Preauthorization is required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

Description

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.

Policy

The use of the Afirma gene expression classifier in fine-needle aspirates of the thyroid may be considered to be medically necessary in the following situations:

- the nodule is 1.0 cm or larger AND
- cytological evaluation of fine needle aspirate is considered to be indeterminate, atypical or suspicious for malignancy as evidenced by:
  - atypia of undetermined significance (AUS)
  - follicular lesion of undetermined significance (FLUS)
  - suspicion for follicular neoplasm (SFN)
  - follicular neoplasm (FN)

The use of a gene expression classifier in fine-needle aspirates of the thyroid is considered investigational in all other situations.

The use of any other gene expression classifier in fine-needle aspirates of the thyroid is considered investigational.

Mutation analysis in fine-needle aspirates of the thyroid is considered to be investigational.

Medicare Advantage

For Medicare Advantage Afirma will be considered medically necessary for the following conditions:

- 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

- Patients with an indeterminate follicular pathology on fine needle aspiration.

**Medicare Advantage Policy Guidelines**

This test is expected to be necessary once per patient lifetime. Should the unlikely situation of a second, unrelated thyroid nodule with indeterminate pathology occur, medical necessity may be considered with support documentation.

**Background**

*FNA of the Thyroid*

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.

Preoperative planning of optimal surgical management in patients with equivocal cytologic results is challenging, as different thyroid malignancies may require different surgical procedures (e.g., unilateral lobectomy versus 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 an FNA in a case of PTC...
is indeterminate, surgical biopsy with intraoperative consultation is most often diagnostic, although its efficacy and therefore use will vary between institutions, surgeons, and pathologists.

For follicular carcinoma, the presence of invasion of the tumor capsule or of blood vessels is diagnostic and cannot be determined by cytology, as 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 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.

**Mutations Associated With Thyroid Cancer**

Various mutations have been discovered in thyroid cancer. The four gene mutations that are the most common and carry the highest impact on tumor diagnosis and prognosis are BRAF and RAS point mutations and RET/PTC and PAX8/PPARγ rearrangements.

Papillary carcinomas carry point mutations of the BRAF and RAS genes, as well as RET/PTC and TRK rearrangements, all of which are able to activate the mitogen-activated protein kinase (MAPK) pathway. These mutually exclusive mutations are found in more than 70% of papillary carcinomas. BRAF mutations are highly specific for PTC. Follicular carcinomas harbor either RAS mutations or PAX8/PPARγ rearrangement. These mutations are also mutually exclusive and 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 cancer and have higher prevalence in less differentiated thyroid carcinomas. Additional mutations 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 point mutations located in the RET gene.

**Available Molecular Diagnostic Testing**

**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. 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 ThyGenX™ 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 eight 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 two “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 one 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. The Afirma BRAF is designed to be used for nodules with “suspicious” results on Afirma GEC.

Regulatory Status

Testing for mutations associated with thyroid cancer via sequencing or rtPCR are laboratory-developed tests (LDTs). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; LDTs must meet the general regulatory standards of the Clinical Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing.

In 2013, the U.S. Food and Drug Administration (FDA) approved through the premarket approval process the THxID™-BRAF kit, which is an in vitro diagnostic device to assess specific BRAF mutations in melanoma tissue via rtPCR. However, there are currently no diagnostic tests for thyroid cancer mutation analysis with approval from FDA.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


32. Hodak SP, Rosenthal For The American Thyroid Association Clinical Affairs Committee DS. Information for clinicians: commercially available molecular diagnosis testing in the evaluation of thyroid nodule fine-needle aspiration specimens. Thyroid. Feb 2013; 23(2):131-134. PMID 22984796


