

**EFFECTIVE DATE:** 01 | 01 | 2023

**POLICY LAST UPDATED:** 12 | 30 | 2022

## OVERVIEW

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.

The following tests are addressed in this policy:

- Afirma (Veracyte)
- RosettaGX Reveal (Rosetta Genomics)
- ThyGeNEXT (Interpace Diagnostics)
- ThyraMIR (Interpace Diagnostics)
- ThyroSeq (Sonic Healthcare USA ThyroSeq Laboratory)
- ThyroSeq Cancer Risk Classifier (CRC) (Sonic Healthcare USA ThyroSeq Laboratory)

## MEDICAL CRITERIA

### Medicare Advantage Plans and Commercial Products

#### Afirma – CPT 81546

The Afirma assay may be considered medically necessary for patients with the following conditions (patients must have 1 and 2):

1. Patients with one or more thyroid nodules with a history or characteristics suggesting malignancy such as:
  - Nodule growth over time
  - Family history of thyroid cancer
  - Hoarseness, difficulty swallowing or breathing
  - History of exposure to ionizing radiation
  - Hard nodule compared with rest of gland consistency
  - Presence of cervical adenopathy
2. Have an indeterminate follicular pathology on fine needle aspiration

**Afirma BRAF and Afirma MTC** are medically necessary after a positive Afirma Genomic Sequencing Classifier.

#### ThyraMIR – CPT 0018U

**ThyGeNEXT – CPT 0245U (Code Effective 4/1/2021. For Dates of Service prior to 4/1/2021, CPT Code 81445 must be used. For Dates of Service 4/1/2021 and after, CPT Code 0245U must be used.)**  
**RosettaGX Reveal thyroid MicroRNA test (Unlisted CPT)**

ThyraMIR, ThyGeNEXT and RosettaGX Reveal services may be considered reasonable and necessary for patients with any of the following conditions:

- An indeterminate pathology on fine needle aspiration
- Patients with one or more thyroid nodules with a history or characteristics suggesting malignancy such as:
  - Nodule growth over time
  - Family history of thyroid cancer
  - Hoarseness, difficulty swallowing or breathing
  - History of exposure to ionizing radiation
  - Hard nodule compared with rest of gland consistency
  - Presence of cervical adenopathy

### **ThyroSeq – 0026U**

### **ThyroSeq CRC - 0287U (New code effective 1/01/2022)**

The use of ThyroSeq in fine needle aspirates of thyroid nodules with indeterminate or suspicious cytologic findings (see definitions below) may be considered medically necessary in patients who meet the following:

- Thyroid nodules meeting Bethesda diagnostic category III, IV or V (see definitions below) to rule in malignancy to guide surgical planning for initial resection rather than a 2-stage surgical biopsy followed by definitive surgery.

### **Definitions**

Indeterminate cytologic findings

- Bethesda diagnostic category III: atypia/follicular lesion of undetermined significance
- Bethesda diagnostic category IV: follicular neoplasm/suspicion for a follicular neoplasm

Suspicious findings

- Bethesda diagnostic category V: suspicious for malignancy

## **PRIOR AUTHORIZATION**

### **Medicare Advantage Plans and Commercial Products**

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products.

There is no specific CPT coding for some of the services referenced in this policy. Therefore, an Unlisted CPT code should be used (see Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

**Note:** Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

## **POLICY STATEMENT**

## Medicare Advantage Plans and Commercial Products

The following tests may be considered medically necessary when the medical criteria above are met:

- Afirma
- RosettaGX Reveal
- ThyGeNEXT
- ThyraMIR
- ThyroSeq
- ThyroSeq CRC

### COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for limitations of benefits/coverage for laboratory tests or when services are not medically necessary.

### BACKGROUND

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.

### Diagnosis

Sampling thyroid cells by fine needle aspirate (FNA) 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.

### 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 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 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 four gene variants are BRAF and RAS single nucleotide variants (SNVs) and RET/PTC and PAX8/PPAR $\gamma$  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.<sup>4</sup> BRAF SNVs are highly specific for PTC. Follicular carcinomas harbor either RAS SNVs or PAX8/PPAR $\gamma$  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.

### **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/PPAR $\gamma$  rearrangements.

The ThyroSeq v3 Next-Generation Sequencing panel (Sonic Healthcare USA ThyroSeq Laboratory) is an NGS panel of 112 genes. According to the Sonic Healthcare USA ThyroSeq Laboratory'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. 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 eight 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.

