MEDICAL POLICY

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MEDICAL POLICY DETAILS	
Medical Policy Title	**Molecular Markers in Fine Needle Aspirates of the Thyroid**
Policy Number	**2.02.49**
Category	**Laboratory Test**
Original Effective Date	**11/19/15**
Committee Approval Date	**09/15/16, 09/21/17, 12/20/18, 12/19/19, 10/22/20, 10/28/21, 10/20/22**
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Archived Review Date	**N/A**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, the use of a gene expression classifier in fine-needle aspirates of the thyroid (e.g., Afirma Genomic Sequencing Classifier) or mutation analysis in fine-needle aspirates of the thyroid (e.g., ThyroSeq, ThyraMIR Micro RNA/ThyGenX Thyroid Oncogene Panel, Afirma Xpression Atlas (XA)) that are cytologically considered to be indeterminate, atypical or suspicious for malignancy is considered **medically appropriate** when surgical decisions will be based on the test results for thyroid nodules involving the following:

A. Cytological diagnosis of atypia of undetermined significance/follicular lesion of either undetermined significance (AUS/FLUS) on fine-needle aspiration (FNA); or
B. Cytological diagnosis of follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) on fine-needle aspiration (FNA); or
C. Bethesda III or IV on FNA cytology (please refer to the Bethesda criteria in the Policy Rationale Section);

AND

D. Size greater than 1.0 cm; and
E. No clinical suspicion of malignancy based on provider judgment and ultrasonography; and
F. No compressive manifestations.

Testing is appropriate once per lifetime per nodule.

II. Based on our criteria and assessment of the peer-reviewed literature, the use of a gene expression classifier in fine-needle aspirates of the thyroid or mutation analysis in fine-needle aspirates of the thyroid not meeting the above criteria are considered **investigational**.

POLICY GUIDELINES

I. Ultrasound features associated with low suspicion of malignancy include:

A. Isoechoic or hyperechoic solid nodules without microcalcifications; or
B. Mixed solid/cystic nodules without microcalcification; or
C. Spongiform nodules.

II. The ThyroSeq v.3 ThyroSeq Genomic Classifier (GC) (CBLPath, Ocala, FL) uses next-generation sequencing technology to interrogate five classes of genetic alterations: (a) point mutations (SNVs); (b) insertions and deletions; (c) gene fusions; (d) gene expression alterations; and (e) copy number alterations (CNAs). The test utilizes a proprietary genomic classifier (GC) that relies on the algorithmic analysis of all detected genetic alterations to report the test result as positive or negative. Per the manufacturer's website, ThyroSeq GC is specifically designed to determine whether a thyroid nodule is benign (not cancerous) or malignant (cancerous) when cytology result is indeterminate. ThyroSeq also provides specific information about genetic makeup of the nodule which allows physicians to determine an individualized course of treatment.

III. The ThyraMIR Micro RNA/ThyGenX Thyroid Oncogene Panel (Interpace Diagnostics, Parsippany, NJ) is a next generation sequencing panel designed to be used in patients with indeterminate thyroid FNA results. The panel includes sequencing of eight genes associated with papillary thyroid carcinoma (PTC) and follicular carcinomas. The ThyraMIR is a miRNA gene expression classifier and is based on the evaluation of expression of 10 miRNAs. When used in combination, ThyraMIR can identify malignancy in nodules that are negative for ThyGenX which potentially improving overall sensitivity and ability to detect malignancy.

IV. The Afirma Genomic Sequencing Classifier (Afirma GSC; Veracyte, San Francisco, CA) analyzes the expression of 142 different genes to determine patterns associated with benign finding on surgical biopsy. It is indicated for thyroid nodules that have an indeterminate classification on FNA. Testing is limited to two thyroid nodules.

V. The Afirma Xpression Atlas (XA) is an RNA sequencing-based test that measures 761 DNA variants and 130 RNA fusions in over 500 genes that have been linked to thyroid cancer. The test may be performed when the Afirma Genomic Sequencing Classifier results are malignant or suspicious to provide additional information that may guide treatment.

DESCRIPTION

Thyroid nodules are common endocrine tumors that appear as palpable nodules in 5% of adults. Up to 50% of women and 20% of men over age 50 are found to have thyroid nodules on ultrasound or autopsy studies. The majority of thyroid nodules are benign but 10-15% may be malignant, most often as papillary thyroid cancer. Fine needle aspiration (FNA) is performed in nodules that require biopsy, with sufficient information obtained to classify the majority of nodules as benign and a smaller percentage as malignant. However, 15-30% of aspirations yield indeterminate cytology including subtypes such as atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), suspicious for follicular neoplasm (FN) or suspicious for malignancy.

Current guidelines recommend either partial (lobectomy) or complete thyroidectomy for those nodules determined to be malignant and those of indeterminate cytology. On histological evaluation only 15-30% of the thyroid nodules of indeterminate cytology are malignant consequently many patients undergo surgery for benign disease when expectant management or other treatments would have been more appropriate with a retrospective assessment. Due to the limitations of the FNA, other methods to assist in determining whether a nodule is benign or malignant prior to surgery have been developed. The ThyroSeq and ThyGenX thyroid Oncogene panel are two tests for point mutations associated with thyroid cancers using next-generation sequencing. The Afirma Genomic Sequencing Classifier (GSC) analyzes genetic alterations through the use of gene expression profiling.

