



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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 for patients who have 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 either of the following types of molecular marker testing or gene variant analysis 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****:

- Afirma Genomic Sequencing Classifier; or
- ThyroSeq.

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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

- Afirma MTC after Afirma Genomic Sequencing Classifier.

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 a single surgery.

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.

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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,

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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/PPAR γ* 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/PPAR γ* 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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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 γ* 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 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) 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 10,196 genes with 1,115 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.

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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 GSC, 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

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 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 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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332
Original Effective Date: 12/19/2012
Current Effective Date: 03/08/2021
Returned to Active Status: 02/21/2018

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 8 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.

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. FDA has chosen not to require any regulatory review of this test.

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

In 2013, the THxID™[†]-BRAF kit (bioMérieux), an in vitro diagnostic device, was approved by the U.S. FDA 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 U.S.FDA. 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
ThyGeNEXT®	ThyGenX® ^a , miRInform® ^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	<ul style="list-style-type: none"> • Benign • Suspicious for malignancy • High risk for medullary carcinoma

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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.

Rationale/Source

Description

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.

Summary of Evidence

To determine which patients need thyroid resection, many physicians will perform a cytologic examination of 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 GSC 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 GSC was reported to have a high NPV (96%; 95% C I, 90%-99%). These results are consistent with an earlier study on the Afirma 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/GSC 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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

malignancy. 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 tests to rule in malignancy and to guide surgical planning, the evidence includes prospective and retrospective studies of clinical validity. Relevant outcomes are disease-specific survival, test accuracy and validity, morbid events, and resource utilization. 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. 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 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. 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 PPV 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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.

2017 Input

Clinical input was sought to help determine whether testing for molecular markers in fine needle aspirates of the thyroid for management of individuals with thyroid nodule(s) with an indeterminate finding on the fine needle aspirates would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. 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.

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

For individuals who have 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]) who receive the following types of molecular marker testing to rule out malignancy and to avoid surgical biopsy:

- Afirma Gene Expression Classifier; or
- ThyroSeq v2

For individuals who have FNA of thyroid nodules with indeterminate cytologic findings or Bethesda diagnostic category V (suspicious for malignancy) who receive the following types of molecular marker testing 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 Gene Expression Classifier; or
- Afirma MTC after Afirma Gene Expression Classifier.

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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.

Further details from clinical input are included in the Supplemental Information section.

Practice Guidelines and Position Statements

American Association of Clinical Endocrinologists et al

The American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione 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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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 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 recommendation.

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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.

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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332
 Original Effective Date: 12/19/2012
 Current Effective Date: 03/08/2021
 Returned to Active Status: 02/21/2018

- 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
<i>Ongoing</i>			
NCT03170804	Genomic Profiling of Nodular Thyroid Disease and Thyroid Cancer	200	Jan 2020

NCT: national clinical trial.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Molecular Markers in Fine Needle Aspirates of the Thyroid”, 2.04.78, 08:2020.
2. 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
3. Chudova D, Wilde JJ, 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
4. 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
5. Nikiforov YE. Molecular diagnostics of thyroid tumors. *Arch Pathol Lab Med*. May 2011; 135(5): 569-77. PMID 21526955
6. 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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

- Study from Four Endocrine Surgery Centers. *Thyroid*. Apr 2016; 26(4): 532-42. PMID 26950846
7. 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
 8. 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
 9. Alzahrani AS, Alsaadi R, Murugan AK, et al. TERT Promoter Mutations in Thyroid Cancer. *Horm Cancer*. Jun 2016; 7(3): 165-77. PMID 26902827
 10. 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
 11. 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
 12. 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
 13. 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
 14. 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
 15. 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
 16. CBLPath. ThyroSeq v.2 Next Generation Sequencing. n.d.; <http://www.cblpath.com/products-and-services/test-menu-cblpath/item/1628-thyroseq-v2>. Accessed May 25, 2018.
 17. 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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

18. 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
19. 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
20. 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
21. 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
22. 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
23. 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
24. 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
25. 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
26. 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
27. 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
28. 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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

29. 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
30. 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
31. 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
32. 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
33. 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
34. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*. Nov 2009; 19(11): 1159-65. PMID 19888858
35. 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
36. 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
37. 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
38. 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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

39. 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
40. 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
41. 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
42. 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
43. 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
44. 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
45. 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
46. 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
47. 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
48. 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
49. 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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

50. 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
51. 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
52. 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
53. 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
54. 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.
55. Palmetto GBA. MolDX: Afirm Assay by Veracyte Coding and Billing Guidelines (M00015). 2018; <https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=53098>.

Policy History

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

- | | |
|------------|--|
| 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 |

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

02/12/2020 Medical Policy Implementation Committee approval. "Afirma GEC" test replaced with new "Afirma GSC" test throughout the policy.

02/04/2021 Medical Policy Committee review

02/10/2021 Medical Policy Implementation Committee approval. Criteria rewritten. No change to coverage. FDA updated.

03/25/2021 Coding update

Next Scheduled Review Date: 02/2022

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 2020 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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

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 Adding code eff 4/1/2021: 0245U
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:

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Molecular Markers in Fine Needle Aspirates of the Thyroid

Policy # 00332

Original Effective Date: 12/19/2012

Current Effective Date: 03/08/2021

Returned to Active Status: 02/21/2018

- 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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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.

©2021 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.