Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332
Original Effective Date: 12/19/2012
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of either Afirma Genomic Sequencing Classifier or ThyroSeq in fine needle aspirates of thyroid nodules with indeterminate cytologic findings (ie, Bethesda diagnostic category III [atypia/follicular lesion of undetermined significance] or Bethesda diagnostic category IV [follicular neoplasm/suspicion for a follicular neoplasm]) to be **eligible for coverage**** 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.

Based on review of available data, the Company may consider 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 to be **eligible for coverage****:

- ThyroSeq;
- ThyraMIR microRNA/ThyGenX;
- Afirma BRAF after Afirma Genomic Sequencing Classifier; or
- Afirma MTC after Afirma Genomic Sequencing Classifier.

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers gene expression classifiers, genetic variant analysis, and molecular marker testing in fine needle aspirates of the thyroid not meeting criteria outlined above, including but not limited to use of RosettaGX Reveal and single-gene TERT testing, to be **investigational.***

Policy Guidelines

In patients who do not undergo surgical biopsy or thyroidectomy on the basis of gene expression classifier or molecular marker results, regular active surveillance is indicated.

Use of molecular marker testing based on fine needle aspirate of a thyroid nodule to rule in malignancy prior to surgical biopsy may guide surgical planning, particularly factors such as choice of surgical facility provider to ensure that the capability is available to conduct a frozen section pathologic reading during surgical biopsy so that surgical approach may be adjusted accordingly in 1 surgery.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard

terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence

Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

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 or atypia of undetermined significance; 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 the 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 an 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 four 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. *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.

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. *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. Also, the co-occurrence of *BRAF* or *RAS* variants with *TERT* or *TP53* variants may identify a subset of thyroid cancers with unfavorable outcomes.

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 v3 Next-Generation Sequencing panel (CBLPath) is an NGS panel of 112 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. 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.

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). Table 1 outlines the testing algorithms for Afirma MTC and Afirma BRAF.

Table 1. Afirma MTC and Afirma BRAF Testing Algorithms

Test 1	Test 1 Result	Reflex to Test 2
Thyroid nodule on fine needle aspirate	"Indeterminate"	Afirma MTC
Afirma GSC	"Malignant" or "suspicious"	Afirma MTC
Afirma GSC	"Suspicious"	Afirma BRAF

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 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Thyroid variant testing and gene expression classifiers are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

In 2013, the THxID™‡-BRAF kit (bioMérieux), an in vitro diagnostic device, was approved by the Food and Drug Administration through the premarket approval process to assess specific *BRAF* variants in melanoma tissue via real-time PCR. However, there are currently no diagnostic tests for thyroid cancer mutation analysis with approval from the Food and Drug Administration. Table 2 provides a summary of commercially available molecular diagnostic tests for indeterminate thyroid pathology.

Table 2. Summary of Molecular Tests for Indeterminate Thyroid Cytopathology FNA Specimens

Test	Predicate	Methodology	Analyte(s)	Report
Afirma® GSC	Afirma®GEC	mRNA gene expression	1,115 genes	Benign/suspicious
Afirma® BRAF		mRNA gene expression	1 gene	Negative/positive
Afirma® MTC		mRNA gene expression		Negative/positive
ThyroSeq v3	ThyroSeq v2	Next-generation sequencing	112 genes	Specific gene variant/translocation

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Test	Predicate	Methodology	Analyte(s)	Report
ThyGeNEXT®	ThyGenX®[a], miR*Inform*®[a]	Next-generation sequencing	10 genes and 32 gene fusions	Specific gene variant/translocation
ThyraMIR™		microRNA expression	10 microRNAs	Negative/positive
RosettaGX™ Reveal		microRNA expression	24 microRNAs	• Benign • Suspicious for malignancy • High risk for medullary carcinoma

FNA: fine needle aspirate; mRNA: messenger RNA. PCR: polymerase chain reaction.
[a] The miR*Inform*®‡ test is the predicate test to ThyGenX™‡ and is not commercially available.

