Medical Policy

PARAMOUNT

HMO AND PPO
ELITE (MEDICARE ADVANTAGE)
MARKETPLACE

Molecular Markers in Fine Needle Aspirates of Thyroid Nodules

Policy Number: PG0298
Last Review: 03/03/2021

GUIDELINES:

- This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder terms, conditions, exclusions, and limitations contract. It does not constitute a contract or guarantee regarding coverage or reimbursement/payment. Self-Insured group specific policy will supersede this general policy when group supplementary plan document or individual plan decision directs otherwise.
- Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards.
- This medical policy is solely for guiding medical necessity and explaining correct procedure reporting used to assist in making coverage decisions and administering benefits.

SCOPE:

X Professional
X Facility

DESCRIPTION:

Thyroid nodules are abnormal growths or lumps that develop in the thyroid gland. Thyroid nodules are present in 5-7% of the U.S. adult population. The vast majority are benign, and most cases of thyroid cancer are curable by surgery if detected early. Fine needle aspiration (FNA) of the thyroid is currently the most accurate procedure to distinguish benign thyroid lesions and malignant ones, reducing the rate of unnecessary thyroid surgery for patients with benign nodules and triaging patients with thyroid cancer to appropriate surgery. Those patients with cytopathology indeterminate nodules are often referred for diagnostic surgery, though most of these nodules turn out to be benign.

Thyroid FNA cytology is classified according to Bethesda System for Reporting Cytopathology: Recommended Diagnostic Categories see below:

The Bethesda System for Reporting Cytopathology: Recommended Diagnostic Categories

Risk Category	Definition	Diagnostics
I	Non-diagnostic 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
II	Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	
IV	Follicular Neoplasm or Suspicious for a Follicular Neoplasm	Specify if Hurthle 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

Various genetic variants have been discovered in thyroid cancer. The 4 gene mutations that are most common and carry the highest impact on tumor diagnosis and prognosis are BRAF and RAS single-nucleotide variants (SNVs) and RET/PTC and PAX8/PPARy rearrangements.

In an attempt to better, identify the need and type of surgical intervention, molecular markers utilizing FNA specimens from the thyroid were developed and include the following tests, but may not be limited to:

Test	Methodology
Afirma GSC (e.g. Afirma Genomic Sequencing Classifier [GSC])	➢ ribonucleic acid (RNA) sequencing technology platform that analyzes thousands of genes at one time to detect alterations
Afirma BRAF	➢ next-generation sequencing (NGS) assay referred to as a malignancy classifier that potentially identifies the presence of BRAF V600E mutations
Afirma Medullary Thyroid Carcinoma (MTC)	➢ gene expression based test that uses specimens obtained via FNA to evaluate over 100 genes to purportedly detect MTC ➢ This assay is also a malignancy classifier and is done alongside or reflexively to Afirma GSC.
Afirma Xpression Atlas (XA)	➢ RNA sequencing test to measure deoxyribonucleic acid (DNA) alterations and RNA fusions in nearly 600 genes possibly linked to thyroid cancer ➢ XA is an add-on test to Afirma GSC.
ThyroSeq Genomic Classifier (GC) (v.3)	➢ next-generation sequencing platform to evaluate DNA and RNA of more than 100 genes linked to thyroid cancer
ThyGeNEXT Thyroid Oncogene Panel (formerly ThyGenX)	➢ DNA and RNA NGS based test that analyzes 10 genes and six RNA fusions supposedly associated with thyroid cancer
ThyraMIR Thyroid miRNA Classifier	➢ microRNA (miRNA) profiling test evaluates the expression of ten miRNAs that may be associated with thyroid cancer ➢ MicroRNA (miRNA) profiling test performed reflexively to ThyGeNEXT.
Multigene panels are performed to identify mutations in a broad set of genes simultaneously (as opposed to single-site gene testing that searches for mutations in one specific gene) and have been proposed for the evaluation of specimens obtained through FNA. Laboratories often offer panels that include genes with established medical management options as well as those without.	
Targeted panels limit the number of genes to those most commonly associated with a condition including thyroid cancer.	
Single-site genetic testing to identify mutations associated with thyroid cancer has been proposed to assist in the reclassification of indeterminate nodules. Genes include, but may not be limited to, BRAF V600E, PAX8/PPARgamma, PIK3CA, RAS (HRAS, KRAS, NRAS).	

