Medical Policy

**Molecular Markers in Fine Needle Aspirates of the Thyroid**

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

The use of either Afirma Gene Expression Classifier or ThyroSeq v2 in fine needle aspirates of thyroid nodules with indeterminate cytologic findings (i.e., Bethesda diagnostic category III [atypia/follicular lesion of undetermined significance] or Bethesda diagnostic category IV [follicular neoplasm/suspicion for a follicular neoplasm]) may be considered **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.

The use of any of the following types of molecular marker testing or gene variant analysis in fine needle aspirates of thyroid nodules with indeterminate findings (Bethesda diagnostic category III [atypia/follicular lesion of undetermined significance] or Bethesda diagnostic category IV [follicular neoplasm/suspicion for a follicular neoplasm]) or suspicious findings (Bethesda diagnostic category V [suspicious for malignancy]) to rule in malignancy to guide surgical planning for initial resection rather than a 2-stage surgical biopsy followed by definitive surgery may be considered **MEDICALLY NECESSARY**:

- ThyroSeq v2;
- ThyraMIR microRNA/ThyGenX;
- Afirma BRAF after Afirma Gene Expression Classifier; or
- Afirma MTC after Afirma Gene Expression Classifier.
Gene expression classifiers, genetic variant analysis, and molecular marker testing in fine needle aspirates of the thyroid not meeting the criteria outlined above, including but not limited to use of RosettaGX Reveal and single-gene TERT testing, 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](https://www.cms.gov).

**Prior Authorization Information**

**Inpatient**
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed **inpatient**.

**Outpatient**
- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed **outpatient**.

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

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
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<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>
<tr>
<td>0018U</td>
<td>Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy</td>
</tr>
<tr>
<td>0026U</td>
<td>Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical</td>
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</tbody>
</table>
**Description**

**THYROID NODULES**
Thyroid nodules are common, present in 5% to 7% of the U.S. adult population; however, most are benign, and most cases of thyroid cancer are curable surgically when detected early.

**Diagnosis**
Sampling thyroid cells by fine needle aspirate (FNA) is currently the most accurate procedure to distinguish benign thyroid lesions from 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 atypia of undetermined significance or follicular neoplasm of undetermined significance or follicular neoplasm categories are often considered indeterminate.

**Management**
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. In 2016, reclassification of encapsulated follicular-variant PTC as a noninvasive follicular tumor with papillary-like nuclei was proposed and largely adopted; this classification removes the word carcinoma from the diagnosis to acknowledge the indolent behavior of these tumors.

For follicular carcinoma, the presence of invasion of the tumor capsule or 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 variant 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.

Genetic Variants Associated With Thyroid Cancer
A number of genetic variants have been discovered in thyroid cancer. The most common 4 gene variants are BRAF and RAS single nucleotide variants (SNVs) and RET/PTC and PAX8/PPARγ rearrangements.

Papillary carcinomas carry SNVs of the BRAF and RAS genes, as well as RET/PTC and TRK rearrangements, all of which can activate the mitogen-activated protein kinase pathway. These mutually exclusive variants are found in more than 70% of papillary carcinomas.4 BRAF SNVs are highly specific for PTC. Follicular carcinomas harbor either RAS SNVs or PAX8/PPARγ rearrangements. These variants have been 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 a higher prevalence in less differentiated thyroid carcinomas. Additional variants 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 SNVs located in the RET gene.

Studies have evaluated the association between various genes and cancer phenotype in individuals with diagnosed thyroid cancer.5-7

Telomerase reverse transcriptase (TERT) promoter variants occur with varying frequency in different thyroid cancer subtypes. Overall, TERT C228T or C250T variants have been reported in approximately 15% of thyroid cancers, with higher rates in the undifferentiated and anaplastic subtypes compared with the well-differentiated subtypes.8 TERT variants are associated with several demographic and histopathologic features such as older age and advanced TNM stage. TERT promoter variants have been reported to be independent predictors of disease recurrence and cancer-related mortality in well-differentiated thyroid cancer.9-11 Also, the co-occurrence of BRAF or RAS variants with TERT or TP53 variants may identify a subset of thyroid cancers with unfavorable outcomes.12-14

Molecular Diagnostic Testing

Variant Detection and Rearrangement Testing
SNVs in specific genes, including BRAF, RAS, and RET, and evaluation for rearrangements associated with thyroid cancers can be accomplished 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. Panel tests for genes associated with thyroid cancer, with varying compositions, are also available. For example, Quest Diagnostics offers a Thyroid Cancer Mutation Panel, which includes BRAF and RAS variant analysis and testing for RET/PTC and PAX8/PPARγ rearrangements.