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Rationale/Source

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 tests to rule out malignancy and to avoid surgical biopsy or resection, the evidence includes a prospective clinical validity study with the Afirma Gene Sequencing Classifier and a chain of evidence to support clinical utility. The relevant outcomes are disease-specific survival, test accuracy and validity, morbid events, and resource utilization. In a multicenter validation study, the Afirma Gene Sequencing Classifier was reported to have a high negative predictive value (NPV 96%; 95% confidence interval, 90%-99%). These results are consistent with an earlier study on the Afirma Gene Expression Classifier (GEC) in the same study population. In other multicenter and single-center studies, there is suggestive evidence that rates of malignancy are low in Afirma patients who are classified as benign, but the exact NPV is unknown. The available evidence suggests that the decisions a physician makes regarding surgery are altered by Afirma GEC/Gene Sequencing Classifier 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 there is only a single study of the marketed test reporting a true NPV. Clinical input, obtained in 2017, supported the use of the previous version of the Afirma test in FNA of thyroid nodules with indeterminate cytologic findings to rule out malignancy and avoid surgical biopsy with an acceptably low trade-off in missed malignancy. The evidence is sufficient to determine that the technology improves the net health outcome.

For individuals with thyroid nodule(s) and indeterminate findings on FNA who receive FNA sample testing with molecular tests to rule in malignancy and to guide surgical planning, the evidence includes prospective and retrospective studies of clinical validity. The relevant outcomes are disease-specific survival, test accuracy and validity, morbid events, and resource utilization. Variant 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. Single-center studies have suggested

that testing for a panel of genetic variants associated with thyroid cancer may allow for the appropriate selection of patients for surgical management for the initial resection. Prospective studies in additional populations are needed to validate these results. Although the presence of certain variants may predict more aggressive malignancies, the management changes that would occur as a result of identifying higher risk tumors, are not well-established. Clinical input, obtained in 2017, considered ThyraMIR microRNA/ThyGenX, Afirma BRAF after Afirma GEC, and Afirma MTC after Afirma GEC to provide a clinically meaningful improvement for patients with cytologic findings suspicious for malignancy to guide surgical planning for the initial resection. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with thyroid nodule(s) and indeterminate findings on FNA who receive FNA sample testing with molecular tests to rule out malignancy and avoid surgical biopsy or to rule in malignancy for surgical planning, the evidence includes multiple retrospective and prospective clinical validation studies for the ThyroSeq test and 2 retrospective clinical validation studies that used a predicate test 17-variant panel (miR*Inform*) test to the current ThyGenX and ThyraMIR. The 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 (miR*Inform*) test and ThyraMIR had a sensitivity of 89%, and an NPV of 94%. A prospective clinical validation study of ThyroSeq v3 reported an NPV of 97% and positive predictive value of 68%. 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 v3 test and combined ThyGenX and ThyraMIR testing would rely on establishing clinical validity. Clinical input, obtained in 2017, considered ThyroSeq v2 to provide a clinically meaningful improvement for patients with indeterminate cytologic findings to rule out malignancy and avoid surgical biopsy and in patients with cytologic findings suspicious for malignancy to guide surgical planning for the initial resection. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 (ie, 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 two-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.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

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2017 Input
In response to requests, clinical input on 7 tests for molecular markers was received from 9 respondents, including 1 specialty society-level response, 1 physician from an academic center, and 7 physicians from 2 health systems while this policy was under review in 2017.

Based on the evidence and independent clinical input, the clinical input supports that the following indications provide a clinically meaningful improvement in the net health outcome and are consistent with generally accepted medical practice:

- Use of the following types of molecular marker testing in fine needle aspirate (FNA) of thyroid nodules with indeterminate cytologic findings (ie, 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 Gene Expression Classifier; 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 two-stage surgical biopsy followed by definitive surgery:
    - ThyroSeq v2;
    - ThyraMIR microRNA/ThyGenX;
    - Afirma BRAF after Afirma Gene Expression Classifier; or
    - Afirma MTC after Afirma Gene Expression Classifier.

Based on the evidence and independent clinical input, the clinical input does not support whether the following indication provides a clinically meaningful improvement in the net health outcome or is consistent with generally accepted medical practice:

- Use of the following types of molecular marker testing in FNA of thyroid nodules:
    - RosettaGX Reveal.

2016 Input
In response to requests, input was received from 2 physician specialty societies (one of which provided 3 responses) and 1 academic medical center while this policy was under review in 2016.

Input focused on the use of gene expression classifiers with a high negative predictive value in nodules indeterminate on FNA. Although individual uses of a gene expression classifier with negative predictive value in these situations varied, there was general agreement that the tests are considered standard in the evaluation of some indeterminate cases of FNA.

2013 Input
In response to requests, input was received from 1 physician specialty society (4 reviewers) and 6 academic medical centers, for a total of 10 reviewers, while this policy was under review in 2013. There was general agreement with the policy statements that variant analysis and use of the gene expression classifier is investigational. The input was mixed as to whether test changes patient management and whether prospective randomized trials are necessary to establish the clinical utility of these tests.

