Medical Policy
Molecular Markers in Fine Needle Aspirates of the Thyroid

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 913
BCBSA Reference Number: 2.04.78
NCD/LCD: Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35025)
Local Coverage Article: MolDX: Afirma™ Assay by Veracyte Billing and Coding Guidelines (A54356)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Mutation analysis in fine-needle aspirates of the thyroid is INVESTIGATIONAL.

The use of the Afirma Gene Expression Classifier in fine needle aspirates of the thyroid that are cytologically considered to be indeterminate (follicular lesion of undetermined significance or follicular neoplasm) may be considered to be MEDICALLY NECESSARY in patients who have the following characteristics:
- Thyroid nodules without strong clinical or radiologic findings suggestive of malignancy.
- In whom surgical decision making would be affected by test results.

Gene expression classifiers in fine needle aspirates of the thyroid not meeting criteria outlined above are considered INVESTIGATIONAL.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the links below.

Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35025)

Local Coverage Article: MolDX: Afirma™ Assay by Veracyte Billing and Coding Guidelines (A54356)
For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

**Prior Authorization Information**

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required. Yes indicates that prior authorization is required. No indicates that prior authorization is not required. N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
</tr>
</tbody>
</table>

**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81545</td>
<td>Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)</td>
</tr>
</tbody>
</table>

**Description**

**FINE NEEDLE ASPIRATES OF THE THYROID**

Thyroid nodules are common, present in 5% to 7% of the U.S. adult population. Most are benign, and most cases of thyroid cancer are curable by surgery when detected early. Fine needle aspirate (FNA) samples of the thyroid is currently the most accurate procedure to distinguish benign thyroid lesions and malignant ones, reducing the rate of unnecessary thyroid surgery for patients with benign nodules and triaging patients with thyroid cancer to appropriate surgery.

About 60% to 70% of thyroid nodules are classified cytologically as benign, and 4% to 10% of nodules are cytologically deemed malignant. However, the remaining 20% to 30% have equivocal findings, usually due to overlapping cytologic features between benign and malignant nodules; these nodules usually require surgery for a final diagnosis. Thyroid FNA cytology is classified by Bethesda System criteria into the following groups: nondiagnostic; benign; follicular lesion of undetermined significance (FLUS) or atypia of undetermined significance (AUS); follicular neoplasm (or suspicious for follicular neoplasm); suspicious for malignancy; and malignant. Lesions with FNA cytology in the AUS or FLUS or follicular neoplasm categories are often considered indeterminate.

There is some individualization of management for patients with FNA-indeterminate nodules, but many patients will require a surgical biopsy, typically thyroid lobectomy, with intraoperative pathology.
Consultation would typically be the next step in diagnosis. Approximately 80% of patients with indeterminate cytology undergo surgical resection; postoperative evaluation has revealed a malignancy rate ranging from 6% to 30%, making this a clinical process with very low specificity. Thus, if analysis of FNA samples could reliably identify the risk of malignancy as low, there is potential for patients to avoid surgical biopsy.

Preoperative planning of optimal surgical management in patients with equivocal cytologic results is challenging, because different thyroid malignancies require different surgical procedures (eg, unilateral lobectomy vs total or subtotal thyroidectomy with or without lymph node dissection) depending on several factors, including histologic subtype and risk-stratification strategies (tumor size, patient age). If a diagnosis cannot be made intraoperatively, a lobectomy is typically performed, and, if on postoperative histology the lesion is malignant, a second surgical intervention may be necessary for completion thyroidectomy.

**THYROID CANCER**

Most thyroid cancers originate from thyroid follicular cells and include well-differentiated papillary thyroid carcinoma (PTC; 80% of all thyroid cancers) and follicular carcinoma (15%). Poorly differentiated and anaplastic thyroid carcinomas are uncommon and can arise de novo or from preexisting well-differentiated papillary or follicular carcinomas. Medullary thyroid carcinoma originates from parafollicular or C cells, and accounts for about 3% of all thyroid cancers.