The ThyroSeq v.2 Next-Generation Sequencing panel (CBLPath) is an NGS panel of more than 60 genes. According to the CBLPath’s website, the test is indicated when FNA cytology suggests atypia of uncertain significance or follicular lesion of undetermined significance, follicular neoplasm or suspicious for follicular neoplasm, or suspicious for malignancy.15 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.

ThyGenX is an NGS panel that sequences 8 genes and identifies specific gene variants and translocations associated with thyroid cancer. ThyGenX is intended to be used in conjunction with the ThyraMIR microRNA expression test when the initial ThyGenX test is negative.
Gene Expression Profiling
Genetic alterations associated with thyroid cancer can be assessed using gene expression profiling, which refers to the analysis of messenger RNA (mRNA) expression levels of many genes simultaneously. Several gene expression profiling tests are available and stratify tissue from thyroid nodules biologically.

The Afirma Gene Expression Classifier (Afirma GEC; Veracyte) 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.

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], Zheng et al [2015]); they are not addressed in this review.

ThyraMIR is a microRNA expression-based classifier intended for use in thyroid nodules with indeterminate cytology on FNA following a negative result from the ThyGenX Thyroid Oncogene Panel.

Algorithmic Testing
Algorithmic testing involves the use of 2 or more tests in a prespecified sequence, with a subsequent test automatically obtained depending on results of an earlier test.

Algorithmic Testing Using Afirma GEC with Afirma MTC and Afirma BRAF
In addition to Afirma GEC, Veracyte also markets 2 "malignancy classifiers" that use mRNA expression-based classification to evaluate for BRAF variants (Afirma BRAF) or variants associated with medullary thyroid carcinoma (Afirma MTC). Table 1 outlines the testing algorithms for Afirma MTC and Afirma BRAF.

Table 1. Afirma MTC and Afirma BRAF Testing Algorithms

<table>
<thead>
<tr>
<th>Test 1</th>
<th>Test 1 Result</th>
<th>Reflex to Test 2</th>
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<tbody>
<tr>
<td>Thyroid nodule on fine needle aspirate</td>
<td>&quot;Indeterminate&quot;</td>
<td>Afirma MTC</td>
</tr>
<tr>
<td>Afirma GEC</td>
<td>&quot;Malignant&quot; or &quot;suspicious&quot;</td>
<td>Afirma MTC</td>
</tr>
<tr>
<td>Afirma GEC</td>
<td>&quot;Suspicious&quot;</td>
<td>Afirma BRAF</td>
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In a description of the Afirma BRAF test, the following have been proposed as benefits of the mRNA-based expression test for BRAF variants: (1) PCR-based methods may have low sensitivity, requiring that a large proportion of the nodule have a relevant variant; (2) testing for only 1 variant may not detect patients with low-frequency variants 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.

The testing strategy for both Afirma MTC and Afirma BRAF is to predict malignancy from an FNA sample with increased pretest probability for malignancy. A positive result with Afirma MTC or Afirma BRAF would inform preoperative planning such as planning for a hemi- vs a total thyroidectomy or performance of a central neck dissection.

Algorithmic Testing Using ThyGenX and ThyraMIR
The ThyGenX Thyroid Oncogene Panel (Interpace Diagnostics; testing done at Asuragen Clinical Laboratory) is an NGS panel designed to assess patients with indeterminate thyroid FNA results. It includes sequencing of 8 genes associated with PTC and follicular carcinomas. ThyGenX has replaced the predicate miR_Inform Thyroid test that assesses for 17 validated gene alterations. ThyraMIR (Interpace Diagnostics) is a microRNA expression-based classifier intended for use in thyroid nodules with indeterminate cytology on FNA following a negative result from the ThyGenX Thyroid Oncogene Panel.
The testing strategy for combined ThyGenX and ThyraMIR testing is first to predict malignancy. A positive result on ThyGenX would "rule in" patients for surgical resection. The specific testing results from a ThyGenX positive test would be used to inform preoperative planning when positive. For a ThyGenX negative result, the reflex testing involves the ThyraMIR microRNA expression test to "rule out" for a surgical biopsy procedure given the high negative predictive value of the second test. Patients with a negative result from the ThyraMIR test would be followed with active surveillance and avoid a surgical biopsy.