Practice Guidelines and Position Statements
American Association of Clinical Endocrinologists et al
The American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazone Medici Endocrinologi (2016) updated their joint guidelines on molecular testing for cytologically indeterminate thyroid nodules, stating:

- "Cytopathology expertise, patient characteristics, and prevalence of malignancy within the population being tested impact the negative predictive values (NPVs) and positive predictive values (PPVs) for molecular testing."
- "Consider the detection of *BRAF* and *RET/PTC* and, possibly, *PAX8/PPARG* and *RAS* mutations if such detection is available."
- "*TERT* mutational analysis on FNA, when available, may improve the diagnostic sensitivity of molecular testing on cytologic samples."
- "Because of the insufficient evidence and the limited follow-up, we do not recommend either in favor of or against the use of gene expression classifiers (GECs) for cytologically indeterminate nodules."

For the role of molecular testing for deciding the extent of surgery the following recommendations were made:

- "Currently, with the exception of mutations such as BRAFV600E that have a PPV approaching 100% for papillary thyroid carcinoma (PTC), evidence is insufficient to

recommend in favor of or against the use of mutation testing as a guide to determine the extent of surgery."

American Thyroid Association

The American Thyroid Association (2016) updated its guidelines on the management of thyroid nodules and differentiated thyroid cancer in adults. These guidelines made the following statements on molecular diagnostics in thyroid nodules that are atypia of undetermined significance or follicular lesion of undetermined significance on cytology and follicular neoplasm or suspicious for follicular neoplasm on cytology (see Table 3).

Table 3. Molecular Diagnostics in Thyroid Nodules That Are AUS or FLUS or FN or SFN on Cytology

Recommendation	SOR	QOE
AUS or FLUS		
"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	Moderate
"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	Low

FN or SFN		
"Diagnostic surgical excision is the long-established standard of care for the management of FN/SFN cytology nodules. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery. Informed patient preference and feasibility should be considered in clinical decision-making."	Weak	Moderate

AUS: atypia of undetermined significance; FLUS: follicular lesion of undetermined significance; FN: follicular neoplasm; FNA: fine needle aspirate; QOE: quality of evidence; SFN: suspicious for follicular neoplasm; SOR: strength of evidence.

The guidelines also stated: "there is currently no single optimal molecular test that can definitively rule in or rule out malignancy in all cases of indeterminate cytology, and long-term outcome data proving clinical utility are needed."

National Comprehensive Cancer Network
National Comprehensive Cancer Network (v.1.2019) guidelines on the treatment of thyroid cancer comment on the use of molecular diagnostics in thyroid cancer. For thyroid nodules evaluated with FNA, molecular diagnostics may be employed when lesions are suspicious for: :

- Follicular or Hürthle cell neoplasms.
- Atypia of undetermined significance or follicular lesions of undetermined significance.

The guidelines state that molecular diagnostics may not perform well for Hurthle cell neoplasms.

U.S. Preventive Services Task Force Recommendations
Not applicable.

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Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

MolDX Program contractors Palmetto GBA, Wisconsin Physicians Service Insurance Corp., and CGS Administrators determined that the Afirma Gene Expression Classifier test meets criteria for analytic and clinical validity and clinical utility as a reasonable and necessary Medicare benefit. Effective 2015, the MolDX Program contractors will reimburse Afirma Gene Expression Classifier services for patients with the following conditions:

- "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
- Have an indeterminate follicular pathology on fine needle aspiration."

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT03170804	Genomic Profiling of Nodular Thyroid Disease and Thyroid Cancer	200	Jan 2020

NCT: national clinical trial.

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Policy History

Original Effective Date: 12/19/2012
Current Effective Date: 03/09/2020

02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Returned to active status.
02/07/2019	Medical Policy Committee review
02/20/2019	Medical Policy Implementation Committee approval. Policy statements revised to add investigational statement for TERT single-gene testing.
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. “Afirma GEC" test replaced with new "Afirma GSC" test throughout the policy.
09/21/2020	Coding update
12/11/2020	Coding update

Next Scheduled Review Date: 02/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0018U, 0026U, 81345, 81445, 81479, 81599 Adding codes eff 10/1/2020: 0204U, 0208U Adding code eff 1/1/2021: 81546 Delete code eff 1/1/2021: 81545
HCPCS	No codes
ICD-10 Diagnosis	C73, D44.0

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety,

effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company

recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.