ThyGeNEXT and ThyraMIR miRNA Gene Expression Classifier

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
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<th>Procedures addressed by this guidelines</th>
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<td>ThyGeNEXT</td>
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<td>ThyraMIR miRNA Gene Expression Classifier</td>
<td>0018U</td>
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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 the number of fusions: ALK (2), BRAF (2), NTRK (8), PPARg (6), RET (14), THADA (5). This test was previously called ThyGenX. Specifically, the manufacturer reports that TERT and ALK mutations have been “newly added” to “predict aggressive biological features of thyroid cancer.”

- Specimens for testing with the combination of ThyGeNEXT + ThyraMIR are obtained when performing FNA. 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

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2018) Thyroid Carcinoma Guidelines state the following:

- “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, atypia of undetermined significance (AUS), follicular lesions of undetermined significance (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.”

American Thyroid Association

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

- “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)"

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:

- “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 BRAFV600E 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?
  
  o “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).”

Literature review

• The evidence base of the combined ThyGenX and ThyraMIR is currently insufficient to assess the effects of this combined test on patient health outcomes.6-10
  
  o Clinical validity studies reported area under the receiver operator curve (AUC) values ranging from 0.89 to 0.94; the test correctly classified 92% of benign lesions as low risk or negative and correctly classified 92% of malignant lesions as high risk or positive.9
  
  o Another study reported that ThyraMIR correctly identified 64% of malignant lesions and 96% of benign lesions. The sensitivity and specificity of the test was reported as 89% (95% confidence interval [CI], 73-97%) and 85% (95% CI, 75-92%), respectively. With a 32% prevalence rate, 61% of the results were considered benign, generating a negative predictive value (NPV) of 94% (95% CI, 85-98%).

• The evidence for clinical validity and clinical utility of the combined ThyGenX and ThyraMIR is sparse and consists of 2 retrospective studies. Direct evidence for clinical utility was not identified in the peer-reviewed literature. Overall, the evidence is insufficient to assess the effects of this combined test on patient health outcomes.

• There is no evidence of analytical validity, clinical validity or clinical utility of the newly named and expanded test, ThyGeNEXT. There is no published evidence evaluating the diagnostic accuracy or clinical utility of the combination test, ThyGeNEXT +ThyraMIR. Therefore, the evidence is insufficient to assess the effects of this combined test on patient health outcomes.

Criteria

• This test is considered investigational and/or experimental.
  
  o Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical.
management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

- In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

References


