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>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
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<tbody>
<tr>
<td>ThyroSeq</td>
<td>0026U</td>
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</table>

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 15-30% 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 mutations, gene fusions, or the expression activity of microRNA.¹

Test information

- ThyroSeq is designed to aid in the classification of thyroid nodules with indeterminate cytology as either malignant or benign.²
- ThyroSeq is a gene sequencing panel used on thyroid cells obtained via fine needle aspiration (FNA) in order to detect genetic mutations known to be associated with thyroid cancer. ThyroSeq detects gene fusions and point mutations in 112 genes related to thyroid cancer. The test is used when cytological examination of cells obtained by FNA are indeterminate, thus helping to either identify malignant nodules and guide therapy (with positive test results) or avoid surgery for those with benign nodules (with negative test results).
- According to the manufacturer, “The test utilizes a proprietary Genomic Classifier (GC) based on the algorithmic analysis of all detected genetic alterations to report the test result as Positive or Negative.”²
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:\(^3\)

- 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?
  - 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:

- “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, 2020) 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.”

Selected Relevant Publications

A number of peer-reviewed expert-authored studies that evaluate ThyroSeq in individuals with indeterminate findings on fine needle aspirate(s) (FNA) of thyroid nodules are available. 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 ThyroSeq testing are reviewed using these criteria.

- ThyroSeq is 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, ThyraMIR microRNA and ThyGeNEXT) 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

ThyroSeq is reimbursed only once per date of service regardless of the number of nodules submitted for testing.

ThyroSeq is indicated only once per thyroid nodule per lifetime.

References

1. Nishino M, Nikiforova M. Update on Molecular Testing for Cytologically Indeterminate Thyroid Nodules. Arch Pathol Lab Med. Apr 2018;142(4):446-457

2. UPMC University of Pittsburgh Medical Center. ThyroSeq® - Thyroid Cancer Next-Generation Sequencing Panel. Available at: https://thtmlhyroseq.com/physicians/test-details/test-description


29. Rossi ED, Pantanowitz L, Faquin WC. The role of molecular testing for the indeterminate thyroid FNA. *Genes (Basel)*. 2019;10(10):736.