Summary
To determine which patients need thyroid resection, many physicians will perform a cytologic examination of fine needle aspirate (FNA) samples from a thyroid lesion; however, this method has diagnostic limitations. As a result, assays using molecular markers have been developed 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 molecular markers to rule out malignancy and to avoid surgical biopsy or resection, the evidence includes a prospective clinical validity study with the Afirma Gene Expression Classifier (GEC) and a chain of evidence to support clinical utility. Relevant outcomes are disease-specific survival, test accuracy and validity, morbid events, and resource utilization. In a 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 [2010]), but the classifiers used in both studies do not appear to be identical. In other multicenter and multiple single-center studies, there is suggestive evidence that rates of malignancy are low in Afirma patients who are benign, but the exact NPV is unknown. The available evidence suggests that the decisions a physician makes regarding surgery are altered by GEC results; however, it should be noted that long-term follow-up of patients with thyroid nodules who avoided surgery based on GEC results is limited. A chain of evidence can be constructed to establish the potential for clinical utility with GEC testing in cytologically indeterminate lesions, but with only a single study of the marketed test reporting a true NPV, the clinical validity is uncertain. For the RosettaGX Reveal test, no prospective clinical studies were identified. 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 rule in malignancy and to guide surgical planning, the evidence includes multiple retrospective and prospective clinical validation studies for the ThyroSeq v2 or v3 test and 2 retrospective clinical validation studies that used a predicate test 17-variant panel (miRInform) test to the current ThyGenX and ThyraMIR. Relevant outcomes are disease-specific survival, test accuracy and validity, morbid events, and resource utilization. In a retrospective validation study on FNA samples, the 17-variant panel (miRInform) test and ThyraMIR had a sensitivity of 89%, and an NPV of 94%. Pooled retrospective and prospective clinical validation studies of ThyroSeq v2 have reported a combined NPV of 96% and positive predictive value of 83% in studies conducted at the institution developing the test but poorer performance at external institutions. No studies were identified demonstrating the diagnostic characteristics of the marketed ThyGenX. No studies were identified...
demonstrating evidence of direct outcome improvements. A chain of evidence for the ThyroSeq v2 test and combined ThyGenX and ThyraMIR testing would rely on establishing clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2017 supports that the following indications provide a clinically meaningful improvement in net health outcome and are consistent with generally accepted medical practice:

- Use of the following types of molecular marker testing in FNA of thyroid nodules with indeterminate cytologic findings (i.e., Bethesda diagnostic category III [atypia/follicular lesion of undetermined significance] or Bethesda diagnostic category IV [follicular neoplasm/suspicion for a follicular neoplasm]) to rule out malignancy and to avoid surgical biopsy:
  - Afirma GEC; or
  - ThyroSeq v2

- Use of the following type of molecular marker testing in FNA of thyroid nodules with indeterminate cytologic findings or Bethesda diagnostic category V (suspicious for malignancy) to rule in the presence of malignancy to guide surgical planning for the initial resection rather than a 2-stage surgical biopsy followed by definitive surgery:
  - ThyroSeq v2;
  - ThyraMIR microRNA/ThyGenX;
  - Afirma BRAF after Afirma GEC; or
  - Afirma MTC after Afirma GEC.

Thus, the above indications may be considered medically necessary considering the suggestive evidence and clinical input support.

However, the clinical input does not support whether the use of RosettaGX Reveal testing in FNA of thyroid nodules provides a clinically meaningful improvement in the net health outcome or is consistent with generally accepted medical practice.

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>1/2018</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>10/2017</td>
<td>Clarified coding information.</td>
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<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>
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<tr>
<td>7/2014</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>5/2013</td>
<td>New references from BCBSA National medical policy.</td>
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<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:


References


13. Song YS, Lim JA, Choi H, et al. Prognostic effects of TERT promoter mutations are enhanced by coexistence with BRAF or RAS mutations and strengthen the risk prediction by the ATA or TNM staging system in differentiated thyroid cancer patients. *Cancer.* May 1 2016;122(9):1370-1379. PMID 26969876


70. Labourier E, Shifrin A, Busseniers AE, et al. Molecular testing for miRNA, mRNA, and DNA on fine-needle aspiration improves the preoperative diagnosis of thyroid nodules with indeterminate cytology. *J Clin Endocrinol Metab.* Jul 2015;100(7):2743-2750. PMID 25965083


