White Paper: Nodular Thyroid Disease Testing and Diagnosis: When is Afirma Thyroid FNA Analysis Medically Necessary?

For Health Plans, Medical Management Organizations and TPAs

Introduction

Thyroid nodules are common and typically benign. Current practice guidelines recommend evaluation with ultrasound followed by fine needle aspiration (FNA) biopsy for most clinically significant thyroid nodules. As many as one third of diagnostic FNA biopsies remain indeterminate. Most of these patients undergo surgical resection, and the majority of these nodules are ultimately found to be benign on final surgical pathology.

Clinical Manifestations of Thyroid Nodules

Most thyroid nodules don’t cause signs or symptoms. However, large nodules maybe felt or seen (often as swelling at the base of the neck), or can compress the esophagus or trachea, causing difficulty swallowing or shortness of breath. Some nodules may produce additional thyroxine and cause symptoms of hyperthyroidism, such as sudden, unexplained weight loss, nervousness, or rapid or irregular heartbeat.

Some thyroid nodules turn out to be malignant, but it’s difficult to tell which nodules are malignant by symptoms alone. Factors suggesting a malignant diagnosis include the following: solitary nodules; hard and fixed nodules; nodular growth; rapid growth; nontender to palpation; age over 60 years or under 20 years; male sex; associated symptoms of dysphagia or dysphonia; history of neck irradiation; prior history of thyroid carcinoma; and presence of cervical lymphadenopathy. Factors suggesting a benign diagnosis include: family history of autoimmune disease (e.g., Hashimoto thyroiditis); family history of benign thyroid nodule or goiter; presence of thyroid hormonal dysfunction (e.g., hypothyroidism, hyperthyroidism); pain or tenderness associated with the nodule; and soft, smooth, and mobile nodule.

Traditional Evaluation Methods for Thyroid Nodules

History and Physical Examination

History and physical examination alone have low accuracy for predicting cancer. However, increased likelihood of malignancy has been associated with several features of clinical evaluation, including history of rapid growth of a neck mass; childhood head and neck irradiation; total body irradiation for bone marrow transplantation; family history of thyroid cancer; and thyroid cancer syndromes (e.g., multiple endocrine neoplasia 2, familial adenomatous polyposis, Cowden syndrome). In addition, a fixed hard mass, obstructive symptoms, cervical lymphadenopathy, or vocal cord paralysis all suggest the possibility of cancer.

Serum Thyroid-Stimulating Hormone (TSH)

Thyroid function should be assessed in all patients with thyroid nodules. If the serum TSH concentration is low (indicating overt or subclinical hyperthyroidism), the possibility that the nodule is hyperfunctioning is increased, and thyroid scintigraphy should be performed next. If the serum TSH concentration is normal or elevated, and the nodule meets criteria for sampling, then FNA biopsy is indicated. In addition, patients with a high serum TSH concentration require an evaluation for hypothyroidism.
Thyroid Scintigraphy

Thyroid scintigraphy is used to determine the functional status of a nodule. A low serum TSH, indicating overt or subclinical hyperthyroidism, increases the possibility that a thyroid nodule is hyperfunctioning. Thus, thyroid scintigraphy should be performed in patients with a low serum TSH concentration.

Thyroid Ultrasonography

Thyroid ultrasound should be performed in all patients with a suspected thyroid nodule or nodular goiter on physical examination or with nodules incidentally noted on other imaging studies. Thyroid ultrasonography visualizes the size and anatomy of the thyroid gland and adjacent structures in the neck. It provides considerably more anatomic detail than thyroid scintigraphy, CT, and physical examination.

FNA Biopsy

For FNA biopsy, tissue samples are obtained for cytological examination using needles, with or without local anesthesia. Ultrasound-guided FNA biopsy can be performed for nonpalpable nodules and for nodules that are technically difficult to aspirate using palpation methods alone.

Diagnostic Categories for Thyroid Nodules

Traditional cytology diagnostic categories designated thyroid nodules as benign, indeterminate, malignant, or nondiagnostic. The National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference (Bethesda Conference) suggests the following revised classification scheme:

- **Benign**: This includes macrofollicular or adenomatoid/hyperplastic nodules, colloid adenomas, nodular goiter, and Hashimoto’s thyroiditis
- **Atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS)**: This includes lesions with atypical cells, or mixed macro- and microfollicular nodules
- **Follicular neoplasm**: This includes microfollicular nodules, including Hürthle cell lesions
- **Suspicious for malignancy**
- **Malignant**
- **Nondiagnostic**

The risk of malignancy with these revised indeterminate categories (AUS/FLUS; follicular neoplasm; suspicious for malignancy) varies. The majority of these patients undergo thyroid surgery, with most patients undergoing surgery for what is ultimately confirmed to be benign disease.

Molecular Genetic Testing

Various mutations in thyroid cancer have been uncovered in recent years and in an attempt to improve diagnostic accuracy of thyroid FNA, mutation analysis and a gene expression classifier have been developed. The design of the mutation analysis is that a positive test is highly associated with a malignant histology and the individual is encouraged to proceed with surgery. The analysis design of the gene expression classifier identifies nodules with a cytology that is highly likely to be benign, foregoing the need for diagnostic surgery.

