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OVERVIEW

Cytologic examination of fine needle aspiration (FNA) samples from a thyroid lesion to identify which patients need to undergo surgery 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

The Afirma[®] Gene Expression Classifier test is covered only when the following clinical conditions are met:

1. One or more thyroid nodules, and
2. An indeterminate follicular pathology on fine needle aspiration, and
3. A history of malignancy or one of the following 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

Commercial Products

Not applicable

PRIOR AUTHORIZATION

BlueCHiP for Medicare

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

Commercial Products

Not applicable

POLICY STATEMENT

BlueCHiP for Medicare

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.

Commercial Products

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

The use of a gene expression classifier in fine-needle aspirates of the thyroid that are cytologically considered to be indeterminate, atypical, or suspicious for malignancy, is 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 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 (inclusive, indeterminate, atypical, suspicious), usually due to overlapping cytologic features between benign and malignant nodules; these nodules usually require surgery for a final diagnosis. Guidelines from the American Thyroid Association recommend repeat FNA for patients with a diagnosis of “atypia of undetermined significance” and lobectomy with or without intraoperative pathology consultation for those with a suspicious diagnosis. Approximately 80% of patients with indeterminate cytology undergo surgical resection; postoperative evaluation reveals a malignancy rate ranging from 6% to 30%, making this a clinical process with very low specificity.

New approaches for improving the diagnostic accuracy of thyroid FNA include mutation 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.

Mutation Testing

Point mutations in specific genes, including *BRAF*, *RAS*, and *RET*, and evaluation for rearrangements associated with thyroid cancers can be accomplished by gene sequencing with Sanger sequencing or pyrosequencing or by real-time polymerase chain reaction (rtPCR). Panels of tests for mutations associated with thyroid cancer 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/PPARγ* rearrangements.

In addition to standard Sanger sequencing or rtPCR-based mutation testing for genes associated with thyroid cancer, next-generation sequencing (NGS) panels that simultaneously evaluate for point mutations or gene fusions in multiple genes have been developed. For example, the ThyroSeq® v.2 Next Generation Sequencing panel (CBLPath, Ocala, FL) includes sequencing of more than 60 genes. According to the ThyroSeq’s manufacturer’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.⁵ In particular, it has been evaluated in patients with follicular neoplasm/suspicious for follicular neoplasm on FNA as a test to increase both sensitivity and specificity for cancer diagnosis.

The ThyGenXT™ Thyroid Oncogene Panel (formerly miRInform® Thyroid; Interpace Diagnostics, Parsippany, NJ; testing done at Asuragen Clinical Laboratory) is another NGS sequencing panel designed to be used in 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 through the use of 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 be used for thyroid nodules that have an “indeterminate” classification on FNA as a method to select patients who are at low risk for cancer (“rule out”).

Veracyte also markets 2 “malignancy classifiers” that use mRNA expression-based classification to evaluate for *BRAF* mutations or mutations associated with medullary thyroid carcinoma (Afirma BRAF and Afirma MTC, respectively). In a description of the generation of the Afirma BRAF test, the authors outline the following proposed 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.⁶ 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. The Afirma BRAF is designed to be used for nodules with “suspicious” results on Afirma GEC.

BlueCHiP for Medicare

Afirma™ completed the Centers for Medicare and Medicaid Services (CMS) MoIDX Program application review and/or technical assessment and has been found to meet Medicare reasonable and necessary criteria.

Commercial Products Mutation Analysis

Analysis for mutations associated with thyroid cancer in fine needle aspirates of the thyroid that are cytologically indeterminate has a high positive predictive value for malignancy. However, patients with an equivocal FNA result would likely proceed to surgery regardless of mutation status, with intraoperative consultation to guide the necessity and extent of surgery. Mutation analysis has the potential to improve the accuracy of an equivocal FNA of the thyroid and may play a role in preoperative risk stratification and surgical planning. One retrospective single-center study suggested that testing for a panel of mutations associated with thyroid cancer may allow the appropriate selection of patients for surgical management with an initial total thyroidectomy. Prospective studies in additional populations are needed to validate these results. Mutation analysis does not achieve a high enough negative predictive value (NPV) to identify which patients can undergo watchful waiting over thyroid surgery. Although the presence of certain mutations may predict more aggressive malignancies, the clinical utility of identifying these mutations preoperatively has not been established. Given the limitations in the evidence base, the use of molecular diagnostics in thyroid FNA samples for mutations associated with thyroid cancer is considered not medically necessary.

Gene Expression Classifier to Predict Benignancy

There is 1 commercially available gene expression classifier (GEC) that has been developed to predict benignancy in thyroid nodules. The reported NPV of the GEC in predicting which thyroid nodules with indeterminate cytology are benign is high. Two relevant retrospective studies on the clinical utility of the GEC have been published and suggest that treatment recommendations for patients with indeterminate cytology are affected by the results of the GEC test. For patients who avoided surgery based on GEC results, limited longer term follow-up data are available. Although the available evidence suggests that this group of patients does well, longer term follow-up has been reported for only a small number of patients. Therefore, the use of a GEC to predict which thyroid nodules with indeterminate cytology are benign is considered not medically necessary.

CODING

Effective January 1, 2016, there will be a specific CPT code for the Afirma Gene Expression Classifier test. The following CPT code is covered for BlueCHiP for Medicare when medical criteria above are met and is considered not medically necessary for Commercial Products.

81545

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

RELATED POLICIES

Preauthorization via Web-Based Tool for Genetic Testing

PUBLISHED

Provider Update, January 2017

Provider Update, January 2016

REFERENCES

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