Molecular Markers in Fine Needle Aspirates of Thyroid Nodules

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Medicare Advantage Medical Coverage Policy

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Related Medicare Advantage Medical/Pharmacy Coverage Policies

Genetic Testing
Thyroid Surgeries (Thyroidectomy and Lobectomy)

Related Documents

Please refer to CMS website for the most current applicable CMS Online Manual System (IOMs)/National Coverage Determination (NCD)/Local Coverage Determination (LCD)/Local Coverage Article (LCA)/Transmittals.
<table>
<thead>
<tr>
<th>Type</th>
<th>Title</th>
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<tr>
<td>LCD</td>
<td>MoIDX: Molecular Diagnostic Tests (MDT)</td>
<td>L36807</td>
<td>J5 - Wisconsin Physicians Service Insurance Corporation</td>
<td>IA, KS, MO, NE</td>
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<td>Thyroid Nodule Molecular Testing</td>
<td>L38968</td>
<td>J6 - National Government Services, Inc. (Part A/B MAC)</td>
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<td>CA, HI, NV, American Samoa, Guam, Northern Mariana Islands</td>
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Molecular Markers in Fine Needle Aspirates of Thyroid Nodules

<table>
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<th>Description</th>
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<td>Laboratory examination of cells in thyroid nodules acquired through fine needle aspiration (FNA) has been proposed to assist in exploring the possibility of thyroid cancer. These tests are used to detect molecular markers that are associated with thyroid cancer and are performed when cytopathology cannot determine if the nodule is malignant or benign. This classification is referred to as indeterminate.</td>
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</table>

Thyroid nodules are abnormal growths or lumps that develop in the thyroid gland. While most are benign, a small percentage are malignant. To determine the likelihood of malignancy, FNA is used to obtain cells from the nodule that is evaluated by cytopathology. FNA results are then assigned to one of 5 categories based on a classification system known as The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Results categorized as indeterminate warrant further evaluation, which may include repeat FNA, thyroid surgery and/or histopathology. Even with the additional examinations, the majority of cases are ultimately classified as benign. Testing for molecular markers in specimens already attained via FNA potentially eliminates the need for repeat FNA or for surgery. Examples include Afirma Genomic Sequencing Classifier (GSC), ThyGeNEXT Thyroid Oncogene Panel, ThyraMIR Thyroid miRNA Classifier and ThyroSeq Genomic Classifier (GC).

Testing for molecular markers in thyroid nodules specimens differs from germline genetic mutation testing. Analysis of molecular markers evaluates specimens for mutations acquired over an individual’s lifetime and are present only in the tissue sampled. Germline DNA is constant and identical in all body tissue types and mutations are inheritable.

Coverage Determination

iCare follows the CMS requirements that only allows coverage and payment for services that are reasonable and necessary for the diagnosis and treatment of illness or injury or to improve the functioning of a malformed body member except as specifically allowed by Medicare.
Genetic tests must demonstrate clinical utility, analytical and clinical validity and fulfill the CMS “reasonable and necessary” criteria. Analytic validity (test accurately identifies the gene variant), clinical validity (test identifies or predicts the clinically defined disorder) and clinical utility (test measurably improves clinical outcomes) of the genetic test is supported by generally accepted standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, specialty society recommendations, and views of physicians practicing in relevant clinical areas. The test must be ordered by a physician who is treating the beneficiary and the results will be used in the management of a beneficiary’s specific medical problem.

For jurisdictions with no Medicare guidance, iCare will utilize the MolDX program and Technical Assessments for molecular assays as the standard to evaluate clinical utility, analytical and clinical validity in conjunction with adhering to Medicare’s reasonable and necessary requirement.

In interpreting or supplementing the criteria above and in order to determine medical necessity consistently, iCare may consider the criteria contained in the following:

Afirma Genomic Sequencing Classifier (81546), ThyGeNext Thyroid Oncogene Panel (0245U) and ThyroSeq Genomic Classifier (0026U) will be considered medically reasonable and necessary when the following requirements are met:

- Presence of one or more nodules in the thyroid gland with a history or characteristics suggesting malignancy including ANY of the following:
  - 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 cervical adenopathy; AND

- Indeterminate follicular pathology on fine needle aspiration (Bethesda System for Reporting Thyroid Cytopathology cytologic categories III or IV); AND

- This test should be performed once per lifetime. Rarely, a second test can be performed in the unlikely situation of a second, unrelated thyroid nodule that has been tested and found to have indeterminate pathology

ThyraMIR Genomic Classifier (0018U) will be considered medically reasonable and necessary when ThyGeNEXT testing has been performed previously and the results are negative.

The use of the criteria in this Medicare Advantage Medical Coverage Policy provides clinical benefits highly likely to outweigh any clinical harms. Services that do not meet the criteria above are not medically
necessary and thus do not provide a clinical benefit. Medically unnecessary services carry risks of adverse outcomes and may interfere with the pursuit of other treatments which have demonstrated efficacy.