Available molecular diagnostic tests for the evaluation of thyroid nodule FNA specimens include:

- **Asuragen Molecular Panel**: Identifies genetic mutations (BRAF and RAS) and genetic rearrangements (RET/PTC and PAX8/PPARg) strongly associated with thyroid cancers
- **Afirma Gene Expression Classifier**: Assesses mRNA from genes isolated from benign and malignant needle washings during a standard FNA procedure
The Asuragen Molecular Panel is an excellent test to “rule in” a thyroid cancer because, once a mutation or rearrangement is identified, there is a 99% certainty that the nodule is malignant. The problem, however, is that 30% of thyroid cancers do not have either a genetic mutation or rearrangement. The best use of the Asuragen panel might be that of helping the surgeon decide whether to perform a total thyroidectomy immediately rather than an initial diagnostic lobectomy and then, weeks later, a completion lobectomy.

Genetic Testing With the Afirma Thyroid FNA Analysis

The Afirma Thyroid FNA Analysis is a 167-gene expression assay that produces a benign or suspicious for malignancy result when analyzing thyroid nodule FNA biopsy specimens that are cytologically indeterminate. The panel is ordered preoperatively to identify benign nodules so that these patients can avoid unnecessary thyroid surgery.

Developing the Afirma Thyroid FNA Analysis involved collecting nearly 250,000 gene transcripts from 400 FNA samples provided by academic and community sites. Each nodule was subsequently diagnosed as benign or malignant using the gold standard of surgical histopathology. Using these data, a computer algorithm was designed to identify benign nodules.

A recently published large, prospective, double-blind, multicenter study (49 sites) examined 265 nodules with indeterminate cytology that underwent Afirma testing. Results of the study showed that the Afirma panel has a high negative predictive value for cytologically indeterminate nodules—95% for an atypical or follicular lesion of undetermined significance, 94% for a follicular neoplasm or lesion suggestive of follicular neoplasm, and 85% for a lesion suggestive of cancer.

Determining Medical Necessity for Afirma Thyroid FNA Analysis

Many health plans cover testing for stated indications. For example, Afirma Thyroid FNA analysis is often covered for assessing FNA samples from thyroid nodules that are indeterminate. However, some plans do not cover testing, stating that molecular markers in FNAs of the thyroid are considered investigational for all applications and that investigational services or procedures are not covered.

The American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) endorse a multistep strategy for the evaluation of thyroid nodules. The recommend clinical assessment, measurement of TSH, ultrasound evaluation, and biopsy of nodules selected according to size and ultrasound characteristics.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Thyroid Carcinoma state that molecular diagnostics may be useful to allow reclassification of follicular lesions (follicular or Hürthle cell neoplasm, or follicular lesion of undetermined significance) as more likely to be benign or more likely to be malignant. In addition, the guidelines recommend considering observation if molecular testing predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less).

With regard to commercially available molecular diagnosis testing in the evaluation of thyroid nodule FNA specimens, the ATA feels that until expert consensus review of existing data (now underway by the ATA Guidelines Task Force) can be completed, no evidence-based recommendation for or against the use of these methods can be made. Until evidence-based recommendations are available, determining whether or not the limited data available support the use of these methods should be considered on a case-by-case basis.

The Role of External Independent Medical Review in Determining Medical Necessity for Molecular Genetic Testing

An independent medical review, which is normally used by healthcare payers, looks at whether or not a specific therapy or procedure was medically necessary. It facilitates effective evaluation and treatment of patients with thyroid nodules, who often undergo necessary surgery, which can have significant health impacts and is costly.

Independent review organizations (IROs) allow ready access to a range of board-certified physician specialists, which healthcare plans may lack internally. The specialists who review cases for IROs keep up-to-date with the latest medical research literature and with the latest standard of care, staying on top of continually evolving therapies as they are studied more extensively and potentially accepted into clinical guidelines.
External independent medical review also helps to avoid conflicts of interest, which can relate to economics, lack of specialists to review cases, and having the same doctor who denied a case review an appeal.

**Summary**

Thyroid nodules are common. All patients with known or suspected thyroid nodules should undergo a thyroid ultrasound and have their TSH levels checked. Thyroid scintigraphy should be performed for a low or low-normal serum TSH concentration, and FNA biopsy should be considered for nodules larger than 1 cm. Traditional diagnostic categories on FNA cytology include benign, malignant, nondiagnostic, and indeterminate. The revised Bethesda 2007 criteria further divided the indeterminate cytology category into AUS/FLUS, follicular neoplasm, and suspicious for malignancy.

Molecular diagnosis is rapidly emerging as a useful tool for evaluation of cytologically indeterminate thyroid nodules that otherwise would require diagnostic surgery. If benign, the Afirma Gene Expression Classifier may help “rule out” thyroid cancer because of the test’s negative predictive value of 95% and 94%, respectively, in the AUS/FLUS and the follicular neoplasm indeterminate category. A genetic test such as the Asuragen Molecular Panel may help instead to “rule in” a thyroid cancer, allowing patients to undergo a single up-front total thyroidectomy.

**Bibliography**


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