MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**MOLECULAR MARKERS IN FINE NEEDLE ASPIRATES OF THE THYROID**
Policy Number	**2.02.49**
Category	**Laboratory Test**
Effective Date	**11/19/15**
Revised Date	**09/15/16, 09/21/17, 12/20/18, 12/19/19**
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 product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare 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.*

POLICY STATEMENT

I. 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 (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 test results* for thyroid nodules with 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 Description section); AND
D. Size greater than 1.0 cm; and
E. Without 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 cutting-edge next-generation sequencing technology to interrogate 5 classes of genetic alterations: (i) point mutations (SNVs), (ii) insertions and deletions, (iii) gene fusions, (iv) gene expression alterations, and (v) 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 if a thyroid nodule is benign (not cancer) or malignant (cancer) 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 8 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 improves 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 2 thyroid nodules.

V. The Afirma® Xpression Atlas (XA) is an RNA sequencing-based test 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.

VI. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

Thyroid nodules are common endocrine tumors which appear as palpable nodules in 5% of adults. Up to 50% of women and 20% of men over age 50 on ultrasound or autopsy studies are found to have thyroid nodules. 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 which 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 as 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 evaluation 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. Additional studies are needed to validate these results. Mutation analysis does not achieve a high enough negative predictive value (NPV) to identify which patients can undergo watchful waiting over thyroid surgery.

Although the presence of certain mutations may predict more aggressive malignancies, the clinical utility of identifying these mutations preoperatively has not been established.

There is one commercially available gene expression classifier (GEC) that has been developed to predict benignancy in thyroid nodules. The reported NPV of the GEC in predicting which thyroid nodules with indeterminate cytology are benign is high. Studies in which patients who avoided surgery based on GEC results need longer follow-up data.

The American Thyroid Association (ATA) statement on Surgical Application of Molecular Profiling for Thyroid Nodules (2015) states 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 National Comprehensive Cancer Network (NCCN) Guidelines for Thyroid Carcinoma (2019) state that molecular diagnostics may be useful to allow reclassification of follicular lesions (i.e., follicular neoplasm, atypia of undetermined significance (AUS), 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 active 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. 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, In addition, 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 cytopathologist, endocrinologists, surgeons, radiologists, and other health care providers.

The 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
81479	Unlisted molecular pathology procedure
81545	Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (e.g., benign or suspicious)
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*™)

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 Expression Classifier (GEC), 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=131&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=All&bc=AAgAAAQBAAAA&

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/details/article-details.aspx?articleId=56199&ver=28&LCDId=35000&ContrId=298&ContrVer=1&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AAgAAAQAgAAA&