DRAFT Medical Coverage Policy | Molecular Markers in Fine Needle Aspirates of the Thyroid

EFFECTIVE DATE: 07|01|2017
POLICY LAST UPDATED: 06|01|2020

OVERVIEW

To determine which patients need thyroid resection, many physicians will perform a cytologic examination of fine needle aspirate (FNA) samples from a thyroid lesion; however, this method has diagnostic limitations. As a result, assays using molecular markers have been developed to improve the accuracy of thyroid FNA biopsies.

The following tests are addressed in this policy:
Afirma (Veracyte)
ThyraMIR (Interspace Diagnostics)
ThyGeNEXT (Interspace Diagnostics)
RosettaGX Reveal (Rosetta Genomics)
ThyroSeq (CBL Path)

MEDICAL CRITERIA

BlueCHiP for Medicare and Commercial Products

Afirma – CPT 81545

The Afirma assay may be considered medically necessary for patients with the following conditions (patients must have 1 *and* 2):

1. 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
2. Have an indeterminate follicular pathology on fine needle aspiration

Afirma BRAF and Afirma MTC are medically necessary after a positive Afirma Genomic Sequencing Classifier.

ThyraMIR – CPT 0018U
ThyGenX – CPT 81445
RosettaGX Reveal thyroid MicroRNA test (Unlisted CPT)

ThyraMIR, ThyGeNEXT and RosettaGX Reveal services may 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

ThyroSeq – 0026U
The use of ThyroSeq in fine needle aspirates of thyroid nodules with indeterminate or suspicious cytologic findings (see definitions below) may be considered medically necessary in patients who meet the following:

- 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.

Definitions
Indeterminate cytologic findings

- Bethesda diagnostic category III: atypia/follicular lesion of undetermined significance
- Bethesda diagnostic category IV: follicular neoplasm/suspicion for a follicular neoplasm

Suspicious findings

- Bethesda diagnostic category V: suspicious for malignancy

PRIOR AUTHORIZATION

BlueCHiP for Medicare and Commercial Products
Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial Products. Prior authorization is obtained via the online tool for participating providers. See the Related Policies section.

There is no specific CPT coding for some of the services referenced in this policy. Therefore, an Unlisted CPT code should be used (see Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial Products and is obtained via the online tool for participating providers. See the Related Policies section.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

BlueCHiP for Medicare and Commercial Products
The molecular markers in fine needle aspirates of the thyroid addressed in this policy may be considered medically necessary when the medical criteria above has been met.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for limitations of benefits/coverage for laboratory tests or when services are not medically necessary.

BACKGROUND

Thyroid nodules are common, present in 5% to 7% of the U.S. adult population. Most are benign, and most cases of thyroid cancer are curable by surgery when detected early.

Diagnosis

Sampling thyroid cells by fine needle aspirate (FNA) 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.

About 60% to 70% of thyroid nodules are classified cytologically as benign, and 4% to 10% of nodules are cytologically deemed malignant. However, the remaining 20% to 30% have equivocal findings usually due to overlapping cytologic features between benign and malignant nodules; these nodules usually require surgery for a final diagnosis. Thyroid FNA cytology is classified by Bethesda System criteria into the following groups: nondiagnostic; benign; follicular lesion of undetermined significance (FLUS) or atypia of undetermined significance (AUS); follicular neoplasm (or suspicious for follicular neoplasm); suspicious for malignancy; and malignant. Lesions with FNA cytology in the AUS or FLUS or follicular neoplasm categories are often considered indeterminate.

Management

There is some individualization of management for patients with FNA-indeterminate nodules, but many patients will require a surgical biopsy, typically thyroid lobectomy, with intraoperative pathology. Consultation would typically be the next step in diagnosis. Approximately 80% of patients with indeterminate cytology undergo surgical resection; postoperative evaluation has revealed a malignancy rate ranging from 6% to 30%, making this a clinical process with very low specificity. Thus, if analysis of FNA samples could reliably identify the risk of malignancy as low, there is potential for patients to avoid surgical biopsy.

Preoperative planning of optimal surgical management in patients with equivocal cytologic results is challenging, because different thyroid malignancies require different surgical procedures (eg, unilateral lobectomy vs total or subtotal thyroidectomy with or without lymph node dissection) depending on several factors, including histologic subtype and risk-stratification strategies (tumor size, patient age). If a diagnosis cannot be made intraoperatively, a lobectomy is typically performed, and, if on postoperative histology the lesion is malignant, a second surgical intervention may be necessary for completion thyroidectomy.

