CLINICAL MEDICAL POLICY	
Policy Name:	Molecular Markers for Fine Needle Aspirates of Thyroid Nodules
Policy Number:	MP-065-MD-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	09/01/2024; 09/01/2023; 09/01/2022; 10/15/2021; 09/21/2020; 10/21/2019; 10/01/2018
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Next Annual Review:	07/2025
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Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
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Policy History

Date	Activity
10/01/2024	Provider Effective date
08/07/2024	PARP Approval
07/17/2024	QI/UM Committee review
07/17/2024	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
10/01/2023	Provider Effective date
08/07/2023	PARP Approval
07/19/2023	QI/UM Committee review
07/19/2023	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
10/01/2022	Provider Effective date
08/08/2022	PARP Approval
07/20/2022	QI/UM Committee review
07/20/2022	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections. Removed the following ICD-10 codes: D44.9, & E04.9. Added the following ICD-10 codes: D34, & E04.0. Added the following statement to the 'Coding Requirements' section: "*ICD-10 codes C73 and D44.2 should not be reported for ThyraMIR (0018U), Afirma (81546), Rosetta GX Reveal (81479), ThyGeNEXT (0245U) or ThyroSeq (0026U)"* per CMS guidance.
11/15/2021	Provider Effective date

09/24/2021	PARP Approval
07/21/2021	QI/UM Committee review
07/21/2021	Annual Review: Added ThyraMIR, RosettaGX Reveal, ThyGeNEXT, and BRAF/BRAF V600E to list of covered tests. Revised and reformatted criteria Procedure section 1. Updated medical necessity language. Added 0018U, 81210, 81479, and 0245U to covered CPT codes. Removed non-covered CPT codes section. Added ICD-10 codes E01.0, and E01.1, and E01.2 to covered diagnosis codes. Corrected 00189U to 0018U in operational guidelines. Updated Governing Bodies Approval, Summary of literature, and References.
10/19/2020	Provider effective date
09/02/2020	PARP approval
07/15/2020	QI/UM Committee review
07/15/2020	Annual Review: Formatting changes; no clinical criteria changes, under #3, add noncoverage for the Afirma Xpression Atlas; updated Operational Guidelines, Summary of Literature and Reference sections.
07/13/2017	Initial policy developed

Disclaimer

Highmark Wholecare℠ medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

Policy Statement

Highmark Wholecare℠ may provide coverage under the medical-surgical benefits of the Company's Medicaid products for medically necessary gene expression classifier for molecular marker evaluation of fine-needle aspirates of thyroid nodules.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

(Current applicable Pennsylvania HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

Definitions

Prior Authorization Review Panel (PARP) – A panel of representatives from within the PA Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

Thyroid Nodule – An abnormal growth of thyroid cells which form a lump within the thyroid. Most nodules are benign with approximately 5% being cancerous.

Fine Needle (FN) Aspiration (FNA) – A minor procedure performed in the provider's office to obtain tissue samples in order to determine if a thyroid nodule is benign or cancerous.

Molecular Markers – Genes and microRNAs that are expressed in benign and cancerous cells. Results can determine if the thyroid biopsy specimen is benign or cancerous.

BRAF Gene – This gene codes for a protein that is involved in signaling pathway and cell growth. BRAF gene mutation in adults appears to cause cancer.

RAS – The RAS family of genes that make proteins involved in cell communication pathways, cell growth, and cell death.

RET/PTC – The RET proto-oncogene encodes receptor tyrosine kinases, which are cell-surface molecules that transduce signals for cell growth and differentiation.

PAX8/PPAR*y* – A gene fusion which appears to be an oncogene. It is most often expressed in follicular carcinomas.

Atypia of Undetermined Significance (AUS) – One of the Bethesda System six category diagnostic categories for reporting thyroid cytopathology indicating an estimated risk of 5% to 15% for malignancy.

Follicular Lesion of Undetermined Significance (FLUS) – One of the Bethesda System category diagnostic categories for reporting thyroid cytopathology indicating an estimated risk of 15% to 30% for malignancy.

