POLICY STATEMENT:

I. Based on our criteria and assessment of the peer-reviewed literature, mutation analysis in fine-needle aspirates of the thyroid (e.g., ThyroSeq®, ThyGenX Thyroid Oncogene Panel) is considered investigational.

II. Based on our criteria and assessment of the peer-reviewed literature, the use of a gene expression classifier in fine-needle aspirates of the thyroid (e.g., Afirma® Gene Expression Classifier) that are cytologically considered to be indeterminate, atypical or suspicious for malignancy is considered medically appropriate when surgical decisions will be based on test results for thyroid nodules with the following:
   A. Cytological diagnosis of atypia of undetermined significance/follicular lesion of either undetermined significance (AUS/FLUS) on fine-needle aspiration (FNA); OR
   B. Cytological diagnosis of follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) on fine-needle aspiration (FNA); OR
   C. Bethesda III or IV on FNA cytology (please refer to the Bethesda criteria in the Description section); and
   D. Size greater than 1.0 cm; and
   E. Without clinical suspicion of malignancy based on provider judgment and ultrasonography; and
   F. No compressive manifestations.

POLICY GUIDELINES:

I. Ultrasound features associated with low suspicion of malignancy include:
   A. Isoechoic or hyperechoic solid nodules without microcalcifications; or
   B. Mixed solid/cystic nodules without microcalcification; or
   C. Spongiform nodules.

II. The ThyroSeq® v.2 Next Generation Sequencing (NGS) panel (CBLPath, Ocala, FL) includes sequencing of more than 60 genes and per manufacturer’s website is indicated when FNA cytology indicates atypical of uncertain significance (AUS) or follicular lesion of undetermined significance (FLUS), follicular neoplasm (FN) or suspicious for follicular neoplasm, or suspicious for malignancy.

III. The ThyGenX Thyroid Oncogene Panel (Interpace Diagnostics, Parsippany, NJ) is a Next Generation Sequencing panel designed to be used in patients with indeterminate thyroid FNA results. The panel includes sequencing of 8 genes associated with papillary thyroid carcinoma (PTC) and follicular carcinomas.

IV. The Afirma® Gene Expression Classifier (Afirma GEC; Veracyte, San Francisco, CA) analyzes the expression of 142 different genes to determine patterns associated with benign finding on surgical biopsy. It is indicated for thyroid nodules that have an indeterminate classification on FNA. Testing is limited to 2 thyroid nodules.

V. The Afirma® BRAF and Afirma MTC are two tests which use mRNA expression-based classification to evaluate for BRAF mutations or mutations associated with medullary thyroid carcinoma. Both tests are options when the Afirma GEC results are malignant or suspicious.

VI. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.
DESCRIPTION:
Thyroid nodules are common endocrine tumors which appear as palpable nodules in 5% of adults. Up to 50% of women and 20% of men over age 50 on ultrasound or autopsy studies are found to have thyroid nodules. The majority of thyroid nodules are benign but 10-15% may be malignant, most often as papillary thyroid cancer. Fine needle aspiration (FNA) is performed in nodules which require biopsy with sufficient information obtained to classify the majority of nodules as benign and a smaller percentage as malignant. However 15-30% of aspirations yield indeterminate cytology including subtypes such as atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), suspicious for follicular neoplasm (FN) or suspicious for malignancy. Current guidelines recommend either partial (lobectomy) or complete thyroidectomy for those nodules determined as malignant and those of indeterminate cytology. On histological evaluation only 15-30% of the thyroid nodules of indeterminate cytology are malignant consequently many patients undergo surgery for benign disease when expectant management or other treatments would have been more appropriate with a retrospective assessment. Due to the limitations of the FNA, other methods to assist in determining whether a nodule is benign or malignant prior to surgery have been developed. The ThyroSeq and ThyGenX thyroid Oncogene panel are two tests evaluation for point mutation associated with thyroid cancers using next-generation sequencing. The Afirma Gene Expression Classifier (GEC) analyzes genetic alterations through the use of gene expression profiling.

RATIONALE:
Analysis for mutations associated with thyroid cancer in fine needle aspirates (FNA) 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. Studies suggest 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. Additional studies 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.

There is one 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. Studies in which patients who avoided surgery based on GEC results need longer follow-up data.

The American Thyroid Association (ATA) statement on Surgical Application of Molecular Profiling for Thyroid Nodules (2015) states techniques for molecular profiling of thyroid cytology specimens have evolved as adjuncts to guide the appropriate management of cytologically indeterminate nodules. However, it must be stressed that the utility of any molecular test is only applicable clinically when combined with clinical and sonographic risk factors for malignancy and with understanding of the prevalence of malignancy for the Bethesda cytologic categories at the reporting institution. Future studies on further refinements and expansion of gene sets in analytic panels will likely improve the diagnostic accuracy of molecular analyses of thyroid cytology specimens and offer promise for personalizing surgical therapy, with the potential for cost and risk reduction in the diagnostic and therapeutic approaches to treating differentiated thyroid cancer.