**Coverage Limitations**

US Government Publishing Office, Electronic code of federal regulations: part 411 – 42 CFR § 411.15 - Particular services excluded from coverage

The following tests may not be considered a benefit (statutory exclusion):

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law;\(^1\) OR
- Tests that confirm a diagnosis or known information;\(^1\) OR
- Tests to determine risk for developing a disease or condition;\(^1\) OR
- Tests performed to measure the quality of a process;\(^1\) OR
- Tests without diagnosis specific indications;\(^1\) OR
- Tests identified as investigational by available literature and/or the literature supplied by the developer and are not a part of a clinical trial\(^1\)

These treatments and services fall within the Medicare program’s statutory exclusion that prohibits payment for items and services that have not been demonstrated to be reasonable and necessary for the diagnosis and treatment of illness or injury (§1862(a)(1) of the Act). Other services/items fall within the Medicare program’s statutory exclusion at 1862(a)(12), which prohibits payment.

The following items for items will not be considered medically reasonable and necessary:

- Bethesda System for Reporting Thyroid Cytopathology cytologic categories Bethesda I, II, V or VI\(^1\)
- Genetic tests that have not demonstrated clinical utility, analytical and clinical validity via the MolDX Program
- Performed once per lifetime. Rarely, a second test can be performed in the unlikely situation of a second, unrelated thyroid nodule that has been tested and found to have indeterminate pathology\(^1\)
- Use of more than one molecular marker assay

A review of the current medical literature shows that the evidence is insufficient to determine that these services are standard medical treatments. There remains an absence of randomized, blinded clinical studies
examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

**Summary of Evidence**

**Molecular Markers in FNA of Thyroid Nodules**
Most thyroid nodules (85-93%) are noncancerous, necessitating various diagnostic tests such as history and physical, laryngoscopy, laboratory analysis, ultrasound, computed tomography, fine needle aspiration (FNA) and surgery for an accurate diagnosis. FNA often yields indeterminate (Bethesda III or IV) results (around 20%) with a 10-40% risk of malignancy. Historically, patients with an indeterminate result (Bethesda III or IV) proceeded to thyroid surgery (lobectomy) with a high proportion (75-95%) being benign. Molecular testing aims to lessen unnecessary thyroid surgeries by providing additional diagnostic insights.  

**Afirma GSC**
The Afirma GSC’s clinical validity is supported by various study types including randomized prospective trials, retrospective analysis of prospectively collected samples and retrospective analysis. On the other hand, its clinical utility is primarily established through retrospective analysis. A validation study of the Afirma GSC which was based on the same samples used for validation as the Afirma gene expression classifier (GEC) (a previous version of the test) (n = 191 of 210 lesions) demonstrated a 91% sensitivity and a specificity of 68%. The negative and positive predictive values were 96% and 47%, respectively, assuming a 24% frequency of malignancy.  

**ThyroSeq**
Study designs to determine clinical validity for ThyroSeq v3 consists of a randomized controlled trial, a prospective cohort study and retrospective cohort studies while clinical utility was evaluated by retrospective studies. In a multicenter validation study involving 257 indeterminate thyroid nodules, ThyroSeq v3 demonstrated a sensitivity of 94%, specificity 82%, negative predictive value of 97%, and positive predictive value of 66%.  

**ThyGeNext and ThyraMIR**
In a study of ThyGeNext and ThyraMIR, 178 indeterminate nodules with histologic confirmation were analyzed; 54 were cancerous. The sensitivity was 95%, specificity 90%, negative predictive value 95% and positive predictive value 75%.  

**Coding Information**
Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.
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<th>Description</th>
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<td>81445</td>
<td>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</td>
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</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<td>81546</td>
<td>Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)</td>
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<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
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<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>
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<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>
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<tr>
<td>0204U</td>
<td>Oncology (thyroid), mRNA, gene expression analysis of 593 genes (including BRAF, RAS, RET, PAX8, and NTR) for sequence variants and rearrangements, utilizing fine needle aspirate, reported as detected or not detected</td>
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<tr>
<td>0245U</td>
<td>Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage</td>
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<td>0287U</td>
<td>Oncology (thyroid), DNA and mRNA, next-generation sequencing analysis of 112 genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high)</td>
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<td>0362U</td>
<td>Oncology (papillary thyroid cancer), gene-expression profiling via targeted hybrid capture–enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, formalin-fixed paraffin embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes</td>
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References


56. UpToDate, Inc. Evaluation and management of thyroid nodules with indeterminate cytology. 

57. UpToDate, Inc. Oncogenes and tumor suppressor genes in thyroid nodules and nonmedullary thyroid cancer. 


findings vs the initial clinical validation findings of a thyroid nodule gene expression classifier: a 

Appendix

Appendix A
Bethesda System Diagnostic Categories for Reporting Thyroid Cytopathology

<table>
<thead>
<tr>
<th>Bethesda Class</th>
<th>Diagnostic Category</th>
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<td>I</td>
<td>Nondiagnostic (unsatisfactory)</td>
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<tr>
<td>II</td>
<td>Benign</td>
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<tr>
<td>III</td>
<td>Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)</td>
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<tr>
<td>IV</td>
<td>Follicular neoplasm (or suspicious for follicular neoplasm)</td>
</tr>
<tr>
<td>V</td>
<td>Suspicious for malignancy</td>
</tr>
<tr>
<td>VI</td>
<td>Malignant</td>
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Change Summary

- 01/01/2024 New Policy.