Gene Expression Classifiers (GEC) – A variety of laboratory tests that analyze DNA, RNA, genes or gene products for the purpose of diagnosing disease, assisting in treatment decisions, predicting future disease, or identifying carriers of disease.

Procedures

Molecular testing should be used to complement, not replace, cytopathologic evaluation or clinical and imaging assessment. In addition, molecular testing is not recommended in patient situations when the results are not expected to alter the decision to proceed with surgery or the extent of surgery.

1. The use of Afirma Gene Expression Classifier, ThyraMIR, Rosetta GX Reveal, ThyGeNEXT, ThyroSeq v3, or BRAF/BRAF V600E for molecular marker evaluation of FNA of a thyroid nodule may be considered medically necessary when ALL of the following criteria are met:
    A. The individual is 18 years or older; AND
    B. The FNA pathology report must indicate that there is a cytological diagnosis of AUS (nuclear atypia)/FLUS (microfollicular); (Bethesda diagnostic category III), follicular neoplasm or suspicious for follicular neoplasm (Bethesda diagnostic category IV); AND
    C. ANY ONE of the following exists:
        a. The specimen for molecular analysis is collected at the same time the initial FNA for cytology is performed; OR
        b. FNA results of AUS; OR
        c. FNA results of FLUS or follicular neoplasm with normal or high TSH; OR

d. FNA results of FLUS or follicular neoplasm with low TSH and non-functioning or indeterminate on radionuclide scanning.

Note: A second FNA for molecular analysis may be considered after an 'indeterminate' cytology diagnosis is received.

2. Contraindications
   There are no known contraindications for molecular markers in thyroid cancer.

3. Molecular markers for thyroid cancer are considered not medically necessary for conditions other than those listed above because scientific evidence has not been established. Examples include, but are not limited to, any of the following:
   - Repeat gene expression classifier testing
   - Molecular diagnostics are not recommended for Hürthle cell neoplasm
   - Current molecular diagnostics has not been validated in the pediatric population
   - Afirma Xpression Atlas is not recommended due to lower testing specificity for prognostication

4. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Wholecare℠ at any time pursuant to the terms of your provider agreement.

5. Place of Service
   The proper place of service for molecular marker testing in thyroid cancer is the outpatient setting.

6. Related Policies
   - MP-010-MD-PA Testing for Genetic Disease
   - MP-062-MD-PA BRAF Mutation Analysis
   - MP-074-MD-PA Oncologic Genetic Testing Panels

Governing Bodies Approval

There are several commercially available panels of molecular markers utilizing FNA specimens from the thyroid that include miRInform™ (Asuragen) and Veracyte® (Afirma). These tests are offered as laboratory-developed tests under Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of CLIA and must be licensed by CLIA for high complexity testing.

CMS
The Centers for Medicare and Medicaid Services (CMS) has issued the following guidance:
- Local Coverage Determination (LCD) Biomarkers for Oncology (L35396). The guidance offers coverage decisions for Afirma, ThyraMIR, ThyGeNEXT, RosettaGX Reveal, and ThyroSeq.
- Local Coverage Article (LCA) Billing and Coding: Biomarkers for Oncology (A52986)

Summary of Literature

Approximately 44,020 Americans were diagnosed with thyroid cancer in 2023. Until recently, the rate of new thyroid cancers was rising, largely due to increased detection during imaging tests such as CT or MRI scans that were performed for other medical problems. These sensitive tests can sometimes detect small thyroid nodules that may not have been found otherwise. Due in part to adoption of more stringent criteria to diagnose thyroid cancer, the incidence rate has declined by about 2% each year since 2014 (American Cancer Society, 2024).

