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OVERVIEW

Cytologic examination of fine needle aspirate (FNA) samples from a thyroid lesion to identify which patients need thyroid resection has diagnostic limitations. Assays using molecular markers have been developed in an attempt to improve the accuracy of thyroid FNA biopsies.

MEDICAL CRITERIA

BlueCHiP for Medicare and Commercial Products

The use of the Afirma Gene Expression Classifier in fine needle aspirates of the thyroid that are cytologically considered to be indeterminate (follicular lesion of undetermined significance or follicular neoplasm) may be considered **medically necessary** in patients who have the following characteristics:

- Thyroid nodules without strong clinical or radiologic findings suggestive of malignancy.
- In whom surgical decision making would be affected by test results.

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.

POLICY STATEMENT

BlueCHiP for Medicare and Commercial Products

The Afirma Gene Expression Classifier test will be considered medically necessary when the medical criteria listed above are met. It is expected that this test will only be performed once per patient lifetime.

Mutation analysis in fine-needle aspirates of the thyroid is considered to be not medically necessary as the clinically utility of this analysis has not been established.

Gene expression classifiers in fine-needle aspirates of the thyroid not meeting the criteria outlined above are considered to be not medically necessary due to limited peer-reviewed scientific literature proving the efficacy of the service.

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. FNA samples 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.

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.

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.

MOLECULAR DIAGNOSTIC TESTING

Mutation and Rearrangement Testing

Point mutations 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 (rtPCR) of single or multiple genes or by next-generation sequencing (NGS) panels. Panels of tests for mutations 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* mutation analysis and testing for *RET/PTC* and *PAX8/PPAR γ* rearrangements.

The ThyroSeq[®] v.2 Next Generation Sequencing panel (CBLPath, Ocala, FL) is a NGS sequencing panel of more than 60 genes. According to the CBLPath's website, the test is indicated when FNA cytology indicates 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.

The ThyGenX[™] Thyroid Oncogene Panel (formerly miRInform[®] Thyroid; Interpace Diagnostics, Parsippany, NJ; testing done at Asuragen Clinical Laboratory) is another NGS panel designed to assess patients with indeterminate thyroid FNA results. It includes sequencing of 8 genes associated with papillary thyroid carcinoma and follicular carcinomas.

Gene Expression Profiling

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

The Afirma Gene Expression Classifier (Afirma GEC; Veracyte, South San Francisco, CA) analyzes the expression of 142 different genes to determine patterns associated with benign findings on surgical biopsy. It

is 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.

Veracyte also markets 2 “malignancy classifiers” that use mRNA expression-based classification to evaluate for *BRAF* mutations (Afirma BRAF) or mutations 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* mutations: (1) PCR-based methods may have low sensitivity, requiring that a large proportion of the nodule have a relevant mutation; (2) testing for only 1 mutation may not detect patients with low-frequency mutations 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 Afirma MTC is an option when the Afirma GEC is ordered for thyroid nodules with an “intermediate” classification on FNA, and can also be used for thyroid nodules with “malignant” or “suspicious” results on Afirma GEC. Afirma BRAF is designed to be used for nodules with “suspicious” results on Afirma GEC.

ThyraMIR™ (Interpace Diagnostics, Parsippany, NJ) is a micro-RNA expression-based classifier intended for use in thyroid nodules with indeterminate cytology on FNA. Other gene expression profiles have been reported in investigational settings, but have not been widely validated or used commercially.

CODING

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

There is a specific CPT code for the Afirma® Gene Expression Classifier test:

81545 Oncology (thyroid), gene expression analysis of 142 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") (Thyraseq Genomic Classifier)

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

RELATED POLICIES

Genetic Testing Services

PUBLISHED

Provider Update, May 2017

Provider Update, January 2017

Provider Update, January 2016

REFERENCES

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