POLICY

CPT CODES		Paramount Commercial Insurance Plans	Elite (Medicare Advantage) Plans
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon	**Prior Authorization**	**Prior Authorization Not required**

	cancer, melanoma), gene analysis, V600 variant(s)	**Not required**	
81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)	**Not Covered if used to report REP-PTC testing after Affirma GSC testing (81406) is Not Covered**	**Not Covered if used to report REP-PTC testing after Affirma GSC testing (81406) is Not Covered**
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	**Prior Authorization required**	**Prior Authorization required**
81479	Unlisted molecular pathology procedure	**Prior Authorization required**	**Prior Authorization required**
~~**81545**~~	Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious) Deleted Code Effective 12/31/2020	**Prior Authorization Not required end-dated 12/31/2020**	**Prior Authorization Not required end-dated 12/31/2020**
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) Effective 01/01/2021	**Prior Authorization Not required**	**Prior Authorization Not required**
81599	Unlisted multianalyte assay with algorithmic analysis	**Prior Authorization required**	**Prior Authorization required**
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	**Non-Covered**	**Prior Authorization required**
0026U	Oncology (thyroid), DNA and mRNA of 112 genes, nextgeneration 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")	~~**Non-Covered**~~ **Prior Authorization required Effective 6/1/2022**	**Prior Authorization required**
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	**Non-Covered**	**Non-Covered**

	aspirate, reported as detected or not detected New Code Effective 10/01/2020		
~~**0208U**~~	Oncology (medullary thyroid carcinoma), mRNA, gene expression analysis of 108 genes, utilizing fine needle aspirate, algorithm reported as positive or negative for medullary thyroid carcinoma New Code Effective 10/01/2020	**Prior Authorization required end-dated 01/01/2023**	**Prior Authorization required end-dated 01/01/2023**
0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using nextgeneration sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage New Code Effective 04/01/2021	**Non-Covered**	**Non-Covered**
0362U	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	**Non-Covered**	**Non-Covered**

COVERAGE CRITERIA:

Paramount Commercial Insurance Plans and Elite (Medicare Advantage) Plans

Afirma GSC (e.g. Afirma Genomic Sequencing Classifier [GSC]) (81546)) to assess fine needle aspirates (FNA) of thyroid nodules may be considered medically necessary when ALL of the following criteria are met:

- Patients with one or more 1 cm thyroid nodules on ultrasound with a clinical 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; and
- Presence of indeterminate follicular pathology on fine needle aspiration cytopathology described as:
  - Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) (i.e. Bethesda category III); or
  - Follicular neoplasm or suspicious for a follicular neoplasm (i.e. Bethesda category IV); and
- Surgical decision-making would be affected by test results; and
- The member is not undergoing thyroid surgery for diagnostic confirmation.

The Afirma GSC is reimbursed only once per date of service regardless of the number of nodules submitted for testing.

The Afirma GSC is indicated only once per thyroid nodule per lifetime.

The use of Afirma® Thyroid FNA Analysis is considered not medically necessary for:

- Repeat testing of the same nodule and all other indications not listed above as medically necessary.

- Evaluation of FNA thyroid cytopathology within any of the following Bethesda cytologic categories:
    - Nondiagnostic, unsatisfactory or insufficient samples (ie, Bethesda I)
    - Benign (ie, Bethesda II)
    - Suspicious for malignancy (SFM/SMC) (ie, Bethesda V)
    - Malignant (ie, Bethesda VI)

Afirma Malignancy Classifiers (Afirma MTC) (0208U) and/or Afirma BRAF (81210) be considered medically necessary when the following criteria are met:

- Afirma Malignancy Classifiers, BRAF and MTC (Medullary Thyroid Cancer) are intended to guide surgical decisions when the Afirma Gene Expression Classifier (GEC) result suggests the patient should be considered for surgery:
    - The Afirma BRAF test (detects the BRAF V600E mutation), following Afirma Gene Expression Classifier (GEC) with a result that is suspicious.
    - The Afirma Medullary Thyroid Cancer (MTC) (0208U), in conjunction with the Afirma Gene Expression Classifier (GEC) for indeterminate thyroid FNA cyytopathology or following Afirma Gene Expression Classifier (GEC) with a result that is suspicious or malignant.

The use of ThyroSeq v3 (0026U), ThyraMIR microRNA (0018U) and ThyGeNEXT Thyroid Oncogene Panel (formerly ThyGenX) (81445) to assess fine needle aspirates (FNA) of thyroid nodules may be considered medically necessary when any of the following criteria are met:

- Presence of indeterminate thyroid FNA cytopathology described as:
    - Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) (i.e. Bethesda category III); or
    - Follicular neoplasm or suspicious for a follicular neoplasm (i.e. Bethesda category IV);or
    - Suspicious findings (i.e. Bethesda category V suspicious for malignancy);or
- Thyroid nodule(s) without a strong clinical or radiologic findings suggestive of malignancy; or
    - Nodule growth over time
    - Family history or 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
- In whom surgical decision making would be affected by tests results:
    - Guide surgical planning for initial resection (hemi vs a total thyroidectomy or performance of central neck dissection), rather than a two-stage surgical biopsy followed by definitive surgery.