Fine-needle aspiration is a minimally invasive way to obtain a cell sample to confirm a diagnosis or guide treatment. Fine-needle aspiration is an alternative to more invasive methods such as incisional or excisional biopsy. It is most commonly used to biopsy newly identified masses in the breast, the thyroid, suspicious lymph nodes, or suspicious skin masses. If the area to undergo fine-needle aspiration is superficial and palpable, then once the area is sterilized, simply inserting the needle into the lesion while gently aspirating is all that is necessary. If the lesion is not palpable, then ultrasound guidance should ensure an appropriate sample is taken. Even if the lesion is palpable, ultrasound can be useful to guide the needle. CT-guided fine-needle aspiration may be performed similarly except under CT guidance (Sigmon, Fatima, 2022).

One way to diagnosis thyroid cancers is by FNA biopsy of the thyroid nodule. FNA is considered the gold standard for preoperative differential diagnosis of thyroid nodules. According to the National Comprehensive Cancer Network (NCCN) guidelines, FNA with ultrasound guidance is the procedure of choice for evaluating suspicious thyroid nodules. If the FNA biopsy does not clearly identify a diagnosis, the biopsy sample can be classified cytologically for mutation analysis by molecular marker testing. The goal of molecular marker testing in thyroid cancer is to accurately assess a thyroid nodule as being benign or malignant prior to surgery. At this time, this testing is not to take the place of clinical and ultrasound assessment (NCCN, 2024).

The Society of Radiologists in Ultrasound (SRU) published a consensus which focused on the management of thyroid nodules identified by ultrasonography The SRU recommendations indicate the particular types of thyroid nodules that should undergo FNA based on nodule size and ultrasound characteristics. These guidelines attempted to define recommendations for nodules that should and should not undergo ultrasound-guided fine-needle aspiration (FNA). The SRU recommendations assert that FNA is appropriate for nodules that are 10 mm or larger and have microcalcifications, nodules that are 15 mm or larger and are solid or have coarse calcifications, nodules that are 20 mm or larger and are mixed solid and cystic, and nodules with substantial growth since the prior ultrasound study. Despite the guidelines, the number of thyroid nodules undergoing ultrasound-guided FNA has continued to increase because more thyroid nodules undergo biopsy as a result of fear of missing a malignancy (Hobbs, Bahl, Nelson, Eastwood, et al., 2014).

The American Thyroid Association (Ferris, 2015) published a Statement on Surgical Application of Molecular Profiling for Thyroid Nodules: Current Impact on Perioperative Decision Making and reported the following:
“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. For example, a ''rule out'' test such as the gene expression classifier

(GEC) will perform better in a setting of lower cancer frequency, as well as in a cytologic category of low cancer frequency such as AUS/FLUS or FN, than it will in a setting of higher cancer frequency such as suspicious for malignant cells (SMC) or a site with a high prevalence of malignancy in a given cytologic category."

The American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi (AACE/ACE/AME) 2016 Clinical Practice Guidelines for the Diagnosis and Management of Thyroid Nodules state the following: "In nodules with indeterminate cytologic results, no single cytochemical or genetic marker is specific or sensitive enough to rule out malignancy with certainty. However, the use of immunohistochemical and molecular markers may be considered together with the cytologic subcategories and data from US (ultrasound), elastography, or other imaging techniques to obtain additional information for management of these patients."

When an FNA is positive in diagnosing thyroid cancer, the cancer will almost always be papillary cancer. The other possible biopsy outcomes of FNA are negative results, "indeterminate" results, or non-diagnostic results. Observation and follow-up may be considered for patients with negative results to ensure nodule stability. If an FNA biopsy result is found to be "indeterminate," it is commonly reported as "follicular neoplasm." If a follicular neoplasm is benign, it is called a follicular adenoma. If the follicular neoplasm is cancer, it is called a follicular carcinoma (Faust, 2016).

Follicular cell and Hurthle cell cancers are two different types of cancer, but they are often considered in the same category. A Hurthle cell is a kind of thyroid cell that has a distinctive look; appearing to be bigger than a follicular cell with pink staining cellular material. Hurthle cell cancer and follicular thyroid cancer are often inappropriately lumped together, and some of the differences include:

- Hurthle cell cancers are much rarer than thyroid malignancies.
- Hurthle cell cancers more commonly spread to neck lymph nodes.
- Hurthle cell cancers have a higher risk of spreading to distant sites in the body.
- Hurthle cell cancers produce the marker of thyroid cancers, thyroglobulin, more than follicular thyroid cancers (both produce, but the amounts are increased).
- Hurthle cell cancers tend to occur in later decades of life.
- Radioactive iodine may be less effective against Hurthle cell cancers. (Clayman Thyroid Cancer Center, 2018).