The diagnosis of malignancy in the case of PTC is primarily based on cytologic features. If FNA in a case of PTC is indeterminate, surgical biopsy with intraoperative pathology consultation is most often diagnostic, although its efficacy and therefore its use will vary across institutions, surgeons, and pathologists.

For follicular carcinoma, the presence of invasion of the tumor capsule or of blood vessels is diagnostic and cannot be determined by cytology, because tissue sampling is necessary to observe these histologic characteristics. Intraoperative diagnosis of follicular carcinoma is challenging and often not feasible, because extensive sampling of the tumor and capsule is usually necessary and performed on postoperative permanent sections.

New approaches for improving the diagnostic accuracy of thyroid FNA include mutation analysis for somatic genetic alterations, to more accurately classify which patients need to proceed to surgery (and may include the extent of surgery necessary), and a gene expression classifier to identify patients who do not need surgery and can be safely followed.

**MUTATIONS ASSOCIATED WITH THYROID CANCER**

Various mutations have been discovered in thyroid cancer. The most common 4 gene mutations that carry the highest impact on tumor diagnosis and prognosis are *BRAF* and *RAS* point mutations and *RET/PTC* and *PAX8/PPARγ* rearrangements.

Papillary carcinomas carry point mutations of the *BRAF* and *RAS* genes, as well as *RET/PTC* and *TRK* rearrangements, all of which are able to activate the mitogen-activated protein kinase pathway. These mutually exclusive mutations are found in more than 70% of papillary carcinomas. *BRAF* mutations are highly specific for PTC. Follicular carcinomas harbor either *RAS* mutations or *PAX8/PPARγ* rearrangement. These mutations identified in 70% to 75% of follicular carcinomas. Genetic alterations involving the PI3K/AKT signaling pathway also occur in thyroid tumors, although they are rare in well-differentiated thyroid cancers and have higher prevalence in less differentiated thyroid carcinomas. Additional mutations known to occur in poorly differentiated and anaplastic carcinomas involve the *TP53* and *CTNNB1* genes. Medullary carcinomas, which can be familial or sporadic, frequently possess point mutations located in the *RET* gene.

Studies have evaluated the association between various genes and cancer phenotype in individuals with diagnosed thyroid cancer.4-6
MOLECULAR DIAGNOSTIC TESTING

Mutation and Rearrangement Testing
Point mutations in specific genes, including \textit{BRAF}, \textit{RAS}, and \textit{RET}, and evaluation for rearrangements associated with thyroid cancers can be accomplished by with Sanger sequencing or pyrosequencing or with real-time polymerase chain reaction (PCR) of single or multiple genes or by next-generation sequencing (NGS) panels. Panels of tests for mutations associated with thyroid cancer, with varying compositions, are also available. For example, Quest Diagnostics offers a Thyroid Cancer Mutation Panel, which includes \textit{BRAF} and \textit{RAS} mutation analysis and testing for \textit{RET/PTC} and \textit{PAX8/PPARγ} rearrangements.

The ThyroSeq\textsuperscript{®} v.2 Next Generation Sequencing panel (CBLPath, Ocala, FL) is a NGS sequencing panel of more than 60 genes. According to the CBLPath’s website, the test is indicated when FNA cytology indicates atypia of uncertain significance or follicular lesion of undetermined significance, follicular neoplasm or suspicious for follicular neoplasm, or suspicious for malignancy.\textsuperscript{7} In particular, it has been evaluated in patients with follicular neoplasm and/or suspicious for follicular neoplasm on FNA as a test to increase both sensitivity and specificity for cancer diagnosis.

The ThyGenX\textsuperscript{TM} Thyroid Oncogene Panel (formerly miRNform\textsuperscript{®} Thyroid; Interpace Diagnostics, Parsippany, NJ; testing done at Asuragen Clinical Laboratory) is another NGS panel designed to assess patients with indeterminate thyroid FNA results. It includes sequencing of 8 genes associated with papillary thyroid carcinoma and follicular carcinomas.

Gene Expression Profiling
Genetic alterations associated with thyroid cancer can be assessed using gene expression profiling, which refers to analysis of messenger RNA (mRNA) expression levels of many genes simultaneously. Several gene expression profiling tests are now available to biologically stratify tissue from thyroid nodules.