Thyroid Cancer

Most thyroid cancers originate from thyroid follicular cells and include well-differentiated papillary thyroid carcinoma (PTC; 80% of all thyroid cancers) and follicular carcinoma (15%). Poorly differentiated and anaplastic thyroid carcinomas are uncommon and can arise de novo or from preexisting well differentiated papillary or follicular carcinomas. Medullary thyroid carcinoma originates from parafollicular or C cells and accounts for about 3% of all thyroid cancers.

The diagnosis of malignancy in the case of PTC is primarily based on cytologic features. If FNA in a case of PTC is indeterminate, surgical biopsy with intraoperative pathology consultation is most often diagnostic, although its efficacy and therefore its use will vary across institutions, surgeons, and pathologists. In 2016, reclassification of encapsulated follicular-variant PTC as a noninvasive follicular tumor with papillary-like nuclei was proposed and largely adopted; this classification removes the word carcinoma from the diagnosis to acknowledge the indolent behavior of these tumors.

For follicular carcinoma, the presence of invasion of the tumor capsule or of blood vessels is diagnostic and cannot be determined by cytology, because tissue sampling is necessary to observe these histologic characteristics. Intraoperative diagnosis of follicular carcinoma is challenging and often not feasible because

extensive sampling of the tumor and capsule is usually necessary and performed on postoperative permanent sections.

New approaches for improving the diagnostic accuracy of thyroid FNA include variant analysis for somatic genetic alterations, to more accurately classify which patients need to proceed to surgery (and may include the extent of surgery necessary), and a gene expression classifier to identify patients who do not need surgery and can be safely followed.

Genetic Variants Associated with Thyroid Cancer
A number of genetic variants have been discovered in thyroid cancer. The most common four gene variants are BRAF and RAS single nucleotide variants (SNVs) and RET/PTC and PAX8/PPARγ rearrangements.

Papillary carcinomas carry SNVs of the BRAF and RAS genes, as well as RET/PTC and TRK rearrangements, all of which can activate the mitogen-activated protein kinase pathway. These mutually exclusive variants are found in more than 70% of papillary carcinomas.4,BRAF SNVs are highly specific for PTC. Follicular carcinomas harbor either RAS SNVs or PAX8/PPARγ rearrangements. These variants have been identified in 70% to 75% of follicular carcinomas. Genetic alterations involving the PI3K/AKT signaling pathway also occur in thyroid tumors, although they are rare in well-differentiated thyroid cancers and have a higher prevalence in less differentiated thyroid carcinomas. Additional variants known to occur in poorly differentiated and anaplastic carcinomas involve the TP53 and CTNNB1 genes. Medullary carcinomas, which can be familial or sporadic, frequently possess SNVs located in the RET gene.

Studies have evaluated the association between various genes and cancer phenotype in individuals with diagnosed thyroid cancer.

Molecular Diagnostic Testing
Variant Detection and Rearrangement Testing
SNVs in specific genes, including BRAF, RAS, and RET, and evaluation for rearrangements associated with thyroid cancers can be accomplished with Sanger sequencing or pyrosequencing or with real-time polymerase chain reaction (PCR) of single or multiple genes or by next-generation sequencing (NGS) panels. Panel tests for genes associated with thyroid cancer, with varying compositions, are also available. For example, Quest Diagnostics offers a Thyroid Cancer Mutation Panel, which includes BRAF and RAS variant analysis and testing for RET/PTC and PAX8/PPARγ rearrangements.

The ThyroSeq v3 Next-Generation Sequencing panel (CBLPath) is an NGS panel of 112 genes. According to the CBLPath's website, the test is indicated when FNA cytology suggests atypia of uncertain significance or follicular lesion of undetermined significance, follicular neoplasm or suspicious for follicular neoplasm, or suspicious for malignancy. In particular, it has been evaluated in patients with follicular neoplasm and/or suspicious for follicular neoplasm on FNA as a test to increase both sensitivity and specificity for cancer diagnosis. ThyGenX is an NGS panel that sequences eight genes and identifies specific gene variants and translocations associated with thyroid cancer. ThyGenX is intended to be used in conjunction with the ThyraMIR microRNA expression test when the initial ThyGenX test is negative.