Molecular testing aids have been studied in the management of thyroid nodules with indeterminate cytopathology in adults. However, this diagnostic approach has not yet been validated in pediatric patients (Francis et al., 2015). Gene Expression classifiers have been validated to corroborate a benign diagnosis in adults with indeterminate nodules, and there are no studies determining its usefulness in the evaluation of the indeterminate pediatric thyroid nodule (Francis et al., 2015).

Three approaches for the molecular characterization of FNA aspirates available in the United States include:

- Identification of particular molecular markers of malignancy, such as BRAF and RAS mutational status
- Use of high-density genomic data for molecular classification (a genomic sequencing classifier)
- Use of an FNA-trained miRNA classifier combined with molecular markers of malignancy

ThyroSeq v3
The ThyroSeq v3 molecular marker test is utilized in thyroid nodules with an undetermined cytology. This test is a next generation sequencing panel that sequences 112 genes used in individuals with follicular neoplasm and/or suspicious neoplasm on FNA. This test has been reported to have the best negative predictive value (NPPV) and positive predictive value combined. It can be used to rule in or rule out thyroid cancer. One prospective cohort multicenter study (Steward et al, 2017) reported the test was able to produce negative predictive value of 97%, positive predictive value of 66%, with 94% sensitivity and 82% specificity in 286 samples. Three percent of the samples were found to be false-negatives but all were found to be low-risk follicular carcinoma tumors, without vascular invasion.

ThyGenX and ThyraMIR
ThyGenX is a genetic alteration mutational panel used for the detection of eight genes associated with thyroid papillary and follicular cancer. ThyraMIR testing is a microRNA (miRNA) gene expression classifier that evaluates 10 miRNAs. The ThyGenX and the ThyraMIR tests are designed to reduce the need for surgery in thyroid nodule biopsies are indeterminate. The tests are marketed to be used in combination since the ThyraMIR can identify malignancy when the ThyGenX has a negative result.

Rosetta GX Reveal
The Rosetta GX Reveal is performed from on a slide of the initial FNA biopsy and measures a set of miRNAs to distinguish benign from malignant thyroid nodules. A recent study reported on the additional evidence on the validity of this diagnostic assay (Lithwick, 2017). The authors concluded that initial results are promising, however, 'additional cohorts, both academic and nonacademic, could help to further validate the performance of the assay.'

The Afirma Gene Expression Classifier utilizes a proprietary classifier which categorizes nodules as either benign or suspicious. The Afirma analyzes the expression of 142 different genes to determine patterns associated with benign findings on surgical biopsy. ThyGenX™ (formerly known as miRInform) is an oncogene panel of eight analytically validated molecular markers associated with papillary thyroid carcinoma and follicular thyroid carcinoma. This testing is an example of next generation sequencing.

The utility of molecular testing options for thyroid nodules with indeterminate FNA findings was reported as helpful in stratification and triage of patients (Rossi, Pantanowitz & Faquin, 2019). Each test that is currently available has different advantages and limitations (Afirma, ThyroSeqv.3, and ThyGenX/ThyroMIR). As these tests continue to improve making them more accurate and less expensive, the testing will continue to become a more integral part of thyroid nodule evaluation.