The ThyroSeq CRC is a next-generation sequencing analysis of 112 genes. According to thyroseq.com website, the ThyroSeq Cancer Risk Classifier is a test for thyroid cancer diagnosed as Malignant (Bethesda class VI) cytology in fine needle aspiration samples or cancer in formalin fixed paraffin-embedded thyroid resection samples. The test predicts risk of cancer recurrence required for selecting the extent of surgical management and further therapeutic options for patients with thyroid cancer.

### ***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) analyzed the expression of 142 different genes to determine patterns associated with benign findings on surgical biopsy. It was 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. In 2017, Veracyte migrated the Afirma GEC microarray analysis to a next-generation RNA sequencing platform and now markets the Afirma Gene Sequencing Classifier (Afirma GSC) which evaluates 10196 genes with 1115 core genes.

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 two 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 GSC, Veracyte also markets two "malignancy classifiers" that use mRNA expression-based classification to evaluate for BRAF variants (Afirma BRAF) or variants 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 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 one 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 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 central neck dissection.

#### ***Algorithmic Testing Using ThyGenX and ThyraMIR***

The ThyGenX Thyroid Oncogene Panel (Interpace Diagnostics; testing is done at Asuragen Clinical Laboratory) is an NGS panel designed to assess patients with indeterminate thyroid FNA results. It includes sequencing of eight genes associated with PTC and follicular carcinomas. ThyGenX has replaced the predicate miRInform 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.

## **CODING**

The following CPT codes may be considered medically necessary for Medicare Advantage Plans and Commercial Products when the medical criteria above are met:

These codes can be used for ThyGeNEXT:

**(For Dates of Service prior to 4/1/2021, CPT Code 81445 must be used. For Dates of Service 4/1/2021 and after, CPT Code 0245U must be used.)**

**0245U** Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage **(New Code Effective 4/1/2021)**

**81445** Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis (Text Revision Effective 1/1/2023) **(Code 81445 must be used for Dates of Service prior to 4/1/2021)**

These codes can be used for Afirma:

**81546** Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious) **(New Code Effective 1/1/2021)**

**81545** Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious) **(Deleted Effective 12/31/2020)**

This code can be used for ThyraMIR:

**0018U** 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

This code can be used for ThyroSeq:

**0026U** 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")

This code can be used for ThyroSeq CRC:

**0287U** 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) (New code effective 1/01/2022)

The following CPT code requires prior authorization for Medicare Advantage Plans and Commercial Products. The code can be used for any test identified in this policy that does not have a specific CPT code.

**81479** Unlisted molecular pathology procedure

## **RELATED POLICIES**

Genetic Testing Services

Proprietary Laboratory Analyses (PLA)

## PUBLISHED

Provider Update, December 2022  
Provider Update, June 2021  
Provider Update, December 2020  
Provider Update, April 2020  
Provider Update, May 2017  
Provider Update, January 2017

