Molecular Markers in Fine Needle Aspirates of the Thyroid

Description of Procedure or Service

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 marker have been developed in an attempt to improve the accuracy of thyroid FNA biopsies.

**Fine needle aspiration (FNA) of the thyroid**

Thyroid nodules are common, present in 5-7% of the U.S. adult population. The vast majority are benign, and most cases of thyroid cancer are curable by surgery if detected early. Fine needle aspiration (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 60-70% of thyroid nodules are classified cytologically as benign, and 4-10% of nodules are cytologically deemed malignant. However, the remaining 20-30% have equivocal findings (inclusive, indeterminate, atypical or suspicious), 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.
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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 ~3% of all thyroid cancers. The diagnosis of malignancy in the case of PTC is primarily based on cytologic features. If a FNA in a case of PTC is indeterminate, 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, as 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 molecular analysis for somatic genetic alterations, in order 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 4 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 70-75% 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 AX8/PPARγ rearrangements.

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.
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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 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.

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**

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.

These commercially available, laboratory-developed tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

**Policy**

BCBSNC will provide coverage for molecular markers in fine needle aspirates of the thyroid when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

**Benefits Application**
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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When molecular markers in fine needle aspirates of the thyroid are covered

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

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

When molecular markers in fine needle aspirates of the thyroid are not covered

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

The use of a gene expression classifier in fine-needle aspirates of the thyroid that do not meet criteria outlined above is considered to be investigational.

Policy Guidelines

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.

For individuals with thyroid nodule(s) and indeterminate findings on FNA who receive FNA sample testing with the Afirma Gene Expression Classifier (GEC) to predict benignancy, the evidence includes 1 prospective clinical validity study with the marketed test, and an indirect chain of evidence to support clinical utility. Relevant outcomes are disease-specific survival, test accuracy and validity, morbid events, and resource utilization. In 1 multicenter validation study, the Afirma GEC was reported to have a high negative predictive value (NPV; range, 90%-95%). These results are supported by an earlier development and clinical validation study (Chudova et al), but the classifiers used in the 2 studies do not appear to be identical. In an additional multicenter and multiple single-center studies, there is suggestive evidence that rates of malignancy are low in Afirma benign patients, but the exact NPV is unknown. The available has evidence suggested that physician decision making about surgery is altered by GEC results, although long-term follow-up of patients with thyroid nodules who avoided surgery based on GEC results is limited. An indirect chain of evidence can be constructed to establish the potential for clinical utility with GEC testing in cytologically indeterminate lesions, but with only 1 study of the marketed test reporting a true NPV, the clinical validity is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with thyroid nodule(s) and indeterminate findings on FNA who receive FNA sample testing with molecular markers to predict malignancy, the evidence includes prospective and retrospective studies of clinical validity. Relevant outcomes are disease-specific survival, test accuracy and validity, morbid events, and resource utilization. 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.
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Single-center studies have suggested that testing for a panel of mutations associated with thyroid cancer may allow for the appropriate selection of patients for surgical management with an initial complete thyroidectomy. Prospective studies in additional populations are needed to validate these results. Mutation analysis does not achieve a high enough NPV to identify which patients can undergo active surveillance over thyroid surgery. Although the presence of certain mutations may predict more aggressive malignancies, the management changes that would occur as a result of identifying higher risk tumors are not well-established. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input has supported the use of a gene expression classifier with a high NPV for individuals with FNA found to be cytologically indeterminate. Although the current evidence for the clinical validity of the Afirma GEC is not entirely conclusive, given the suggestive evidence with supportive clinical input, this test may be considered medically necessary in the evaluation of FNAs of the thyroid that are cytologically considered to be indeterminate (follicular lesion of undetermined significance or suspicious for follicular neoplasm).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

**Applicable codes:** 81210, 81275, 81401, 81403, 81404, 81405, 81406, 81445, 81545, G0452

**Diagnoses that are subject to medical necessity review:** 241, 241.0, 241.1, 241.9

**ICD-10 Diagnosis Codes:** E04.1, E04.2, E04.8, E04.9

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

**Mutation Analysis in Fine Needle Aspirates of the Thyroid**


Medical Director – 3/2012


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American Thyroid Association Guidelines Taskforce on Thyroid N, Differentiated Thyroid C, Cooper DS et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. http://www.thyroid.org/thyroid-guidelines/revised/taskforce/


Sr. Medical Director Review 11/2015


Medical Director review 11/2016

Policy Implementation/Update Information

Mutation Analysis in Fine Needle Aspirates of the Thyroid

3/30/12 New policy. “Mutation analysis in fine-needle aspirates of the thyroid that are cytologically considered to be indeterminate, atypical or suspicious for malignancy is considered to be investigational.” (btw)

9/4/12 Specialty Matched Consultant Advisory Panel review 8/15/2012. No change to policy. (btw)

12/28/12 Removed the following statement from the Billing/Coding section; “According to the Asuragen website, the following CPT codes would be used to report miRInform™ Thyroid: 83913, 83907, 83891, 83902, 83896, 83898, 83909, 83912.”. Added the following codes 81401, 81404, 81405, 81406, and G0452 to Billing/Coding section. (btw)
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5/28/13 Name changed from Mutation Analysis in Fine Needle Aspirates of the Thyroid to Molecular Markers in Fine Needle Aspirates of the Thyroid. Description section updated. Reference to Mutation Analysis changed to Molecular Markers throughout policy as necessary. The When Not covered statement changed from “Mutation analysis in fine-needle aspirates of the thyroid that are cytologically considered to be indeterminate, atypical or suspicious for malignancy is considered to be investigational.” to “Mutation analysis in fine-needle aspirates of the thyroid is considered to be investigational. 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 investigational.” Policy Guidelines updated. Added “Diagnoses that are subject to medical necessity review: 241, 241.0, 241.1, 241.9 to the Billing/Coding section. No change to policy intent. Senior Medical Director review 5/18/13. References added. (btw)

7/1/13 ICD-10 diagnosis codes added to Billing/Coding section. (btw)

9/10/13 Specialty Matched Consultant Advisory Panel review 8/21/2013. No change to policy intent. (btw)


5/27/14 References updated. No changes to Policy Statements. (mco)

7/1/14 Removed ICD-10 effective date from Billing/Coding section. (mco)

9/9/14 Specialty matched consultant advisory panel review 8/26/2014. No change to policy statement. (lpr)

10/1/15 Reference added. Specialty Matched Consultant Advisory Panel review 8/26/2015. No change to policy statement. (lpr)

11/24/15 Updated the Description and Regulatory status sections. Added CPT code 81445 to the “Billing/Coding” section. Sr. Medical Director review 11/2015. (lpr)

12/30/15 Added CPT code 81545 to Billing/Coding section for effective date 1/1/2016. (lpr)

9/30/16 Specialty Matched Consultant Advisory Panel review 8/31/2016. No change to policy statement. (lpr)

1/27/17 Updated and revised Description and Policy Guidelines sections. Revised Policy Statement to reflect medical necessity coverage. Under When Covered section added medically necessary indication for Afirma: “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 conditions: 1) Thyroid nodules without strong clinical or radiologic findings suggestive of malignancy; 2) In whom surgical decision making would be affected by test results.” Medical Director review 11/2016. Reference added. (lpr)

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