GUIDELINES
This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder contract. Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards. This guideline is solely for explaining correct procedure reporting and does not imply coverage and reimbursement.

DESCRIPTION
Thyroid nodules are 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. Those patients with cytologically indeterminate nodules are often referred for diagnostic surgery, though most of these nodules turn out to be benign.

In an attempt to better identify the need and type of surgical intervention, molecular markers utilizing FNA specimens from the thyroid were developed and include the following tests:
- Afirma® Thyroid FNA Analysis (Veracyte, South San Francisco, CA)
- Thyroseq® (CBLPath, Ocala, FL)
- ThyGenX® Thyroid Oncogene Panel (Interpace® Diagnostics, Parsippany, NJ)
- ThyraMIR™ Thyroid miRNA classifier (Interpace® Diagnostics, Parsippany, NJ)
- RosettaGX® (Rosetta Genomics™, Philadelphia, PA)

The Afirma® “gene expression classifier” (GEC) is a proprietary diagnostic test offered by Veracyte, which claims to classify a thyroid nodule with indeterminate cytology as benign (with >95% negative predictive value) or as suspicious for malignancy (>50% risk of malignancy). The GEC measures the gene expression of 142 genes and applies a multi-dimensional algorithm to classify whether a nodule with an indeterminate cytologic diagnosis is benign or suspicious. Test results may help patients avoid unnecessary surgeries.

The ThyroSeq® test was developed at the University of Pittsburg and uses the next-generation sequencing (NGS) technique to simultaneously test multiple mutations in thyroid cancer. There is insufficient published evidence on ThyroSeq® therefore, it cannot be recommended for use at this time. The main evidence deficiencies for ThyroSeq® are insufficient data on analytical validity, clinical validity, and clinical utility.

ThyraMIR™ is an miRNA gene expression classifier based on evaluation of expression of 10 miRNAs. ThyGenX® is a mutational panel based off of the miRInform test. ThyGenX assesses common genetic alterations across 8 genes associated with papillary carcinoma and follicular carcinoma. Both tests are marketed by Interpace Diagnostics (Parsippany, NJ) and the company reports they can be used in combination for “highly predictive results”.

The RosettaGX® is a diagnostic assay designed to classify indeterminate thyroid smears as benign or suspicious for malignancy. The assay uses routinely prepared FNA cytology smears and measures a set of miRNAs by quantitative RT-PCR to classify a nodule. Also measured is a miRNA specific to medullary carcinoma.

The commercially available, laboratory-developed molecular marker 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.

POLICY
Afirma® Thyroid FNA Analysis (81545) does not require prior authorization for all product lines.

These tests are non-covered for all product lines:
- Thyroseq® (0026U)
- ThyGenX® Thyroid Oncogene Panel
- ThyraMIR™ Thyroid miRNA classifier (0018U)
- RosettaGX®
HMO, PPO, Individual Marketplace, Elite, Advantage

Afirma® Thyroid FNA Analysis is covered when assessing adults with thyroid nodules that are ≥ 1cm in size and are not clearly benign or malignant based on fine-needle aspiration biopsy results alone.

The use of Afirma® Thyroid FNA Analysis is considered not medically necessary for repeat testing of the same nodule and all other indications not listed above as medically necessary.

The use of other molecular marker evaluations of thyroid nodules are considered not medically necessary and are therefore non-covered including but not limited to:

- Thyroseq® (0026U)
- ThyGenX® Thyroid Oncogene Panel
- ThyraMIR™ Thyroid miRNA classifier (0018U)
- RosettaGX®

Paramount has determined that these tests are experimental and investigational and therefore non-covered because there is insufficient evidence in the peer-reviewed medical literature of the effectiveness of these procedures.

CODING/BILLING INFORMATION
The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

<table>
<thead>
<tr>
<th>CPT CODE</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>0018U</td>
<td>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</td>
</tr>
<tr>
<td>0026U</td>
<td>Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result (&quot;Positive, high probability of malignancy&quot; or &quot;Negative, low probability of malignancy&quot;)</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81545</td>
<td>Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious) (New Code Effective 1/1/16)</td>
</tr>
</tbody>
</table>

TAWG REVIEW DATES: 07/18/2014, 04/23/2015, 12/17/2015, 03/25/2016, 05/27/2016, 06/24/2016, 03/22/2018

REVISION HISTORY EXPLANATION
07/18/14: Gene expression tests (e.g., Afirma®) are covered without prior authorization per TAWG review. Policy created per TAWG to reflect most current clinical evidence.
11/05/14: Removed CPT code 84999 and add CPT code 81479.
04/23/15: Changed title of policy from Molecular Marker of Thyroid Nodules to Afirma® Thyroid FNA Analysis. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
12/17/15: Added effective 1/1/16 new code 81545. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
03/25/16: Added effective 1/1/16 new code 81545. Policy reviewed and updated per TAWG to reflect most current clinical evidence.
05/27/16: Afirma® Thyroid FNA Analysis (81545) now requires prior authorization for all product lines. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
06/24/16: Afirma® Thyroid FNA Analysis (81545) does not require prior authorization for all product lines. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
03/22/18: Combined PG0334 ThyroSeq® v.2 Next Generation Sequencing with PG0298 Afirma® Thyroid FNA Analysis. Title changed to Molecular Markers in Fine Needle Aspirates of Thyroid Nodules. Added codes 0018U (ThyraMIR) & 0026U (Thyroseq) as non-covered. Added ThyGenX, ThyraMIR, & RosettaGX tests as non-covered. Policy reviewed and updated to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).

REFERENCES/RESOURCES
Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services
Ohio Department of Medicaid http://jfs.ohio.gov/
Industry Standard Review
Hayes, Inc.