Gene Expression Profiling
Genetic alterations associated with thyroid cancer can be assessed using gene expression profiling, which refers to the analysis of messenger RNA (mRNA) expression levels of many genes simultaneously. Several gene expression profiling tests are available and stratify tissue from thyroid nodules biologically.

The Afirma Gene Expression Classifier (Afirma GEC; Veracyte) analyzed the expression of 142 different genes to determine patterns associated with benign findings on surgical biopsy. It was designed to evaluate thyroid nodules that have an "indeterminate" classification on FNA as a method to select patients ("rule out") who are at low-risk for cancer. In 2017, Veracyte migrated the Afirma GEC microarray analysis to a next-generation RNA sequencing platform and now markets the Afirma Gene Sequencing Classifier (Afirma GSC) which evaluates 10196 genes with 1115 core genes.

Other gene expression profiles have been reported in investigational settings, but have not been widely validated or used commercially (eg, Barros-Filho et al [2015], Zheng et al [2015]); they are not addressed in this review.

ThyraMIR is a microRNA expression-based classifier intended for use in thyroid nodules with indeterminate cytology on FNA following a negative result from the ThyGenX Thyroid Oncogene Panel.

Algorithmic Testing
Algorithmic testing involves the use of two or more tests in a prespecified sequence, with a subsequent test automatically obtained depending on results of an earlier test.

Algorithmic Testing Using Afirma GEC With Afirma MTC and Afirma BRAF
In addition to Afirma GSC , Veracyte also markets two "malignancy classifiers" that use mRNA expression-based classification to evaluate for BRAF variants (Afirma BRAF) or variants associated with medullary thyroid carcinoma (Afirma MTC).

In a description of the Afirma BRAF test, the following have been proposed as benefits of the mRNA-based expression test for BRAF variants: (1) PCR-based methods may have low sensitivity, requiring that a large proportion of the nodule have a relevant variant; (2) testing for only one variant may not detect patients with low-frequency variants that result in the same pattern of pathway activation; and (3) PCR-based approaches with high analytic sensitivity may require a large amount of DNA that is difficult to isolate from small FNA samples.

The testing strategy for both Afirma MTC and Afirma BRAF is to predict malignancy from an FNA sample with increased pretest probability for malignancy. A positive result with Afirma MTC or Afirma BRAF would inform preoperative planning such as planning for a hemi- vs a total thyroidectomy or performance of central neck dissection.

Algorithmic Testing Using ThyGenX and ThyraMIR
The ThyGenX Thyroid Oncogene Panel (Interpace Diagnostics; testing is done at Asuragen Clinical Laboratory) is an NGS panel designed to assess patients with indeterminate thyroid FNA results. It includes sequencing of eight genes associated with PTC and follicular carcinomas. ThyGenX has replaced the predicate miRInform Thyroid test that assesses for 17 validated gene alterations.

ThyraMIR (Interpace Diagnostics) is a microRNA expression-based classifier intended for use in thyroid nodules with indeterminate cytology on FNA following a negative result from the ThyGenX Thyroid Oncogene Panel.

The testing strategy for combined ThyGenX and ThyraMIR testing is first to predict malignancy. A positive result on ThyGenX would "rule in" patients for surgical resection. The specific testing results from a ThyGenX positive test would be used to inform preoperative planning when positive. For a ThyGenX negative result, the reflex testing involves the ThyraMIR microRNA expression test to "rule out" for a surgical biopsy procedure given the high negative predictive value of the second test. Patients with a negative result from the ThyraMIR test would be followed with active surveillance and avoid a surgical biopsy.

CODING
The following CPT codes are covered for BlueCHiP for Medicare and Commercial products when medical criteria above are met.

CPT Code	Brand Name	Code Description
81445	ThyGeNEXT®	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
81545	Afirma®	Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)
0018U	ThyraMIR™	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
0026U	ThyroSeq	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")

Specific CPT codes have not been assigned for all testing referenced in this policy. In these cases, claims should be filed using an unlisted code.

RELATED POLICIES

Genetic Testing Services
Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update, April 2020
Provider Update, May 2017
Provider Update, January 2017
Provider Update, January 2016

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