## REFERENCES

1. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35160)
2. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: AFIRMA™ Assay by Veracyte (A54356)
3. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): Biomarkers for Oncology (L35396)
4. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: Biomarkers for Oncology (A52986)
5. Adeniran AJ, Theoharis C, Hui P, et al. Reflex BRAF testing in thyroid fine-needle aspiration biopsy with equivocal and positive interpretation: a prospective study. *Thyroid*. Jul 2011; 21(7): 717-23. PMID 21568726
6. Chudova D, Wilde JI, Wang ET, et al. Molecular classification of thyroid nodules using high-dimensionality genomic data. *J Clin Endocrinol Metab*. Dec 2010; 95(12): 5296-304. PMID 20826580
7. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors. *JAMA Oncol*. Aug 01 2016; 2(8): 1023-9. PMID 27078145
8. Nikiforov YE. Molecular diagnostics of thyroid tumors. *Arch Pathol Lab Med*. May 2011; 135(5): 569-77. PMID 21526955
9. Han PA, Kim HS, Cho S, et al. Association of BRAF V600E Mutation and MicroRNA Expression with Central Lymph Node Metastases in Papillary Thyroid Cancer: A Prospective Study from Four Endocrine Surgery Centers. *Thyroid*. Apr 2016; 26(4): 532-42. PMID 26950846
10. Yip L, Nikiforova MN, Yoo JY, et al. Tumor genotype determines phenotype and disease-related outcomes in thyroid cancer: a study of 1510 patients. *Ann Surg*. Sep 2015; 262(3): 519-25; discussion 524-5. PMID 26258321
11. Lin JD, Fu SS, Chen JY, et al. Clinical Manifestations and Gene Expression in Patients with Conventional Papillary Thyroid Carcinoma Carrying the BRAF(V600E) Mutation and BRAF Pseudogene. *Thyroid*. May 2016; 26(5): 691-704. PMID 26914762
12. Alzahrani AS, Alsaadi R, Murugan AK, et al. TERT Promoter Mutations in Thyroid Cancer. *Horm Cancer*. Jun 2016; 7(3): 165-77. PMID 26902827
13. Landa I, Ganly I, Chan TA, et al. Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. *J Clin Endocrinol Metab*. Sep 2013; 98(9): E1562-6. PMID 23833040
14. Liu X, Bishop J, Shan Y, et al. Highly prevalent TERT promoter mutations in aggressive thyroid cancers. *Endocr Relat Cancer*. Aug 2013; 20(4): 603-10. PMID 23766237
15. Liu T, Wang N, Cao J, et al. The age- and shorter telomere-dependent TERT promoter mutation in follicular thyroid cell-derived carcinomas. *Oncogene*. Oct 16 2014; 33(42): 4978-84. PMID 24141777
16. Xing M, Liu R, Liu X, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. *J Clin Oncol*. Sep 01 2014; 32(25): 2718-26. PMID 25024077
17. 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 01 2016; 122(9): 1370-9. PMID 26969876

18. Nikiforova MN, Wald AI, Roy S, et al. Targeted next-generation sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer. *J Clin Endocrinol Metab.* Nov 2013; 98(11): E1852-60. PMID 23979959
19. Sonic Healthcare USA ThyroSeq Laboratory. ThyroSeq/ThyroSeq CRC. <https://www.thyroseq.com/physicians/test-ordering/>. Accessed November 30, 2021.
20. Barros-Filho MC, Marchi FA, Pinto CA, et al. High Diagnostic Accuracy Based on CLDN10, HMGA2, and LAMB3 Transcripts in Papillary Thyroid Carcinoma. *J Clin Endocrinol Metab.* Jun 2015; 100(6): E890-9. PMID 25867809
21. Zheng B, Liu J, Gu J, et al. A three-gene panel that distinguishes benign from malignant thyroid nodules. *Int J Cancer.* Apr 01 2015; 136(7): 1646-54. PMID 25175491
22. Diggans J, Kim SY, Hu Z, et al. Machine learning from concept to clinic: reliable detection of BRAF V600E DNA mutations in thyroid nodules using high-dimensional RNA expression data. *Pac Symp Biocomput.* 2015: 371-82. PMID 25592597
23. Patel KN, Angell TE, Babiarz J, et al. Performance of a Genomic Sequencing Classifier for the Preoperative Diagnosis of Cytologically Indeterminate Thyroid Nodules. *JAMA Surg.* Sep 01 2018; 153(9): 817-824. PMID 29799911
24. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *N Engl J Med.* Aug 23 2012; 367(8): 705-15. PMID 22731672
25. Santhanam P, Khthir R, Gress T, et al. Gene expression classifier for the diagnosis of indeterminate thyroid nodules: a meta-analysis. *Med Oncol.* Feb 2016; 33(2): 14. PMID 26749587
26. Liu Y, Pan B, Xu L, et al. The Diagnostic Performance of Afirma Gene Expression Classifier for the Indeterminate Thyroid Nodules: A Meta-Analysis. *Biomed Res Int.* 2019; 2019: 7150527. PMID 31531363
27. Angell TE, Frates MC, Medici M, et al. Afirma Benign Thyroid Nodules Show Similar Growth to Cytologically Benign Nodules During Follow-Up. *J Clin Endocrinol Metab.* Nov 2015; 100(11): E1477-83. PMID 26353010
28. Sipos JA, Blevins TC, Shea HC, et al. LONG-TERM NONOPERATIVE RATE OF THYROID NODULES WITH BENIGN RESULTS ON THE AFIRMA GENE EXPRESSION CLASSIFIER. *Endocr Pract.* Jun 2016; 22(6): 666-72. PMID 26789352
29. Deaver KE, Haugen BR, Pozdeyev N, et al. Outcomes of Bethesda categories III and IV thyroid nodules over 5 years and performance of the Afirma gene expression classifier: A single-institution study. *Clin Endocrinol (Oxf).* Aug 2018; 89(2): 226-232. PMID 29791966
30. Valderrabano P, Hallanger-Johnson JE, Thapa R, et al. Comparison of Postmarketing Findings vs the Initial Clinical Validation Findings of a Thyroid Nodule Gene Expression Classifier: A Systematic Review and Meta-analysis. *JAMA Otolaryngol Head Neck Surg.* Jul 18 2019. PMID 31318389
31. Harrell RM, Eyerly-Webb SA, Golding AC, et al. STATISTICAL COMPARISON OF AFIRMA GSC AND AFIRMA GEC OUTCOMES IN A COMMUNITY ENDOCRINE SURGICAL PRACTICE: EARLY FINDINGS. *Endocr Pract.* Feb 2019; 25(2): 161-164. PMID 30383497
32. Duick DS, Klopper JP, Diggans JC, et al. The impact of benign gene expression classifier test results on the endocrinologist-patient decision to operate on patients with thyroid nodules with indeterminate fine-needle aspiration cytopathology. *Thyroid.* Oct 2012; 22(10): 996-1001. PMID 22873825
33. Aragon Han P, Olson MT, Fazeli R, et al. The impact of molecular testing on the surgical management of patients with thyroid nodules. *Ann Surg Oncol.* Jun 2014; 21(6): 1862-9. PMID 24522987
34. Noureldine SI, Olson MT, Agrawal N, et al. Effect of Gene Expression Classifier Molecular Testing on the Surgical Decision-Making Process for Patients With Thyroid Nodules. *JAMA Otolaryngol Head Neck Surg.* Dec 2015; 141(12): 1082-8. PMID 26606459
35. Abeykoon JP, Mueller L, Dong F, et al. The Effect of Implementing Gene Expression Classifier on Outcomes of Thyroid Nodules with Indeterminate Cytology. *Horm Cancer.* Aug 2016; 7(4): 272-8. PMID 27102883
36. Chaudhary S, Hou Y, Shen R, et al. Impact of the Afirma Gene Expression Classifier Result on the Surgical Management of Thyroid Nodules with Category III/IV Cytology and Its Correlation with Surgical Outcome. *Acta Cytol.* 2016; 60(3): 205-10. PMID 27344463
37. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. *Thyroid.* Nov 2009; 19(11): 1159-65. PMID 19888858



