CareFirst

Medical Policy

11.01.055 Gene Expression Classifier Testing of Thyroid Biopsy to Determine Risk for Cancer (example: Afirma®)

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Description

Thyroid nodules are classified as benign (70%-75%) malignant (5%) or indeterminate (20%-25%) based on cytopathology of tissue from fine needle aspiration (FNA) biopsy. The follow-up of indeterminate lesions often includes surgical resection of the nodule or partial or total thyroidectomy. In most cases the surgery will prove unnecessary as most indeterminate lesions (80%) are found to be benign. The Afirma® Thyroid FNA analysis test is an example of a genetics-based test that was recently developed as a diagnostic aid to help identify indeterminate lesions with a high probability of being benign and thus allowing the patient to avoid unnecessary surgery and instead allow the physician to monitor the patient periodically. The test uses a proprietary gene expression classifier (GEC) to identify expression patterns characteristic of benign lesions. The result is reported as either "benign" or "suspicious". An important limitation is the need for an adequate sample size, which may require more than one FNA sampling, otherwise the tissue cannot be analyzed by GEC.

Policy

Gene expression classifier testing of tissue from thyroid FNA biopsy for identification of cancer-suspicious tissue is considered medically necessary for indeterminate tissue samples.

Gene expression classifier testing of tissue from thyroid FNA biopsy where histologic examination has resulted in a definitive diagnosis is considered not medically necessary,

Policy Guidelines

Rationale:

1. The technology must have final approval from the appropriate government regulatory bodies:
No approval by the FDA is required for the Afirma® analysis, as it was developed in-house by Veracyte, Inc. All tests are performed by Veracyte in their laboratory which is certified under the Clinical Laboratory Improvement Amendments.

2. The scientific evidence must permit conclusions concerning the effect on health outcomes:

**Analytical validity**

A single study has examined the analytical validity of the Afirma® analysis. Chudova and colleagues (2010) reported on the development process and performance validation of the GEC. Microarray data was generated from 178 thyroid tissue specimens representing the 8 most common types of benign and malignant lesions. Messenger RNA transcripts were used to develop a molecular classifier. After testing of the final test set, the sensitivity was determined to be 100%, and the specificity at 73.3%, to yield a negative predictive value (NPV) of 96%.

**Clinical validity**

Clinical validity of the GEC was evaluated by Alexander et. al. (2012) in a multicenter study of independently and prospectively collected thyroid FNA specimens. Of 3789 samples, 265 were classified as indeterminate, had an adequate specimen for analysis, and had results of a histopathological examination, and were included in the analysis. 142 genes were used in the main GEC, which would classify the FNA samples as benign or suspicious. Of the 265 indeterminate specimens, 85 were classified as malignant after evaluation of thyroid tissue. Of these 85 specimens, 78 were correctly classified as suspicious by the Afirma® analysis for a sensitivity of 92%. There were therefore 7 incorrectly classified malignancies. Of the 180 nonmalignant samples, 93 were correctly classified as benign by the GEC for a specificity of 52%. For the entire set of test samples the positive predictive value (PPV) and NPV was reported at 47% and 93% respectively.

**Clinical utility**

A single study ((Duick et al, 2012) has documented the impact of the Afirma® FNA analysis on the management of patients with indeterminate thyroid nodules. In a retrospective, multicenter study the researchers evaluated data from endocrinology practices that ordered the Afirma® analysis for which the result was benign for at least three patients. A total of 51 endocrinologists from 21 centers reported data on a total of 368 patients. Physicians reported on their management decisions for each patient. According to the survey, surgery was performed in 28 patients with a benign GEC result; the reasons most often given for surgery was nodule size, a nodule causing symptoms of pressure, and a rapidly growing nodule. Hemithyroidectomy was performed in 19 and total thyroidectomy was recommended in 8. The percentage of patients who were operated on (7.4%) represented a significant decrease from the previously
reported rate of diagnostic surgery (74%).

3. The technology must improve the net health outcome:

Based on limited evidence, it is possible that use of the Afirma® FNA analysis can improve health outcomes by helping the physician to rule out the need for thyroid surgery. The procedure itself involves no risks other than a false-negative result, which could adversely affect health outcomes. The 2013 guidelines from the National Comprehensive Cancer Network (NCCN) state that "molecular diagnostics...using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate. "Rather than proceeding to immediate surgical resection, patients can be followed by observation if the application of a specific molecular diagnostic test results in a predicted risk of malignancy that is comparable to the rate seen in cytologically benign FNAs (approximately 5% or less)." The guidelines reference the Chudova and Alexander studies as the basis for the recommendation.

4. The technology must be as effective as any established alternatives:

The alternative would include a detailed review of the patient's family history with a detailed physical examination, evaluation of thyroid stimulating hormone, high resolution diagnostic ultrasound, thyroid scan, and histopathological examination of resected tissue. Testing may also include serum biomarkers associated with thyroid malignancies. There are no studies comparing patient outcomes where the more traditional approach was used with the Afirma® test.

5. The improvement must be attainable outside the investigational settings:

The Afirma® test is already in use outside the investigational settings. It is not known how patient outcomes compare with those in the clinical utility study by Duick et al.

The results of the studies to date need independent verification to confirm ability of the test to improve outcomes and patient decision making. Therefore the test is presently considered experimental / investigational.

**Update, March 2015**

The Afirma® test has rapidly gained acceptance based on its ability to reliably determine whether a histologically indeterminate sample from a FNA of a thyroid nodule is benign or malignant. NCCN guidelines now contain language supporting its use, and it is employed routinely outside of the investigational settings, based on moderate quality evidence. Therefore, the test is considered medically necessary for indeterminate FNA biopsy samples.

**References**

The following were among the resources reviewed and considered in developing


National Comprehensive Cancer Network, NCCN Practice Guidelines in Oncology (NCCN Guidelines) v. 2.2013, Thyroid Carcinoma. Available at: www.nccn.org/professionals

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