# Test Specific Guidelines

# ThyroSeq

**MOL.TS.270.A**
**v1.0.2023**

## 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.**

| Procedure addressed by this guideline | Procedure code |
|---|---|
| ThyroSeq GC [Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or Negative, low probability of malignancy")] | 0026U |
| ThyroSeq CRC [Oncology (thyroid), DNA and mRNA, next-generation sequencing analysis of 112 genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high)] | 0287U |

## 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 detects gene fusions, point mutations, copy number variants, and expression changes in 112 genes related to thyroid cancer.[2]

ThyroSeq GC is designed to aid in the classification of thyroid nodules with indeterminate cytology on FNA as either malignant or benign, and results are reported as either positive or negative.[2]

ThyroSeq CRC is designed to aid in the recurrence risk classification for thyroid nodules determined to be malignant after thyroid resection or FNA (Bethesda VI) and results are reported as low, intermediate, or high risk.[3,4]

## 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 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:[6]**

**"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:[7]**

**"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."

"Molecular diagnostic testing may be useful to determine the status of follicular lesions or lesions of indeterminate significance (including follicular neoplasms, AUS or FLUS) as more or less likely to be malignant based on the genetic profile."

"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 ThyroSeq GC in individuals with fine needle aspirate(s) (FNA) of thyroid nodules are available. Limited peer-reviewed studies specifically evaluating ThyroSeq CRC have been published.[8-47]

Studies demonstrate the ability of ThyroSeq GC to rule out or rule in malignant disease in FNA samples with indeterminate results. Although there is limited evidence that use of ThyroSeq GC 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 GC**

**ThyroSeq GC 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.**

**ThyroSeq CRC**

**This test is considered investigational and experimental.**

**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.**

**Billing and Reimbursement**

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

**ThyroSeq GC is indicated only once per thyroid nodule per lifetime.**

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