38. Lithwick-Yanai G, Dromi N, Shtabsky A, et al. Multicentre validation of a microRNA-based assay for diagnosing indeterminate thyroid nodules utilising fine needle aspirate smears. *J Clin Pathol*. Jun 2017; 70(6): 500-507. PMID 27798083
39. Walts AE, Sacks WL, Wu HH, et al. A retrospective analysis of the performance of the RosettaGX (R) Reveal thyroid miRNA and the Afirma Gene Expression Classifiers in a cohort of cytologically indeterminate thyroid nodules. *Diagn Cytopathol*. Nov 2018; 46(11): 901-907. PMID 30353692
40. Fnais N, Soobiah C, Al-Qahtani K, et al. Diagnostic value of fine needle aspiration BRAF(V600E) mutation analysis in papillary thyroid cancer: a systematic review and meta-analysis. *Hum Pathol*. Oct 2015; 46(10): 1443-54. PMID 26232865
41. Kloos RT, Monroe RJ, Traweek ST, et al. A Genomic Alternative to Identify Medullary Thyroid Cancer Preoperatively in Thyroid Nodules with Indeterminate Cytology. *Thyroid*. Jun 2016; 26(6): 785-93. PMID 26992356
42. Xing M, Clark D, Guan H, et al. BRAF mutation testing of thyroid fine-needle aspiration biopsy specimens for preoperative risk stratification in papillary thyroid cancer. *J Clin Oncol*. Jun 20 2009; 27(18): 2977-82. PMID 19414674
43. Yin DT, Yu K, Lu RQ, et al. Clinicopathological significance of TERT promoter mutation in papillary thyroid carcinomas: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. Aug 2016; 85(2): 299-305. PMID 26732020
44. Bernet V, Hupart KH, Parangi S, et al. AACE/ACE disease state commentary: molecular diagnostic testing of thyroid nodules with indeterminate cytopathology. *Endocr Pract*. Apr 2014; 20(4): 360-3. PMID 24727662
45. Yip L, Wharry LI, Armstrong MJ, et al. A clinical algorithm for fine-needle aspiration molecular testing effectively guides the appropriate extent of initial thyroidectomy. *Ann Surg*. Jul 2014; 260(1): 163-8. PMID 24901361
46. Ferris RL, Baloch Z, Bernet V, et al. American Thyroid Association Statement on Surgical Application of Molecular Profiling for Thyroid Nodules: Current Impact on Perioperative Decision Making. *Thyroid*. Jul 2015; 25(7): 760-8. PMID 26058403
47. Nikiforova MN, Mercurio S, Wald AI, et al. Analytical performance of the ThyroSeq v3 genomic classifier for cancer diagnosis in thyroid nodules. *Cancer*. Apr 15 2018; 124(8): 1682-1690. PMID 29345728
48. Steward DL, Carty SE, Sippel RS, et al. Performance of a Multigene Genomic Classifier in Thyroid Nodules With Indeterminate Cytology: A Prospective Blinded Multicenter Study. *JAMA Oncol*. Feb 01 2019; 5(2): 204-212. PMID 30419129
49. Valderrabano P, Khazai L, Leon ME, et al. Evaluation of ThyroSeq v2 performance in thyroid nodules with indeterminate cytology. *Endocr Relat Cancer*. Mar 2017; 24(3): 127-136. PMID 28104680
50. Taye A, Gurciullo D, Miles BA, et al. Clinical performance of a next-generation sequencing assay (ThyroSeq v2) in the evaluation of indeterminate thyroid nodules. *Surgery*. Jan 2018; 163(1): 97-103. PMID 29154079
51. Moses W, Weng J, Sansano I, et al. Molecular testing for somatic mutations improves the accuracy of thyroid fine-needle aspiration biopsy. *World J Surg*. Nov 2010; 34(11): 2589-94. PMID 20703476
52. Ohori NP, Nikiforova MN, Schoedel KE, et al. Contribution of molecular testing to thyroid fine-needle aspiration cytology of follicular lesion of undetermined significance/atypia of undetermined significance. *Cancer Cytopathol*. Feb 25 2010; 118(1): 17-23. PMID 20099311
53. Beaudenon-Huibregtse S, Alexander EK, Guttler RB, et al. Centralized molecular testing for oncogenic gene mutations complements the local cytopathologic diagnosis of thyroid nodules. *Thyroid*. Oct 2014; 24(10): 1479-87. PMID 24811481
54. 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): 2743-50. PMID 25965083
55. Gharib H, Papini E, Garber JR, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS, AMERICAN COLLEGE OF ENDOCRINOLOGY, AND ASSOCIAZIONE MEDICI ENDOCRINOLOGI MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND MANAGEMENT OF THYROID NODULES--2016 UPDATE. *Endocr Pract*. May 2016; 22(5): 622-39. PMID 27167915

56. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. Jan 2016; 26(1): 1-133. PMID 26462967
57. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma. Version 1.2019.  
[https://www.nccn.org/professionals/physician\\_gls/pdf/thyroid.pdf](https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf). Accessed June 20, 2019
58. Palmetto GBA. MolDX: Afirma Assay by Veracyte Coding and Billing Guidelines (M00015). 2018;  
<https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=53098>. Accessed June 20, 2019.

**CLICK THE ENVELOPE ICON BELOW TO SUBMIT COMMENTS**

This medical policy is made available to you for informational purposes only. It is not a guarantee of payment or a substitute for your medical judgment in the treatment of your patients. Benefits and eligibility are determined by the member's subscriber agreement or member certificate and/or the employer agreement, and those documents will supersede the provisions of this medical policy. For information on member-specific benefits, call the provider call center. If you provide services to a member which are determined to not be medically necessary (or in some cases medically necessary services which are non-covered benefits), you may not charge the member for the services unless you have informed the member and they have agreed in writing in advance to continue with the treatment at their own expense. Please refer to your participation agreement(s) for the applicable provisions. This policy is current at the time of publication; however, medical practices, technology, and knowledge are constantly changing. BCBSRI reserves the right to review and revise this policy for any reason and at any time, with or without notice. Blue Cross & Blue Shield of Rhode Island is an independent licensee of the Blue Cross and Blue Shield Association.

