Molecular Markers in Fine Needle Aspirates of Thyroid Nodules

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Medical Coverage Policy

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Description

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.

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 are 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.

The following are clinically available tests that analyze 10 to over 10,000 genes at one time to identify molecular markers relevant to thyroid cancer using specimens obtained through FNA:

- **Afirma Genomic Sequencing Classifier (GSC)** is a ribonucleic acid (RNA) sequencing technology platform that analyzes thousands of genes at one time to detect alterations.
    - **Afirma Xpression Atlas (XA)** has been consolidated with Afirma GSC and is no longer offered as a separate test for a physician to order. Results of Afirma XA are automatically included in the Afirma GSC report. **(Refer to Coverage Limitations section)**
- **ThyGeNEXT Thyroid Oncogene Panel** is a DNA and RNA NGS-based test that analyzes genes and RNA fusions associated with thyroid cancer. **ThyraMIRv2 Thyroid miRNA Classifier** is a microRNA (miRNA) profiling test performed reflexively to ThyGeNEXT. ThyraMIR evaluates the expression of miRNAs that may be associated with thyroid cancer. ThyGenNEXT and ThyraMIR are referred to as combination testing. **(Refer to Coverage Limitations section)**
- **ThyroSeq v3 Genomic Classifier (GC)** uses an NGS platform to evaluate DNA and RNA of genes associated with thyroid cancer by examining indeterminate FNA.
- **ThyroSeq v3 Cancer Risk Classifier (CRC)** also uses NGS to analyze the DNA and RNA of over 100 genes in cytologically malignant FNA or resected thyroid tissue to purportedly aid in determining risk of recurrence. **(Refer to Coverage Limitations section)**
- **Multigene (or expanded) panels** analyze a broad set of genes simultaneously (as opposed to single gene testing that searches for variants in one specific gene) and have been proposed to evaluate the DNA of an individual with a personal and/or family history of more than one hereditary condition or syndrome. Panels often include medically actionable genes but may also include those with unclear medical management. **Targeted (or focused) multigene panels** analyze a limited number of genes targeted to a specific condition. **(Refer to Coverage Limitations section)**
- **Single-site genetic testing** to identify mutations associated with thyroid cancer have been proposed to assist in the reclassification of indeterminate nodules. Genes include, but may not be limited to, *PAX8/PPARgamma, RET/PTC* and *TERT*. **(Refer to Coverage Limitations section)**

Molecular profiling for papillary thyroid carcinoma has also been proposed to determine risk of recurrence. An example includes Thyroid GuidePx. **(Refer to Coverage Limitations section)**

Testing for molecular markers in thyroid nodule 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

Any state mandates for molecular markers in FNA of thyroid nodules take precedence over this medical coverage policy.

Humana members may be eligible under the Plan for any of the following **molecular markers assays to assess thyroid nodules specimens obtained by FNA**:

- Afirma GSC (81546), ThyGeNext Thyroid Oncogene Panel (0245U) or ThyroSeq GC (0026U) to assess thyroid nodule specimens when the following criteria are met:
  - Thyroid nodule 1 cm or greater on ultrasound; **AND**
  - Indeterminate thyroid FNA cytopathology***** described as:
    - Atypia of undetermined significance (AUS (Bethesda III); **OR**
    - Follicular neoplasm (FN) (Bethesda IV)

Humana members may be eligible under the Plan for **ThyraMIR Genomic Classifier** (0018U) when ThyGeNEXT testing has been performed previously and the results are negative.

*****Alternative terms for indeterminate thyroid FNA cytopathology include atypical follicular lesion, cellular follicular lesion or rule out neoplasm

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for **molecular markers in thyroid nodule specimens obtained by FNA** for any indications or tests other than those listed above including, but may not be limited to:

- Afirma GSC or ThyroSeq GC for the following:
  - Evaluation of FNA thyroid cytopathology with Bethesda I, II, V or VI cytologic categories
  - Evaluation of thyroid nodule less than 1 cm
  - Repeat molecular marker testing of FNA aspirates for any indication
  - Testing more than 1 nodule when an individual presents with multiple nodules
- Evaluation of papillary thyroid carcinoma (eg, Thyroid GuidePx [0362U])

- Multigene panels (expanded or targeted) for the evaluation of indeterminate thyroid FNA cytopathology

- Single-site mutational analysis for the evaluation of indeterminate thyroid FNA cytopathology for any genes including, but may not be limited to:

  - *DICER*
  - *EIF1AX*
  - *NTRK*
  - *PAX8/PPARgamma*
  - *PIK3CA*
  - *PTEN*
  - *RAS* (*HRAS*, *KRAS*, *NRAS)*
  - *RET/PTC*
  - *TERT*

- ThyroSeq v3 Cancer Risk Classifier (CRC) (0287U)

- Use of more than one molecular marker assay

These are considered experimental/investigational as they are not identified as widely used and generally accepted for any other proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may NOT be eligible under the Plan for **Afirma XA (0204U)**. This is considered not medically necessary as defined in the member's individual certificate. Please refer to the member's individual certificate for the specific definition.

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.

CPT® Code(s)	Description	Comments
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)	**Not Covered if used to report any test outlined in Coverage Limitations section**
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)	**Not Covered if used to report any test outlined in Coverage Limitations section**

81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)	**Not Covered if used to report any test outlined in Coverage Limitations section**
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)	**Not Covered if used to report any test outlined in Coverage Limitations section**
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis	**Not Covered if used to report any test outlined in Coverage Limitations section**
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant	**Not Covered if used to report any test outlined in Coverage Limitations section**
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant	**Not Covered if used to report any test outlined in Coverage Limitations section**
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)	**Not Covered if used to report any test outlined in Coverage Limitations section**
81401	MOLECULAR PATHOLOGY PROCEDURE LEVEL 2	**Not Covered if used to report any test outlined in Coverage Limitations section**
81403	MOLECULAR PATHOLOGY PROCEDURE LEVEL 4	**Not Covered if used to report any test outlined in Coverage Limitations section**
81404	MOLECULAR PATHOLOGY PROCEDURE LEVEL 5	**Not Covered if used to report any test outlined in Coverage Limitations section**
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	**Not Covered if used to report any test outlined in Coverage Limitations section**

81479	Unlisted molecular pathology procedure	**Not Covered if used to report any test outlined in Coverage Limitations section**
81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)	
81599	Unlisted multianalyte assay with algorithmic analysis	**Not Covered if used to report any test outlined in Coverage Limitations section**
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")	
0204U	Oncology (thyroid), mRNA, gene expression analysis of 593 genes (including BRAF, RAS, RET, PAX8, and NTRK) for sequence variants and rearrangements, utilizing fine needle aspirate, reported as detected or not detected	**Not Covered**
0245U	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	
0287U	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)	**Not Covered**
0362U	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	**Not Covered**
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		

HCPCS Code(s)	Description	Comments
No code(s) identified		

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Appendix

Appendix A
Bethesda System Diagnostic Categories for Reporting Thyroid Cytopathology[1]

Bethesda Class	Diagnostic Category
I	Nondiagnostic
II	Benign
III	Atypia of undetermined significance (AUS)
IV	Follicular neoplasm
V	Suspicious for malignancy
VI	Malignant

Change Summary

- 02/29/2024 Annual Review, Coverage Change. Updated Coding Information.