Afirma Thyroid Cancer Classifier Tests

Introduction

Afirma thyroid cancer classifier tests are addressed by this guideline.

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 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afirma Genomic Sequencing Classifier</td>
<td>81599</td>
</tr>
<tr>
<td>Afirma Gene Expression Classifier</td>
<td>81545</td>
</tr>
<tr>
<td>BRAF V600 Targeted Mutation Analysis</td>
<td>81210</td>
</tr>
<tr>
<td>Afirma Xpression Atlas</td>
<td>81479</td>
</tr>
</tbody>
</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 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

Introduction

Afirma testing may include a combination of cytopathology and molecular testing.² This guideline addresses only the molecular testing component.
The Afirma Genomic Sequencing Classifier (GSC) is intended for:

- cytologically indeterminate FNA biopsy samples including atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), and
- follicular or Hürthle Cell Neoplasms. When indicated, the Afirma tests must be used in conjunction with cytopathology, ultrasound assessment, and other clinical factors to determine an individual's risk of thyroid cancer and the necessity of thyroid surgery.

When Afirma testing is performed

A FNA sample can be submitted for cytopathology assessment.

<table>
<thead>
<tr>
<th>If the cytopathology assessment is ...</th>
<th>Then ...</th>
</tr>
</thead>
<tbody>
<tr>
<td>benign or malignant</td>
<td>the analysis is complete.</td>
</tr>
<tr>
<td>indeterminate</td>
<td>the GSC is performed.</td>
</tr>
</tbody>
</table>

Afirma GSC

The Afirma Genomic Sequencing Classifier (GSC) is a second generation test that has replaced the original Gene Expression Classifier (GEC). The GSC test assesses more than 1000 core genes via next generation RNA sequencing, allowing for assessment of expression levels as well as analysis of copy number and loss of heterozygosity. The purpose of the GSC is to further differentiate indeterminate FNA. The positive predictive value of the GSC is 47.1%.

Results

Afirma GSC results may help guide surgical decision making in patients with thyroid nodules. "Operation rates in patients classified as benign with Afirma testing are comparable to those with benign results on cytopathology." Based on the results of the Afirma GSC, additional testing may be requested or performed, such as the Afirma Malignancy Classifiers, BRAF and MTC.

Afirma Malignancy Classifiers

The Afirma Malignancy Classifiers, BRAF and MTC, are intended to help guide surgical decisions when the cytopathology or Afirma GSC result suggests the individual should be considered for surgery.
<table>
<thead>
<tr>
<th>Test</th>
<th>Detection</th>
<th>When test is performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afirma BRAF</td>
<td>BRAF V600E mutation</td>
<td>This test is performed when there is</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• malignant or suspicious for malignancy cytopathology, or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• a suspicious GSC result.2</td>
</tr>
<tr>
<td>Afirma Medullary Thyroid Cancer (MTC)</td>
<td>Medullary thyroid carcinoma before surgery</td>
<td>This test is performed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• when there is malignant or suspicious for malignancy cytopathology, or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• in conjunction with the GSC at the time of an indeterminate result.2</td>
</tr>
</tbody>
</table>

**Afirma Xpression Atlas**

The Afirma Xpression Atlas is an RNA sequencing-based test. The test is designed to analyze 761 variants and 130 fusions that have been linked to thyroid cancer. This testing is performed on nodules that are suspicious for malignancy.2

**Guidelines and evidence**

**Introduction**

This section includes relevant guidelines and evidence pertaining to Afirma GSC testing.

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (NCCN, 2018) 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, 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:8

- “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:9

- 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?
  - 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

Patel et al. (2018) examined the performance of the Afirma GSC test:

- They used 191 of the 210 FNA samples used to validate the GEC test.
- GSC demonstrated 91.1% sensitivity (identified 41 of 45 malignant samples) with a 68.3% specificity (identified 99 of 145 non-malignant samples) in patients with indeterminate Bethesda III or IV cytology. Prevalence of malignancy in the study population was 22.4%. The NPV was 96.1% and the PPV was 47.1%.
- The GEC test had 90% sensitivity (malignancy) and 52% specificity (benign) on samples with indeterminate Bethesda III or IV cytology. Prevalence of malignancy in study population was 24%.

No peer-reviewed clinical studies evaluating the clinical validity or clinical utility of the Xpression Atlas test were identified. Given the lack of peer-reviewed publications, no conclusions can be made regarding the clinical validity, clinical utility, or the overall value of the Xpression Atlas as an add-on to the Afirma GSC test.

Criteria

Introduction

Requests for Afirma GSC testing are reviewed using these criteria.

Afirma Genomic Sequencing Classifier (GSC)

- Testing Multiple Samples:
The Afirma GSC is reimbursed only once per date of service regardless of the number of nodules submitted for testing, and

- The Afirma GSC is indicated only once per thyroid nodule per lifetime.

**Required Clinical Characteristics:**

- Afirma GSC is indicated for thyroid nodules with indeterminate FNA results that are included in the following cytopathology categories:
  - Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), or
  - Follicular or Hürthle cell neoplasm, and

- The patient is not undergoing thyroid surgery for diagnostic confirmation.

**Required Testing Process:**

- If FNA of a nodule is indicated to evaluate for malignancy, and the sample is sent to Veracyte for cytopathology, the classifier is only indicated when the result is indeterminate, and

- Supporting documentation of an appropriate indeterminate cytology result will be required for reimbursement.

**Afirma Malignancy Classifiers**

**Afirma MTC**

- Afirma MTC testing will be reimbursed if it is performed as part of the GSC as outlined above, and

- The Afirma MTC testing must be billed as part of the Afirma GSC. The Afirma MTC may not be billed separately using an additional unit or procedure code.

**Afirma BRAF V600E**

- Afirma BRAF testing may be considered for either GSC or FNA suspicious or malignant results. See Somatic Mutation Testing – Solid Tumors guideline for criteria.

- Afirma BRAF testing in conjunction with a GSC indeterminate result will not be reimbursed.

**Afirma Xpression Atlas**

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.

**Billing and Reimbursement Considerations**

CPT code 81545 is specific to and therefore intended to be used for Afirma's Gene Expression Classifier test, not the Genomic Sequencing Classifier. Requests for this CPT code when the GSC is being performed will be redirected to a more appropriate CPT code.

**References**

**Introduction**

These references are cited in this guideline.