Additionally, ThyroSeq (0026U) may be considered medically necessary when:

- Thyroid nodules meeting Bethesda diagnostic category III, IV or V (see definitions below) to rule in malignancy to guide surgical planning for initial resection rather than a 2-stage surgical biopsy followed by definitive surgery.

RosettaGX Reveal thyroid MicroRNA test (81479), an assay used for the classification of indeterminate thyroid nodules, will be considered reasonable and necessary when the conditions outlined above for ThyraMIR, THYGENEXT and Affirma are met.

Exclusions:

Paramount has determined that the following Genomic Sequencing Classifier (GSC) genetic variant analysis and molecular marker testing in fine needle aspirates of the thyroid tests are experimental and investigational and therefore non-covered because there is insufficient evidence in the peer-reviewed medical literature of the effectiveness of these procedures, including but not limited to:

- Single-gene TERT (telomerase reverse transcriptase) promoter mutations
- Afirma Xpression Atlas (XA) (0204U)
- REP-PTC testing after Affirma GSC testing (81406)
- Single-site mutational analysis for the evaluation of indeterminate thyroid FNA cytopathology for any gene including, but may not be limited to:

    - PAX8/PPARgamma
    - PIK3CA
    - RAS (HRAS, KRAS, NRAS)
    - These are considered experimental/investigational, as they are not identified as widely used and generally accepted for any other proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.
- NGS mutation analysis of 10 genes, 37 RNA fusions and expression of four mRNA markers (ie, ThyGeNEXT Thyroid Oncogene Panel) (0245U)

CODING/BILLING INFORMATION:
The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

REVISION HISTORY EXPLANATION: ORIGINAL EFFECTIVE DATE: 07/18/2014

Date	Explanation & Changes
07/18/14	• Gene expression tests (e.g., Afirma®) are covered without prior authorization per TAWG review • Policy created per TAWG to reflect most current clinical evidence
11/05/14	• **Removed CPT code 84999 and add CPT code 81479**
04/23/15	• Changed title of policy from Molecular Marker of Thyroid Nodules to Afirma® Thyroid FNA Analysis • Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG)
12/17/15	• Added effective 1/1/16 new code 81545 • Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
03/25/16	• Added effective 1/1/16 new code 81545 • Policy reviewed and updated per TAWG to reflect most current clinical evidence
05/27/16	• Afirma® Thyroid FNA Analysis (81545) now requires prior authorization for all product lines • Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG)
06/24/16	• Afirma® Thyroid FNA Analysis (81545) does not require prior authorization for all product lines • Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG)
03/22/18	• Combined PG0334 ThyroSeq® v.2 Next Generation Sequencing with PG0298 Afirma® Thyroid FNA Analysis • Title changed to Molecular Markers in Fine Needle Aspirates of Thyroid Nodules • Added codes 0018U (ThyraMIR) & 0026U (Thyroseq) as non-covered • Added ThyGenX, ThyraMIR, & RosettaGX tests as non-covered • Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG)
12/19/2020	• Medical policy placed on the new Paramount Medical Policy Format
03/03/2021	• Medical Policy updated/revised to reflect most current clinical evidence/industry standards • Procedure 81546 added to medical policy - replacement - for end-dated procedure 81545
01/23/2023	• Paramount added new 2023 procedure code 0362U – Non-Covered, effective 01/01/2023

	• Paramount updated procedure code 0026U to reflect changes made in medical policy PG0041 previously (covered with prior authorization for HMO, PPO, Individual Marketplace, effective 6/1/2022)
02/20/2023	• Medical Policy updated to reflect Medicaid coverage to Anthem as of 02/01/2023
10/25/2023	• Updated the medical policy to indicate the end-dates of procedures 81545 and 0208U
03/07/2024	• Medical policy placed on the new Paramount Medical Policy Format

Paramount reserves the right to review and revise our policies periodically when necessary. When there is an update, we will publish the most current policy to https://www.paramounthealthcare.com/providers/medical-policies/policy-library

REFERENCES/RESOURCES

Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs

American Medical Association, *Current Procedural Terminology (CPT®)* and associated publications and services https://www.ama-assn.org/amaone/cpt-current-procedural-terminology

Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release and Code Sets https://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/HCPCS-Quarterly-Update

U.S. Preventive Services Task Force, https://www.uspreventiveservicestaskforce.org/uspstf/
Industry Standard Review

Hayes, Inc., https://www.hayesinc.com/

Industry Standard Review