The Afirma\textsuperscript{®} Gene Expression Classifier (Afirma GEC; Veracyte, South San Francisco, CA) analyzes the expression of 142 different genes to determine patterns associated with benign findings on surgical biopsy. It is designed to evaluate thyroid nodules that have an “indeterminate” classification on FNA as a method to select patients (“rule out”) who are at low risk for cancer.

Veracyte also markets 2 “malignancy classifiers” that use mRNA expression-based classification to evaluate for \textit{BRAF} mutations (Afirma BRAF) or mutations associated with medullary thyroid carcinoma (Afirma MTC). In a description of the Afirma BRAF test, the following have been proposed as benefits of the mRNA-based expression test for \textit{BRAF} mutations: (1) PCR-based methods may have low sensitivity, requiring that a large proportion of the nodule have a relevant mutation; (2) testing for only 1 mutation may not detect patients with low-frequency mutations that result in the same pattern of pathway activation; and (3) PCR-based approaches with high analytic sensitivity may require a large of amount of DNA that is difficult to isolate from small FNA samples.\textsuperscript{8} Afirma MTC is an option when Afirma GEC is ordered for thyroid nodules with an “intermediate” classification on FNA, and can also be used for thyroid nodules with “malignant” or “suspicious” results on Afirma GEC. Afirma BRAF is designed to be used for nodules with “suspicious” results on Afirma GEC.

ThyraMIR\textsuperscript{™} (Interpace Diagnostics, Parsippany, NJ) is a micro-RNA expression-based classifier intended for use in thyroid nodules with indeterminate cytology on FNA.

Other gene expression profiles have been reported in investigational settings, but have not been widely validated or used commercially (eg, Barros-Filho et al [2015], \textsuperscript{9} Zheng et al [2015]\textsuperscript{10}); these are not addressed in this review.

Summary
Cytologic examination of fine needle aspirate (FNA) samples from a thyroid lesion to identify which patients need thyroid resection has diagnostic limitations. Assays using molecular markers have been developed in an attempt to improve the accuracy of thyroid FNA biopsies.

For individuals with thyroid nodule(s) and indeterminate findings on FNA who receive FNA sample testing with the Afirma Gene Expression Classifier (GEC) to predict benignancy, the evidence includes 1 prospective clinical validity study with the marketed test, and an indirect chain of evidence to support clinical utility. Relevant outcomes are disease-specific survival, test accuracy and validity, morbid events, and resource utilization. In 1 multicenter validation study, the Afirma GEC was reported to have a high negative predictive value (NPV; range, 90%-95%). These results are supported by an earlier development and clinical validation study (Chudova et al), but the classifiers used in the 2 studies do not appear to be identical. In an additional multicenter and multiple single-center studies, there is suggestive evidence that rates of malignancy are low in Afirma benign patients, but the exact NPV is unknown. The available evidence suggested that physician decision making about surgery is altered by GEC results, although long-term follow-up of patients with thyroid nodules who avoided surgery based on GEC results is limited. An indirect chain of evidence can be constructed to establish the potential for clinical utility with GEC testing in cytologically indeterminate lesions, but with only 1 study of the marketed test reporting a true NPV, the clinical validity is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with thyroid nodule(s) and indeterminate findings on FNA who receive FNA sample testing with molecular markers to predict malignancy, the evidence includes prospective and retrospective studies of clinical validity. Relevant outcomes are disease-specific survival, test accuracy and validity, morbid events, and resource utilization. Mutation analysis has the potential to improve the accuracy of an equivocal FNA of the thyroid and may play a role in preoperative risk stratification and surgical planning.

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2016</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>10/2015</td>
<td>New medically necessary criteria added. Effective 10/1/2015.</td>
</tr>
<tr>
<td>1/2015</td>
<td>Investigational indications clarified. Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541) added.</td>
</tr>
<tr>
<td>7/2014</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>5/2013</td>
<td>New references from BCBSA National medical policy.</td>
</tr>
<tr>
<td>2/04/2013</td>
<td>New policy describing non-coverage.</td>
</tr>
</tbody>
</table>

### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

### References