RATIONALE

Analysis for mutations associated with thyroid cancer in fine needle aspirates (FNA) of the thyroid that are cytologically indeterminate has a high positive predictive value for malignancy. However, patients with an equivocal FNA result would likely proceed to surgery regardless of mutation status, with intraoperative consultation to guide the necessity and extent of surgery. Mutation analysis has the potential to improve the accuracy of an equivocal FNA of the thyroid and may play a role in preoperative risk stratification and surgical planning. Studies suggest that testing for a panel of mutations

associated with thyroid cancer may allow the appropriate selection of patients for surgical management with an initial total thyroidectomy.

The American Thyroid Association (ATA) statement on Surgical Application of Molecular Profiling for Thyroid Nodules (2015) states that techniques for molecular profiling of thyroid cytology specimens have evolved as adjuncts to guide the appropriate management of cytologically indeterminate nodules. However, it must be stressed that the utility of any molecular test is only applicable clinically when combined with clinical and sonographic risk factors for malignancy and with understanding of the prevalence of malignancy for the Bethesda cytologic categories at the reporting institution. Future studies on further refinements and expansion of gene sets in analytic panels will likely improve the diagnostic accuracy of molecular analyses of thyroid cytology specimens and offer promise for personalizing surgical therapy, with the potential for cost and risk reduction in the diagnostic and therapeutic approaches to treating differentiated thyroid cancer.

The 2022 NCCN Guidelines for Thyroid Carcinoma state that molecular diagnostics may be useful to allow reclassification of follicular lesions, i.e., follicular neoplasm, atypia of undetermined significance (AUS), or follicular lesions of undetermined significance (FLUS) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing, in conjunction with clinical and ultrasound features, predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider nodule surveillance. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient. Molecular diagnostic testing to detect individual mutations (e.g., BRAF V600E, RET/PTC, RAS, PAX8/PPAR) or pattern recognition approaches using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate to assist in management decisions. The BRAFV600E mutation occurs in about 45% of patients with papillary carcinoma and is the most common mutation. Some studies have linked the BRAFV600E mutation to poor prognosis, especially when occurring with TERT promoter mutation. The choice of the precise molecular test depends on the cytology and the clinical questions being asked. Indeterminate groups include follicular or Hürthle cell neoplasms and AUS/FLUS. The NCCN Panel recommends consideration of molecular diagnostic testing for these indeterminate groups. Molecular diagnostic testing may include multigene assays (e.g., GEC) or individual mutational analysis. In addition to their utility in diagnostics, molecular markers may drive decisions related to targeted therapy for advanced disease and inform eligibility for some clinical trials. The presence of some mutations may have prognostic importance.

In 2007, the National Cancer Institute (NCI) Thyroid FNA State of Science Conference, developed the Bethesda System for Reporting Thyroid Cytopathology. The purpose of the conference was to develop a uniform reporting system for thyroid FNA to facilitate effective communication among cytopathologists, endocrinologists, surgeons, radiologists, and other health care providers. The reporting system was revised in 2017 and reaffirms that every thyroid FNA report should begin with one of six diagnostic categories, the names of which remain unchanged since they were first introduced.

The 2017 Bethesda System for Reporting Thyroid Cytopathology

Risk Category	Definition	Diagnostics
I	Nondiagnostic or Unsatisfactory	Cyst fluid only Virtually acellular specimen Other (obscuring blood, clotting artifact, etc.)
II	Benign	Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.) Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context Consistent with granulomatous (subacute) thyroiditis Other
III	Atypia of Undetermined Significance *or* Follicular	

	Lesion of Undetermined Significance	
IV	Follicular Neoplasm or Suspicious for a Follicular Neoplasm	Specify if Hürthle cell (oncocytic) type
V	Suspicious for Malignancy	Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma Other
VI	Malignant	Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features (specify) Metastatic carcinoma Non-Hodgkin lymphoma Other

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81479	Unlisted molecular pathology procedure
81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious (*Afirma Genomic Sequencing Classifer, Veracyte, Inc*.)
0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy *(ThyraMIR™, Interpace Diagnostics)*
0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy") (*Thyroseq Genomic Classifier, CBLPath, Inc., University of Pittsburgh Medical Center*)

Code	Description
0204U	Oncology (thyroid), mRNA, gene expression analysis of 593 genes (including BRAF, RAS, RET, PAX8, and NTRK) for sequence variants and rearrangements, utilizing fine needle aspirate, reported as detected or not detected (*Afirma Xpression Atlas, Veracyte, Inc.*)
0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage (*ThyGeNEXT® Thyroid Oncogene Panel, Interpace Diagnostics*)
0287U	Oncology (thyroid), DNA and mRNA, next-generation sequencing analysis of 112 genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high) (*ThyroSeq® CRC, CBLPath, Inc, University of Pittsburgh Medical Center*) (effective 1/1/2022)

HCPCS Codes

Code	Description
No specific codes	

ICD10 Codes

Code	Description
C73	Malignant neoplasm of thyroid gland
D34	Benign neoplasm of thyroid gland
D44.0	Neoplasm of uncertain behavior of thyroid gland

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*Key Article

KEY WORDS

ThyroSeq, Afirma Gene Sequencing Classifier (GSC), fine needle aspiration of the thyroid, molecular markers of thyroid, ThyGenX Thyroid Oncogene Panel

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=133&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=All&bc=AAgAAAQBIAAA&

There is currently a Local Coverage Article (LCA) for Molecular Pathology Procedures. Please refer to the following LCA website for Medicare members: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=56199&ver=67&

There is a Local Coverage Determination (LCD) for Thyroid Nodule Molecular Testing. Please refer to the following LCD website for Medicare members: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38968&ver=4&keyword=Thyroid%20Nodule%20Molecular%20Testing&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1

There is a proposed Local Coverage Article (LCA) for Thyroid Nodule Molecular Testing. Please refer to the following LCA website for Medicare members: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=58655&ver=3