MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Molecular Marker Testing of the Thyroid**
Policy Number	**2.02.49**
Category	**Technology Assessment**
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, 11/16/23**
Current Effective Date	**03/15/24**
Archived Date	**N/A**
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 either of the following types of molecular marker testing or gene variant analysis in fine needle aspirates (FNA) of thyroid nodules with indeterminate cytologic findings (i.e., Bethesda diagnostic category III or IV, refer to Policy Guideline VII) for individuals who have thyroid nodules without strong clinical or radiologic findings suggestive of malignancy in whom surgical decision making would be affected by test results may be considered **medically necessary**:
   A. Afirma Genomic Sequencing Classifier; or
   B. ThyroSeq.

II. Based upon our criteria and assessment of the peer-reviewed literature, the use of the following types of molecular marker testing or gene variant analysis in fine needle aspirates of thyroid nodules with indeterminate cytologic findings (i.e., Bethesda diagnostic category III, IV or V, refer to Policy Guideline VII) to rule in malignancy to guide surgical planning for initial resection rather than a 2-stage surgical biopsy followed by definitive surgery may be considered **medically necessary**:
   A. ThyroSeq;
   B. ThyraMIR microRNA/ThyGenX;
   C. Afirma BRAF after completion of Afirma Genomic Sequencing Classifier Testing; or
   D. Afirma MTC after completion of Afirma Genomic Sequencing Classifier Testing.

III. Based upon our criteria and assessment of the peer-reviewed literature, gene expression classifiers, genetic variant analysis, and molecular marker testing of the thyroid not meeting criteria outlined above, including but not limited to use of RosettaGX Reveal, single-gene TERT testing or Thyroid GuidePx are considered **investigational**.

POLICY GUIDELINES

I. The Health Plan and its employees adhere to all state and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. 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.

V. Testing is appropriate once per lifetime per thyroid nodule.

VI. 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.

VII. 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 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

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

DESCRIPTION

Thyroid nodules are common endocrine tumors that appear as palpable nodules in five (5) to seven (7) percent of the United States adult population. 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 professional 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 so 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.

Current molecular testing uses several combinations of genomic sequencing, messenger RNA (mRNA) analysis, and/or microRNA (miRNA) expression analysis of cancer-associated genes, with high diagnostic accuracy documented in multiple studies. Molecular testing was recommended for use in several settings in the 2020 guidelines of the American Association of Endocrine Surgeons (AAES). In addition to providing diagnostic information, preoperative molecular testing can provide prognostic value for individuals with suspected or known thyroid malignancy because different mutations often are associated with thyroid cancer subtypes and can provide prognostic information (especially preoperatively) for long-term management. Molecular testing provides a safe and cost-effective strategy that decreases the rate of diagnostic thyroidectomy in the management of indeterminate nodules.

Summary of Molecular Tests for Indeterminate Thyroid Cytopathology Fine Needle Aspirate Specimens

TEST	METHODOLGY	ANALYTE(S)	REPORT
Afirma GSC	mRNA gene expression	1115 genes	Benign/suspicious
Afirma BRAF	mRNA gene expression	1 gene	Negative/positive
Afirma MTC	mRNA gene expression	108 genes	Negative/positive
Afirma Xpression Atlas	mRNA gene expression	593 genes	Negative/positive
ThyroSeq v3	Next-generation sequencing	112 genes	Specific gene variant/translocation
ThyGeNEXT	Next-generation sequencing	10 genes and 32 gene fusions	Specific gene variant/translocation
ThyraMIR	microRNA expression	10 microRNAs	Negative/positive
RosettaGXReveal	microRNA expression	24 microRNAs	Benign/suspicious for malignancy

			• High risk for medullary carcinoma

Telomerase reverse transcriptase (*TERT*) promoter is a targeted genomic sequence analysis panel which occur with varying frequency in different thyroid cancer subtypes. *TERT* promoter variants have been reported to be independent predictors of disease recurrence and cancer-related mortality in well-differentiated thyroid cancer.

