Test Specific Guidelines

ThyGeNEXT and ThyraMIR miRNA Gene Expression Classifier

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Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guidelines	Procedure codes
ThyGeNEXT	0245U
ThyraMIR miRNA Gene Expression Classifier	0018U

What Are Thyroid Nodules?

Definition

Thyroid nodules are a common occurrence, especially in an aging population. Fine-needle aspiration (FNA) with accompanying cytology examination is the standard method for distinguishing between benign and malignant nodules and subsequent removal of tumors. Approximately 15 to 30% of thyroid nodules examined using FNA and traditional cytology examination are considered indeterminate. Clinicians are then faced with the decision to either remove the nodule unnecessarily or leave a potentially malignant nodule in place.[1]

Additional diagnostic procedures have been developed to help further classify indeterminate nodules as either benign or malignant. These procedures usually involve assessment of known genetic point mutations or through the expression activity of microRNA.[1]

Test Information

Thyroid nodules are traditionally assessed through inspection of cell cytology; however, some aspirate samples may be indeterminate. ThyraMIR uses an algorithm of 10 microRNAs previously validated using nodules with known malignancy to assist in determining if indeterminate cytology is malignant. It is used in conjunction with ThyGeNEXT. The ThyGeNEXT panel identifies DNA

mutations (ALK, BRAF, GNAS, HRAS, KRAS, NRAS, PIK3CA, PTEN, RET, and TERT), and the RNA panel identifies a number of fusions: ALK (2), BRAF (2), NTRK (8), PPARg (6), RET (14), THADA (5).[2-5]

Specimens for testing with the combination of ThyGeNEXT + ThyraMIR are obtained when performing FNA.[5] When a thyroid fine needle aspirate sample is found to be indeterminate, the ThyGeNEXT test is run on the sample. If the ThyGeNEXT test result is negative for malignancy, the ThyraMIR miRNA classifier test is then used to increase the overall sensitivity and specificity of the test combination. The overall test result is either positive or negative for malignancy.

Guidelines and Evidence

American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi (AACE/ACE/AME) Guidelines

The AACE/ACE/AME (2016) Clinical Practice Guidelines for the Diagnosis and Management of Thyroid Nodules state the following:[5]

"In nodules with indeterminate cytologic results, no single cytochemical or genetic marker is specific or sensitive enough to rule out malignancy with certainty. However, the use of immunohistochemical and molecular markers may be considered together with the cytologic subcategories and data from US (ultrasound), elastography, or other imaging techniques to obtain additional information for management of these patients."

When molecular testing should be considered:

"To complement not replace cytologic evaluation (BEL 2, GRADE A)."

"The results are expected to influence clinical management (BEL 2, GRADE A)."

"As a general rule, not recommended in nodules with established benign or malignant cytologic characteristics (BEL 2, GRADE A)."

Molecular testing for cytologically indeterminate nodules:

"Cytopathology expertise, patient characteristics, and prevalence of malignancy within the population being tested impact the NPV and PPV for molecular testing (BEL 3, GRADE B)."

"Consider detection of BRAF and RET/PTC and, possibly PAX8/PPARG and RAS mutations if such detection is available (BEL 2, GRADE B)."

"Because of the insufficient evidence and limited follow-up, we do not recommend either in favor of or against the use of gene expression classifiers (GECs) for cytologically indeterminate modules (BEL 2 GRADE B)."

Role of molecular testing for deciding the extent of surgery

"Currently, with the exception of mutations such as BRAF V600E that have a PPV approaching 100% for papillary thyroid carcinoma (PTC), the evidence is insufficient to recommend in favor of or against the use of mutation testing as a guide to determine the extent of surgery (BEL 2, GRADE A)."

How should patient with nodules that are negative at mutation testing be monitored?

"Since the false-negative rate for indeterminate nodules is 5 to 6% and the experience and follow-up for mutation negative nodules or nodules classified as benign by a GEC are still insufficient, close follow-up is recommended (BEL 3, GRADE B)."

American Thyroid Association

The American Thyroid Association (ATA, 2016) makes the following statement regarding molecular testing and FNA-indeterminate thyroid nodules:[4]

"For nodules with AUS/FLUS cytology, after consideration of worrisome clinical and sonographic features, investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. Informed patient preference and feasibility should be considered in clinical decision-making. (Weak recommendation, Moderate-quality evidence)"

"If repeat FNA cytology, molecular testing, or both are not performed or inconclusive, either surveillance or diagnostic surgical excision may be performed for an AUS/FLUS thyroid nodule, depending on clinical risk factors, sonographic pattern, and patient preference. (Strong recommendation, Low-quality evidence)"

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2021) Thyroid Carcinoma Guidelines state the following:[3]

"The diagnosis of follicular carcinoma or Hürthle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (i.e. follicular neoplasm, AUS, FLUS) as either more or less likely to be benign or malignant based on the genetic profile. ...If molecular testing, in conjunction with clinical and ultrasound features, predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider active surveillance. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient."

"Because the published studies have focused primarily on adult patients with thyroid nodules, the diagnostic utility of molecular diagnostics in pediatric

patients remains to be defined. Therefore proper implementation of molecular diagnostics into clinical care requires an understanding of both the performance characteristics of the specific molecular tests and its clinical meaning across a range of pre-test disease probabilities."

"While molecular diagnostic testing may be useful for diagnosing NIFTP [noninvasive follicular thyroid neoplasms with papillary-like nuclear features] in the future, currently available tests were not validated using NIFTP samples. ... However, multiple studies investigating the performance of molecular diagnostics for this subtype have reported that most thyroid nodules histologically diagnosed as NIFTP are classified as "suspicious" by GEC, possibly leading to a more aggressive surgical treatment than is necessary. Therefore the validation of molecular diagnostics with NIFTP samples will be necessary to ensure that the tests are accurately classifying these."

Selected Relevant Publications

A number of peer-reviewed expert-authored studies that evaluate ThyGeNEXT and ThyraMIR in individuals with indeterminate findings on fine needle aspirate(s) (FNA) of thyroid nodules are available.[6-17] These studies demonstrate the ability of the test to rule out or rule in malignant disease. Although there is limited evidence that use of the tests reduces the need for surgical biopsy or resection, clinical practice guideline recommendations generally support molecular testing of indeterminate thyroid nodules for clinical decisions regarding next steps in the treatment pathway.

Criteria

Introduction

Requests for ThyraMIR microRNA and ThyGeNEXT testing are reviewed using these criteria.

ThyraMIR microRNA and ThyGeNEXT are indicated for thyroid nodules with indeterminate FNA results that are included in the following cytopathology categories:

Bethesda diagnostic category III (atypia/follicular lesion of undetermined significance), or

Bethesda diagnostic category IV (follicular neoplasm/suspicion for a follicular neoplasm), AND

Clinical or radiologic findings are not strongly suggestive of malignancy, AND

The testing result will be used to determine surgical planning, AND

No previous molecular multi marker or gene expression assay (e.g. Afirma GSC, ThyroSeq) performed on the same nodule when a result was successfully obtained, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Billing and Reimbursement

ThyraMIR microRNA and ThyGeNEXT are reimbursed only once per date of service regardless of the number of nodules submitted for testing. If ThyGeNEXT is performed and yields a result suggestive of malignancy, reflex to ThyraMIR will not be reimbursed.

ThyraMIR microRNA and ThyGeNEXT are indicated only once per thyroid nodule per lifetime.

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