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>
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<td>ThyroSeq</td>
<td>0026U</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 25% 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.

- ThyroSeq is a gene sequencing panel used on thyroid cells obtained using fine needle aspiration (FNA) 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).

- The ThyroSeq test has an overall negative predictive value of 97% and a positive predictive value of 66% in a tested population with a 28% prevalence of thyroid cancer.
cancer.\textsuperscript{2} Results from the sequencing test give a prediction as either positive or negative for malignancy.

- Depending on the Bethesda thyroid cancer grade the following risks of malignancy are observed with negative and positive ThyroSeq results:\textsuperscript{2}
  
  o Bethesda III Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS) with 14% risk of malignancy:
    
    - ThyroSeq Negative: 3% risk of malignancy
    - ThyroSeq Positive: 64% risk of malignancy
  
  o Bethesda IV Follicular neoplasm/suspicion for a follicular neoplasm (FN/SFN) with 27% risk of malignancy:
    
    - ThyroSeq Negative: 2% risk of malignancy
    - ThyroSeq Positive: 68% risk of malignancy

### Guidelines and evidence

#### National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2018) Thyroid Carcinoma Guidelines incorporate the use of molecular tests in the evaluation of indeterminate thyroid nodules (category 2B). For FNA results consistent with Follicular or Hürthle Cell Neoplasms, or atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) with a “High clinical suspicion of malignancy”, they state:\textsuperscript{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, 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:\textsuperscript{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)"

**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 )
• 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 current published peer-reviewed literature is comprised of several analytical and clinical validity studies that report wide variation among the diagnostic accuracy values (sensitivity, specificity, PPV and NPV). These are likely due to the heterogeneity of the included sample sets, such as malignancy prevalence in the overall population; overall sample size; the Bethesda Type; the proportions of each Bethesda Type; and variable definitions used for benign nodule classification.6-18

Evidence derived from randomized, multicenter trials evaluating direct clinical utility of the impact of ThyroSeq v2 on health outcomes, such as survival and quality of life, is still lacking. Early evidence suggests a potential for clinical utility, but additional well-designed studies of ThyroSeq v2 are needed to evaluate the impact of clinical decisions on health outcomes. Given the heterogeneity across the available studies as well as other the inherent study limitations, it is difficult to draw definitive conclusions regarding the clinical usefulness of the ThyroSeq v2 panel to ascertain initially indeterminate FNA cytology results.

Larger, prospective studies are needed to evaluate the behavior of cytologically indeterminate thyroid nodules that are deemed to be negative on the ThyroSeq v2 panel (ruling out disease) and to substantiate positive ThyroSeq v2 results (ruling in disease) with surgical biopsy. Clinical utility studies that follow up benign cases are also necessary to determine the degree of influence ThyroSeq v2 may have on disease management and if changes in disease management lead to clinically relevant improved outcomes, such as sparing patients from future invasive surgery, reducing the incidence of morbidity, and improving disease-specific survival over the long term.

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

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