Thyroid GuidePx (Protean BioDiagnostics) is a next generation sequencing test that provides gene expression profiling via targeted hybrid capture-enrichment RNA sequencing of 82 content genes and 10 housekeeping genes for molecular sub-classification of papillary thyroid cancer and assists in decision making around cancer management.

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 National Cancer Institute (NCI) Thyroid FNA State of Science Conference (2007) developed the Bethesda System for Reporting Thyroid Cytopathology 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 (Please refer to the Policy Guideline Section for the 2017 Bethesda System for Reporting Thyroid Cytopathology).

The V4.2023 National Comprehensive Cancer Network (NCCN) Guidelines for Thyroid Carcinoma state that the diagnosis of follicular carcinoma or oncocytic carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (i.e., follicular neoplasm, AUS, FLUS) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing suggests papillary thyroid carcinoma, especially in the case of BRAF V600E, then diagnostic imaging or fine needle aspirate is recommended dependent on size of nodule. Given the challenges of cytology to explicitly diagnose medullary thyroid carcinoma in limited samples, molecular tests may be used to identify them. 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. If molecular diagnostics are technically inadequate or not done, then repeat FNA. The NCCN guideline also endorses the American Thyroid Association (ATA) and American College of Radiology (ACR) recommendations for nodule surveillance.

In 2022, Babazadeh et al. reported on the clinical utility of Afirma Xpression Atlas (XA) testing during two years of clinical use. Afirma XA became available in 2018 and assesses 593 genes, including 905 potential variants and 235

fusions. Afirma XA was performed on 136 indeterminate nodules (103 of these met inclusion criteria). Forty-three of those had positive Afirma XA results, 83.7% of which were follicular cell-derived thyroid cancer on surgical histopathology. Overall positive predictive value (PPV) among Afirma GSC-suspicious indeterminate nodules during the same timeframe was 82.5%, similar to the Afirma XA results. Of the 60 nodules that tested negative with Afirma XA, 73.3% were follicular cell-derived thyroid cancer on surgical histopathology. The authors concluded that the Afirma XA positivity is predictive of follicular cell-derived thyroid cancer with PPV similar to that of GSC suspicious results alone at the institution where the study took place. It is still uncertain whether Afirma XA results significantly increase the preoperative risk of malignancy for cytologically indeterminate nodules. More extensive studies on variants and fusions associated with varied risks of malignancy are needed with longer term data collection of Afirma XA results and related clinical variables.

There is currently insufficient evidence to support the use of RosettaGX Reveal, Thyroid GuidePx or Telomerase reverse transcriptase (*TERT*) promoter for determination of thyroid carcinoma and additional large clinical studies are needed to support the efficacy of these molecular tests.

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.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/appropriate = (NMN).*

CPT Codes

Code	Description
81345 (***E/I** for Thyroid Carcinoma)	TERT (telomerase reverse transcriptase) (e.g., thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (e.g., promoter region)
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., 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 (***E/I** for RosettaGX Reveal Testing)	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 (e.g., 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)*

Code	Description
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*)
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*)
0362U **(E/I)**	Oncology (papillary thyroid cancer), gene-expression profiling via targeted hybrid capture-enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, formalin-fixed paraffin embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes *(Includes Thyroid GuidePx, Protean BioDiagnostics, Protean BioDiagnostics) (Effective 01/01/2023)*

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, RosettaGX Reveal, single-gene TERT testing, Thyroid GuidePx

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (L3500) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare members: [https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35000&ver=138&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=All&bc=AAgAAAQBIAAA&=] accessed 11/29/23.

There is currently a Local Coverage Article (A56199) for Molecular Pathology Procedures. Please refer to the following LCA website for Medicare members: [Article - Billing and Coding: Molecular Pathology Procedures (A56199) (cms.gov)] accessed 11/29/23.

There is a Local Coverage Determination (L38968) 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] accessed 11/29/23.

There is a Local Coverage Article (A58656) 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=58656&ver=6&keyword=Thyroid%20Nodule%20Molecular%20Testing&keywordType=starts&areaId=all&docType=6,3,5,1&contractOption=all&sortBy=relevance&bc=1] accessed 11/29/23.