The National Comprehensive Cancer Network (NCCN) Guidelines for Thyroid Carcinoma (2017) state that the choice of the precise molecular test depends on the cytology and the clinical question being asked. Indeterminate groups include follicular or Hürthle cell neoplasms and atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS). The NCCN panel recommends molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS that are low clinical suspicion of malignancy. Molecular diagnostic testing is not recommended for suspected Hürthle cell neoplasms. Molecular diagnostic testing may include multigene assays (e.g., the gene expression classifier) or individual mutational analysis. Patients can be
followed with observation if the application of a specific molecular diagnostic test (in conjunction with clinical and ultrasound features) results in a predicted risk of malignancy that is comparable to the rate seen in cytologically benign fine needle aspiration (FNA). It is important to note that the positive predictive value of molecular diagnostics may be significantly influence by the pre-test probability of disease associated with the various FNA cytology groups. Furthermore, in the cytologically indeterminate groups, the risk of malignancy for FNA can vary widely between institutions. Proper implementation of molecular diagnostics into clinical care requires an understanding of both the performance characteristics of the molecular test and its clinical meaning across a range of pre-test probabilities.

In 2007, the National Cancer Institute (NCI) Thyroid FNA State of Science Conference, developed the *Bethesda System for Reporting Thyroid Cytopathology*. The purpose of the conference was to develop a uniform reporting system for thyroid FNA to facilitate effective communication among cytopathologist, endocrinologists, surgeons, radiologists, and other health care providers.

The *Bethesda System for Reporting Thyroid Cytopathology*

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Definition</th>
<th>Diagnostics</th>
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<tbody>
<tr>
<td>I</td>
<td>Nondiagnostic or Unsatisfactory</td>
<td>Cyst fluid only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Virtually acellular specimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other (obscuring blood, clotting artifact, etc.)</td>
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<tr>
<td>II</td>
<td>Benign</td>
<td>Consistent with a benign follicular nodule (includes adenomatoid nodule,</td>
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<tr>
<td></td>
<td></td>
<td>colloid nodule, etc.)</td>
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<tr>
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<td></td>
<td>Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical</td>
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<td>context</td>
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<tr>
<td></td>
<td></td>
<td>Consistent with granulomatous (subacute) thyroiditis</td>
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<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>III</td>
<td>Atypia of Undetermined Significance or Follicular Lesion of Undetermined</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Significance</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm</td>
<td>Specify if Hürthle cell (oncocytic) type</td>
</tr>
<tr>
<td>V</td>
<td>Suspicious for Malignancy</td>
<td>Suspicious for papillary carcinoma</td>
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<tr>
<td></td>
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<td>Suspicious for medullary carcinoma</td>
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<td></td>
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<td>Suspicious for metastatic carcinoma</td>
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<tr>
<td></td>
<td></td>
<td>Suspicious for lymphoma</td>
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<tr>
<td></td>
<td></td>
<td>Other</td>
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<tr>
<td>VI</td>
<td>Malignant</td>
<td>Papillary thyroid carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poorly differentiated carcinoma</td>
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<tr>
<td></td>
<td></td>
<td>Medullary thyroid carcinoma</td>
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<tr>
<td></td>
<td></td>
<td>Undifferentiated (anaplastic) carcinoma</td>
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<td></td>
<td></td>
<td>Squamous cell carcinoma</td>
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<td></td>
<td></td>
<td>Carcinoma with mixed features (specify)</td>
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<td></td>
<td></td>
<td>Metastatic carcinoma</td>
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<tr>
<td></td>
<td></td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
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<td>Other</td>
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**CODES:**

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<td>Eligibility for reimbursement is based upon the benefits set forth in the member’s subscriber contract.</td>
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SUBJECT: MOLECULAR MARKERS IN FINE NEEDLE
ASPIRATES OF THE THYROID

POLICY NUMBER: 2.02.49
CATEGORY: Laboratory Test

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND
GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

CPT: 81445 Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and
RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2,
KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET),
interrogation for sequence variants and copy number variants or rearrangements, if
performed

81479 Unlisted molecular pathology procedure

81545 Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate,
algorithm reported as a categorical result (e.g., benign or suspicious)

0018U (E/I) Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences,
utilizing fine needle aspirate, algorithm reported as a positive or negative result for
moderate to high risk of malignancy (ThyraMIR™, Interpace Diagnostics)(effective
11/1/2017)

HCPCS: No specific codes

ICD9: 193 Malignant neoplasm of thyroid gland
226 Benign neoplasm of thyroid glands
237.4 Neoplasm of uncertain behavior of other and unspecified endocrine glands

ICD10: C73 Malignant neoplasm of thyroid gland
D34 Benign neoplasm of thyroid gland
D44.0 Neoplasm of uncertain behavior of thyroid gland

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Bernet V, et al. AACE/ACE disease state commentary: molecular diagnostic testing of thyroid nodules with

Proprietary Information of Excellus Health Plan, Inc.


* key article

KEY WORDS:
ThyroSeq®, Afirma® Gene Expression Classifier (GEC), fine need aspiration of the thyroid, molecular markers of thyroid, ThyGenX Thyroid Oncogene Panel
Based on our review, molecular Markers in Fine Needle Aspirates of the Thyroid is not addressed in National or Regional Medicare coverage determinations or policies. However Palmetto GBA has the following LCD for the Afirma Assay by Veracyte and includes Coding and Billing Guidelines. Please refer to the following website for Medicare Members:
http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Covered%20Tests~8Q7MRU7038?open&navmenu=%7C%7C