Medica Coverage Policy

<table>
<thead>
<tr>
<th>Policy Name:</th>
<th>Genetic Testing of Thyroid Nodules for Thyroid Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Date:</td>
<td>3/20/2019</td>
</tr>
</tbody>
</table>

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica plans. Please refer to the member’s plan document for specific coverage information. If there is a difference between this general information and the member’s plan document, the member’s plan document will be used to determine coverage. With respect to Medicare and Minnesota Health Care Programs, this policy will apply unless those programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica coverage policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

Coverage Policy

Molecular profiling of thyroid nodules in fine-needle aspirates of the thyroid for thyroid cancer is COVERED when using one of the following tests:

1. Afirma® Gene Expression Classifier
2. Afirma® BRAF and MTC reflex testing
3. ThyroSeq® Genomic Classifier
4. ThyroSeq® v.3
5. ThyraMIR™
6. ThyGenX® with or without ThyraMIR™

All other genetic molecular profiling of thyroid nodules in fine-needle aspirates of the thyroid for thyroid cancer is investigational and therefore NOT COVERED.

Note: For pharmacogenetic testing required by the FDA, see Medica related coverage policy, Genetic and Pharmacogenetic Testing.

Description

Thyroid nodules are a common clinical finding. Epidemiological studies show prevalence of palpable thyroid nodules of about 5% in the United States population for ages 50 and older. Thyroid nodules are approximately 4 times more common in women than in men. Thyroid cancer, however, is uncommon, with a risk of less than 1% in the U.S.

Fine needle aspiration (FNA) biopsy (or FNAB) is the gold standard for preoperative differential diagnosis of thyroid nodules. However, in 20% - 25% of cases, nodules are indeterminate, usually due to overlapping cytologic features between benign and malignant nodules. Follow-up of patients with indeterminate results on FNA often includes surgical resection of the nodule or entire thyroid gland. However, nearly 80% of indeterminate nodules are benign based upon histopathology results. Recent studies have sought to identify genetic or genomic markers that may differentiate between benign and malignant thyroid tumors to help improve the diagnostic accuracy of
indeterminate thyroid nodule cytology results and avoid unnecessary surgical resection. Currently, there are three methods of analysis of FNA aspirates available: 1) Use of a gene expresser classifier, such as the Afirma® Thyroid FNA Analysis, 2) Identification of molecular biomarkers of malignancy or malignancy classifier, such as BRAF and RAS mutational status as well as panels that include multiple genes, and 3) Combination of malignancy classifiers (cancer mutational analyses) with gene expression classifier.

**Gene Expression Classifier:** 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 using microarray analysis. There are two gene expression profiling tests now available to biologically stratify tissue from thyroid nodules: Afirma® and ThyraMIR™. The Afirma® Gene Expression Classifier (Veracyte®) is a proprietary diagnostic test that analyzes the expression of 167-gene mRNA expressions to determine patterns associated with benign findings on surgical biopsy. ThyraMIR™ is a seven gene panel with a gene expression classifier involving 10 microRNAs.

**Malignancy Classifier:** Mutation analysis testing examines specific molecular markers in genes and evaluates them for rearrangements which could be associated with thyroid cancers. 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 thyroid carcinomas (PTCs) carry point mutations of the BRAF and RAS genes as well as RET/PTC and TRK rearrangements. These mutations are found in more than 70% of PTCs. BRAF mutations, such as the BRAF V600E gene, are highly specific for PTCs. Follicular carcinomas harbor either RAS mutations or PAX8/PPARγ rearrangements. These mutations are 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. Medullary carcinomas, which can be familial or sporadic, frequently possess point mutations located in the RET gene.

Point mutations associated with thyroid cancer can be analyzed using Sanger sequencing, pyrosequencing, and real-time polymerase chain reaction (rtPCR). Panels of tests are also available and Next-generation sequencing (NGS) that simultaneously evaluate for point mutations or gene fusions in multiple genes have been developed. For example, the ThyroSeq® v.3 Genomic Classifier uses NGS of DNA and RNA to analyze sequencing of more than 112 genes. The ThyGenX™ Thyroid Oncogene Panel (formerly miRInform® Thyroid) 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. ThyGenX™ is intended to be used in conjunction with the ThyraMIR™ microRNA expression test when the initial ThyGenX™ test is negative.

**Gene expression and malignancy classifier combined:** Afirma® (Veracyte®) 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).

**FDA Approval**
Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. Premarket approval from the FDA is not required as long as the assay is performed in a laboratory facility that observes CLIA regulations and does not market the test for distribution.

**Prior Authorization**
Prior authorization is not applicable. Claims for this service are subject to retrospective review and denial of coverage, as investigative services are not eligible for reimbursement.
Coding Considerations
Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

CPT Codes
- 0018U - 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
- 0026U - Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy")
- 81545 - Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)

Original Effective Date: 5/1/2014

Re-Review Date(s):
1/4/2016 – Administrative update – code added
3/16/2016
10/1/2017 – Administrative update – code added
3/20/2019
4/19/2019 – Administrative update – code added