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>Procedures addressed by this guideline</th>
<th>Procedure code</th>
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<tbody>
<tr>
<td>RosettaGX Reveal</td>
<td>81479</td>
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</tbody>
</table>

What are thyroid nodules

Definition

Thyroid nodules are relatively common; however, only an estimated 15% of nodules are malignant.

The standard of diagnosis of thyroid nodules is fine needle aspiration (FNA), and for a majority of patients, an analysis of FNA smears results in a definitive and accurate designation of benign or malignant. However, approximately 10-40% of FNA results yield a cytologically indeterminate diagnosis.\(^1\) Approximately 6% of indeterminate diagnoses receive a malignant status, yet the majority of patients undergo diagnostic surgery in the form of a thyroid lobectomy or a total thyroidectomy.\(^2\)

A post-surgery evaluation provides a conclusive diagnosis or rules out malignancy. For those with benign cytologies, thyroid excision can lead to decreased quality of life (QoL) due to issues with subsequent hypothyroidism, irreversible hormonal changes, chronic fatigue, potential laryngeal nerve injury, and life-long implementation of hormone-replacement supplements.\(^1\)

Mutation analysis of molecular markers found in thyroid microRNA isolated in FNA smears can be indicative of cancer status. The analysis of microRNA in thyroid nodules has been suggested as a means of distinguishing between expression profiles that are malignant and those that are benign.\(^1\)

Test information

Introduction

RosettaGX Reveal™ is a thyroid microRNA classifier that assesses if a suspicious thyroid nodule is benign or malignant in patients with indeterminate cytology results for thyroid cancer.
This assay seeks to diagnose indeterminate thyroid nodules utilizing stained fine-needle aspiration (FNA) smears prepared from the patient's original biopsy, potentially reducing the need for additional surgical excisions.\(^3\)

RosettaGX Reveal is a diagnostic assay that utilizes quantitative reverse transcription polymerase chain reaction (qRT-PCR) to measure levels of 24 microRNA species; these levels are then analyzed with a proprietary classifier algorithm in order to predict whether the lesion is either benign or suspicious for malignancy.\(^4\)

RosettaGX Reveal utilizes air-dried Romanowsky-type stained slides and alcohol-fixed Papanicolaou slides, which are the same types of slides used for standard morphologic analysis. This assay can assess thyroid cancer status regardless of latency between collection and analysis of smear, temperature in which the smear was stored, and the overall age of the smear. RosettaGX Reveal can be utilized on minute or limited RNA amounts as small as 20ng/uL.\(^1\)

**Guidelines and evidence**

**Introduction**

The following section includes relevant guidelines and evidence pertaining to RosettaGX Reveal testing.

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (NCCN, 2019) 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:\(^5\)

“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 (ATA) and ATA Guidelines Task Force have released the following commentary with regards to Bethesda Category III nodules in adults.\(^6\)
• “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)"

• “There is insufficient evidence regarding the utility of molecular testing aids in the evaluation of indeterminate pediatric thyroid nodules.”

**Thyroid Scientific Committee of American Association of Clinical Endocrinologists**

The Thyroid Scientific Committee of American Association of Clinical Endocrinologists (AACE) (2016) issued the following commentary regarding current assays assessing molecular diagnostic testing of thyroid nodules with indeterminate cytopathology:

• “Only the BRAFV600E and RET/PTC rearrangement are associated with a PPV that approaches 100%...molecular testing is meant to complement and not replace clinical judgment, sonographic assessment, and visual cytopathology interpretation[.] Prospective multicenter studies are required to validate all of these tests used either singly or in tandem.”

**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:
  
  o To complement not replace cytologic evaluation (BEL 2, GRADE A)
  
  o The results are expected to influence clinical management (BEL 2, GRADE A)
  
  o 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:
  o 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)
  o Consider detection of BRAF and RET/PTC and, possibly PAX8/PPARG and
  RAS mutations if such detection is available (BEL 2, GRADE B)
  o 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
  o 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 evidence is currently insufficient to support the use of RosettaGX Reveal™ when
evaluating the microRNA of thyroid nodules for determining a thyroid cancer diagnosis.
There is a paucity of studies demonstrating that use of the assay helps patients avoid
unnecessary surgery (lobectomy or thyroidectomy) or improves overall patient-
important health outcomes (avoidance of repeated FNA procedures or life-long
iatrogenic complications from full or partial thyroidectomy).1,2,9

Criteria

Introduction

Requests for RosettaGX Reveal testing are reviewed using the following criteria.
This test is considered investigational and/or 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.

References

Introduction

This guideline cites the following references.


