test approach. Most recently, the clinical validation study by Lupo et al (n = 197) revealed the following test performance: 95% NPV, 74% PPV and a 97% NPV and 75% PPV after prevalence adjustment.[6] 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). [7,8] The 2020 NCCN Guidelines state that "Molecular testing has been shown to be beneficial when making targeted therapy decisions, particularly related to drug therapies or clinical trial participation."[8,9] 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. "In addition, the presence of some mutations may have prognostic importance."[10]

ThyGeNEXT® and ThyraMIR® offer physicians and patients a valuable tool to provide further risk assessment for indeterminate thyroid nodules. This unique, multi-platform test approach can both rule-in and rule-out malignancy with high accuracy. The testing is very convenient, and unlike other testing options, never requires any special shipping or refrigeration. These tests have been shown to be cost-effective[10] and can eliminate the need for repeat FNA biopsies, saving money for both the patient and the health system and sparing the patient lost time and anxiety for a second procedure. Lastly, both ThyGeNEXT® and ThyraMIR® are covered by Medicare and most managed care plans.

References

1. Keutgen XM et al. *Expert Rev Mol Diagn*. 2013;13(6):613-623. **2.** Cibas ES and Ali SZ *THYROID* Volume 27, Number 11, 2017. **3**. Yang X, et al. *J Nucl Med* 2017;58:258-265. **4.** Banizs AB, Silverman JF. *Diagnostic Cytopathology*. 2019;47(4):268-274. **5.** Jackson, S et al. *Diagnostic Cytopathology*. 2019;1–10. **6**. Lupo MA et al – *Diagnostic Cytopathology* 2020 **7**. Haugen BR et al. *THYROID* Volume 26, Number 1, 2016 **8.** NCCN Guidelines – Version 2.2020 - https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf **9**. Xing M et al. 2014 *J Clin Oncol 32:2718-2726.* **10**. Labourier E. *Clinical Endocrinology* (2016), 85, 624–631.