CLINICAL MEDICAL POLICY	
Policy Name:	Molecular Markers for Fine Needle Aspirates of Thyroid Nodules
Policy Number:	MP-065-MD-DE
Approved By:	Medical Management
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Products:	Delaware Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 9

DISCLAIMER

Delaware Highmark Health Options 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 Health Options 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.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

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 gene expression classifier (e.g., Afirma gene expression or ThyroSeq v3) for molecular marker evaluation of a thyroid nodule is considered medically necessary when the following criteria are met:
    A. Patients aged 18 years and older; AND
    B. Patient must have one or more thyroid nodules with a history or characteristics suggestive of malignancy (e.g., family history of thyroid cancer, hoarseness and/or difficulty swallowing or breathing, thyroid nodule growth, history of ionizing radiation, presence of cervical adenopathy; AND
    C. Thyroid nodules 1 cm or larger; AND
    D. In patients whom surgical decision making would be affected by test results; AND
    E. The specimen for molecular analysis is collected at the same time the initial FNA for cytology is performed; AND

F. The FNA pathology report must indicate that there is a cytological diagnosis of AUS/FLUS (Bethesda diagnostic category III), follicular neoplasm or suspicious for follicular neoplasm (Bethesda diagnostic category IV)

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

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

3. When the molecular marker services are not covered
   - Molecular markers for thyroid cancer are not covered and are not medically necessary for conditions other than those listed above because the scientific evidence has not been established. Non-covered tests include but are not limited to any of the following: Molecular diagnostics are not recommended for Hürthle cell neoplasm.
   - Current molecular diagnostics has not been validated in the pediatric population.
   - Repeat gene expression classifier testing is not medically necessary.
   - The Rosetta GX Reveal molecular marker is not covered in the evaluation of thyroid nodules.

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

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

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.

Novitas Solutions
LCD L35396-Biomarkers for Oncology, effective 4/4/2019 lists the following covered thyroid molecular testing:

- BRAF - DX + PRED
- KRAS - PRED for Selumetinib
- HRAS - PRED for Selumetinib
- NRAS - PRED for Selumetinib
- PIK3CA – PRED
- RET – DX
- PAX8/PPARG- DX

ThyraMIR Thyroid (CPT 81479) miRNA classifier (aPCR based microRNA gene expression classifier) (PRED) evaluates the expression levels of 10miRNA genes within an FNA biopsy: miR-29b-1-5p, miR-31-5p, miR-138-1-3p, miR-139-5p, miR-146b-5p, miR-155, miR-204-5p, miR-222-3p, miR-375, and miR-551b-3p.

CPT code 81545, oncology Thyroid, provides gene expression analysis of 142 genes utilizing fine needle aspirate, algorithm reported as a categorical result. (Afirma - PRED).

ThyraMIR is used as a companion test to ThyGenX when ThyGenX results are inconclusive.

ThyraMIR, ThyGenX (CPT 81445) and Afirma services will be considered reasonable and necessary for patients with any of the following conditions:

- An indeterminate pathology on fine needle aspiration
- Patients with one or more thyroid nodules with a 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

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

ThyroSeq is a test utilized to better define the need for thyroid surgery and the type of such surgery. ThyroSeq will be considered reasonable and necessary when the conditions outlined above for ThyraMir, ThyGenX and Afirma are met.

CODING REQUIREMENTS

Procedure Codes

CPT Codes	Description
81545	Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (e.g., benign or suspicious)
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)

Noncovered Codes

CPT Codes	Description
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)
81479	Unlisted molecular pathology procedure (ThyGenX)

Diagnosis Codes

ICD-10 Codes	Description
C73	Malignant neoplasm of thyroid gland
D44.0	Neoplasm of uncertain behavior of thyroid gland
D44.9	Neoplasm of uncertain behavior of unspecified endocrine gland
E04.1	Nontoxic single thyroid nodule
E04.2	Nontoxic multinodular goiter
E04.8	Other specified nontoxic goiter
E04.9	Nontoxic goiter, unspecified
Z92.3	Personal history of irradiation

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

SUMMARY OF LITERATURE

Thyroid nodules are a very common occurrence and are present in 5% to 7% of the adult population in the United States. Most thyroid nodules are benign, and those that are cancerous are curable when detected early.

According to the American Cancer Society (2017), the most recent estimates for thyroid cancer are:

- About 56,870 new cases of thyroid cancer (42,470 in women and 14,400 in men)
- Approximately 2,010 deaths from thyroid cancer (1,090 women and 920 men)

The chance of being diagnosed with thyroid cancer has risen in recent years and is the most rapidly increasing cancer in the United States, tripling in the past three decades. The rise in occurrence appears to be the result of the increased use of thyroid ultrasound which can detect small thyroid nodules that might not have been found in the past.

The actual diagnosis of thyroid cancer is made by fine needle aspiration biopsy of the thyroid nodule. Fine needle aspiration is the gold standard for preoperative differential diagnosis of 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.

The most common cancer types are papillary and follicular carcinoma. The four most common gene mutation in thyroid cancer include BRAF, RAS point mutations, RET/PTC, and PAX8/PPAR*y* rearrangements (Nikiforov 2011). Papillary carcinomas have point mutations of the BRAF and RAS genes, RET/PTC and TRK rearrangements. These mutations are found in more than 70% of papillary carcinomas. Follicular cancers have either RAS mutations or PAX8/PPAR*y* rearrangements.

There are two methods for FNA analysis available: identification of molecular markers of malignancy, such as BRAF and RAS mutational status and the use of a gene expresser classifier, such as the Afirma Thyroid FNA Analysis. Point mutations in specific genes, including BRAF, RAS, and RET and evaluation for rearrangements associated with thyroid cancer can be accomplished by gene sequencing.

The American Thyroid Association (Ferris, 2015) also published a *Statement on Surgical Application of Molecular Profiling for Thyroid Nodules: Current Impact on Perioperative Decision Making* and reported:

> *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 Afirma 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.

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.
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).

Update 2019
A review on the evaluation and management of thyroid nodules with indeterminate cytology was performed (Douglas 2018). 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.

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 () 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.'

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

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POLICY SOURCE(S)

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Policy History

Date	Activity
07/13/2017	Initial policy developed
12/12/2017	QI/UM Committee approval
02/15/2018	Provider effective date
09/11/2018	Annual Review: Updated procedure section 1.D.; Removed the word 'Covered' from the procedure and diagnosis code tables in Attachments B & C; reformatted noncovered section #3; Updated the summary of literature; updated references to include new references and edit existing references. Removed the hyperlinks from all references.
09/11/2018	QI/UM Committee Review Approval
11/15/2018	Provider effective date
09/10/2019	Annual Review: under Procedures added examples of gene expression classifiers in #1, 1.B included additional examples of symptoms, 1.F. added Bethesda Diagnosis categories; updated the noncovered section on repeat molecular testing; under Government Approvals added Novitas Solutions LCD coverage criteria; created noncovered procedure code section for 0018U & 81479, revised diagnosis codes- added C73 & Z92.3, deleted D34, E01.0-E01.2 & E04.0; updated Reference Sources. Added CPT code 0026U as an eligible service.
09/10/2019	QI/UM Committee Review Approval
11/04/2019	Provider Effective Date