The NCCN Thyroid Carcinoma guideline states:

- Fine-needle aspiration (FNA) with ultrasound guidance is the procedure of choice for evaluating suspicious thyroid nodules. Data show that higher thyroid-stimulating hormone (TSH) levels are associated with an increased risk for differentiated thyroid carcinoma in patients with thyroid nodules, although TSH and thyroglobulin (Tg) do not appear to be useful for screening for thyroid cancer.
- Although FNA is a very sensitive test— particularly for papillary carcinoma—false-negative results are sometimes obtained; therefore, a reassuring FNA should not override worrisome clinical or radiographic findings.
- The choice of the precise molecular test depends on the cytology and the clinical question being asked. Indeterminate groups include: 1) follicular or oncolytic neoplasms (Bethesda IV); and 2)

AUS/FLUS (Bethesda III). The NCCN Panel recommends consideration of molecular diagnostic testing for these indeterminate groups (NCCN, 2024).

NCCN also noted that molecular diagnostics do not perform well for Hurthle Cell neoplasms, and often resulted in unnecessary surgery.

Rationale
Yang and colleagues (2016) completed a retrospective analysis from a single institution that performed the Afirma GEC test from August 24, 2012, through April 1, 2014. The study reviewed cases with indeterminate cytology that had Afirma GEC testing and compared the results with histopathology findings with previously published data from the study institution before implementation of GEC testing. A total of 217 cases had GEC testing completed, and 189 were reported as indeterminate cytology. Of the indeterminate cytology cases, 42% were benign and 50% were suspicious by GEC test results. The rate of excision of the undetermined significance and follicular lesion in the pre-GEC category was 63% with the rate decreasing to 47% in the post-GEC category. The malignancy rate of excised thyroids increased from 35% in the pre-GEC group to 47% in the post-GEC category. It was noted that the findings were similar for lesions suspicious for a follicular neoplasm and follicular neoplasm lesion. The authors concluded that the strength of the GEC test appears to lie in its ability to reclassify 42% of indeterminate cytology cases as benign, thereby decreasing the number of unnecessary surgical procedures.

A review on the evaluation and management of thyroid nodules with indeterminate cytology was performed. This review indicated that for patients with a cytologic result showing FLUS/AUS or follicular neoplasm further evaluation of FNA aspirates for molecular markers using either mutational analysis (using a broad next-generation assay with an expanded panel of point mutations and gene fusions), an mRNA classifier system (genomic sequencing classifier), or micro mRNA (miRNA) combined with mutational analysis (Douglas, 2018).

Coding Requirements

Procedure Codes

CPT Code	Description
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81479	Unlisted molecular pathology procedure (ThyGenX)
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)
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)
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 v3 Genomic Classifier)
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)

Diagnosis Codes

ICD-10 Code	Description
C73*	Malignant neoplasm of thyroid gland
D34	Benign neoplasm of thyroid gland
D44.0	Neoplasm of uncertain behavior of thyroid gland
D44.2*	Neoplasm of uncertain behavior of parathyroid gland
E01.0	Iodine-deficiency related diffuse (endemic) goiter
E01.1	Iodine-deficiency related multinodular (endemic) goiter
E01.2	Iodine-deficiency related (endemic) goiter, unspecified
E04.0	Nontoxic diffuse goiter
E04.1	Nontoxic single thyroid nodule
E04.2	Nontoxic multinodular goiter
E04.8	Other specified nontoxic goiter
Z92.3	Personal history of irradiation

* **Note**: ICD-10 codes C73 and D44.2 should not be reported for ThyraMIR (0018U), Afirma (81546), Rosetta GX Reveal (81479), ThyGeNEXT (0245U) or ThyroSeq (0026U).

Informational

Bethesda System for Reporting Thyroid Cytopathology

Diagnostic Category	Risk of Cancer	Usual Management
I. Nondiagnostic or Unsatisfactory	1-4%	Repeat FNA with US
II. Benign	0-3%	Clinical follow up
III. Atypia or Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)	5-15%	Repeat FNA
IV. Follicular Neoplasm or Suspicious for Follicular Neoplasm (FN/SFN)	15-30%	Surgical lobectomy
V. Suspicious for Malignancy	60-75%	Total or lobectomy
VI. Malignant	97-99%	Total thyroidectomy

Baloch ZW et al. Diagn Cytopathol 2008; 36:425
Cibas ES & Ali SZ. Am J Clin Pathol 2009; 132:658

Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

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