Molecular Markers in Thyroid Fine Needle Aspirates

Policy Number:	**M20160126004**
Effective Date:	**12/1/2016**
Sponsoring Department:	**Health Care Services**
Impacted Department(s):	**Health Care Services**

Type of Policy: ☒ Internal ☒ External

Data Classification: ☐Confidential ☐Restricted ☒Public

Applies to (Line of Business):

☐ Corporate (All)
☒ State Products, if yes which plan(s): ☒MediSource; ☒ MediSource Connect; ☒Child Health Plus ☒Essential Plan
☒ Medicare, if yes, which plan(s): ☒MAPD; ☐PDP; ☒ISNP; ☒CSNP
☒ Commercial, if yes, which type: ☒Large Group; ☒Small Group; ☒Individual
☒ Self-Funded Services *(Refer to specific Summary Plan Descriptions (SPDs) to determine any pre-authorization or pre-certification requirements and coverage limitations. In the event of any conflict between this policy and the SPD of a Self-Funded Plan, the SPD shall supersede the policy.)*

Excluded Products within the Selected Lines of Business (LOB)

Applicable to Vendors? Yes ☐ No☒

Purpose and Applicability:

To set forth the medical policy for molecular markers in thyroid fine needle aspirates using the **Afirma™ or Thyroseq3®** test.

Policy:

Background:
The Afirma™ Thyroid FNA Analysis was designed to help differentiate between benign and malignant thyroid lesions in patients with indeterminate fine needle aspirate (FNA) cytology. Afirma™ examines the expression of 167 genes in thyroid FNA specimens with indeterminate cytology, in order to distinguish benign and malignant thyroid nodules, with the goal of avoiding unnecessary surgical procedures. The test utilizes a proprietary algorithm, called the gene expression classifier (GEC), to categorize an indeterminate thyroid nodule as either "benign" or "suspicious." An important limitation of the assay is that the analysis requires adequate sampling of the thyroid nodule, which could lead to the need for multiple FNA biopsies. According to recent data, between 3% and 10% of FNA samples tested with the Afirma™ assay have insufficient RNA yield or quality and are unable to be classified by the GEC.
Thyroseq3®, which was preceded by earlier assay versions, tests for mutations, insertions/deletions, fusions, gene expression, and copy number variations in 112 thyroid-related genes. Mutational analysis identifies molecular markers of malignancy which allows for better risk determination and reduces the need for diagnostic thyroid surgery.

Commercial and Self-Funded: Independent Health covers molecular markers in thyroid fine needle aspirates utilizing the criteria below.

Medicare Advantage:
There is currently a Local Coverage Determination (LCD) for molecular markers in thyroid fine needle aspirates. Please refer to the links listed in the Reference section for Medicare Advantage members.

MediSource, Child Health Plus and Essential Plan:
MediSource, Child Health Plus and Essential Plan do not cover molecular markers in thyroid fine needle aspirates testing.

Clinical Indications

Independent Health considers the use of the Afirma™ (Veracyte, Inc.) and Thyroseq3® (CBLPath) gene expression classifiers in fine-needle aspirates of the thyroid that are cytologically considered to be indeterminate, atypical or suspicious for malignancy ONCE per nodule workup to be medically necessary for members with **ALL** of the following criteria:

- Nodule size greater than 1.0 cm
- **1 or more** of the following:
    - Cytological diagnosis of **atypia of undetermined significance/follicular lesion of either undetermined (AUS/FLUS)**
    - Significant (AUS/FLUS) on **fine-needle aspiration (FNA)**
    - Cytological diagnosis of **follicular neoplasm**/suspicious for follicular neoplasm (FN/SFN) on fine-needle aspiration (FNA)

Bethesda III or IV on FNA cytology (Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance OR Follicular Neoplasm or Suspicious for a Follicular Neoplasm)

NOT COVERED for **Any** of the following:

- State product members

Pre-Authorization Required? Yes ☒ No☐

Pre-authorization is required for this service.

1. The ordering /rendering laboratory is responsible for securing Prior Authorization for Medically Necessary molecular diagnostic testing.

2. The ordering / referring physician is responsible for submitting all relevant member-level clinical information to the rendering laboratory to support the Prior Authorization request.

3. Claims received for molecular diagnostic testing lacking Prior Authorization will deny to the responsibility of the rendering laboratory, and Independent Health members shall not be billed. Therefore, it is imperative for rendering laboratories, with clinical information supplied by ordering / referring physicians, to secure and verify Prior Authorization in accordance with the process above and clinical requirements above.

Definitions

Afirma™ Gene Expression Classifier includes a standard cytopathologic evaluation of FNA specimens and an expression analysis of 167 genes in nodules with indeterminate FNA cytopathology. The molecular portion of the test, which involves an analysis of RNA extracted from thyroid nodule aspirates, utilizes the gene expression classifier to classify indeterminate nodules as either "benign" or suspicious." A nondiagnostic result indicates that the RNA sample was insufficient for analysis.

AUS/FLUS atypia or follicular lesion of undetermined significance is a cytologic result which is often called indeterminate. The risk of malignancy with these cytologic classifications ranges from 10 to 40 percent.

Bethesda System for the Classification of Thyroid Nodules includes 6 categories divided according to the probability of malignancy: nondiagnostic; benign; atypical or follicular lesion of undetermined significance; follicular neoplasm (suspicious for follicular or Hürthle neoplasm); suspicious for malignancy; and malignant. A nodule is considered indeterminate when it is categorized as an atypical or follicular lesion of undetermined significance, a follicular neoplasm (or suspicious for follicular neoplasm), or suspicious for malignancy. A nondiagnostic FNA result indicates that the specimen was insufficient for analysis.

The Bethesda System for Reporting Thyroid Cytopathology

Risk Category	Definition	Diagnostics
I	Nondiagnostic or Unsatisfactory	– Cyst fluid only – Virtually acellular specimen – Other (obscuring blood, clotting artifact, etc.)

II	Benign	– Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.) – Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context – Consistent with granulomatous (subacute) thyroiditis – Other
III	Atypia of Undetermined Significance *or* Follicular Lesion of Undetermined Significance	
IV	Follicular Neoplasm or Suspicious for a Follicular Neoplasm	Specify if Hürthle cell (oncocytic) type
V	Suspicious for Malignancy	– Suspicious for papillary carcinoma – Suspicious for medullary carcinoma – Suspicious for metastatic carcinoma – Suspicious for lymphoma – Other
VI	Malignant	– Papillary thyroid carcinoma – Poorly differentiated carcinoma – Medullary thyroid carcinoma – Undifferentiated (anaplastic) carcinoma – Squamous cell carcinoma – Carcinoma with mixed features (specify) – Metastatic carcinoma – Non-Hodgkin lymphoma – Other

Fine Needle Aspiration (FNA) is an office procedure when tissue samples are obtained for cytological examination using 23 to 27-gauge needles with or without local anesthesia. Ultrasound –guided FNA biopsy can be performed for nonpalpable nodules and for nodules that are technically difficult to aspirate using palpation methods alone. FNA specimens obtained from thyroid nodules are classified based on the Bethesda System for reporting thyroid cytopathology.

Follicular neoplasms may be benign follicular adenomas (including autonomous nodules), follicular cancers, or follicular variant papillary cancers.

ThyroSeq3® test utilizes next-generation sequencing (NGS) of DNA and RNA to analyze 112 genes, providing information on > 12,000 mutation hotspots and > 150 gene fusion types. The test uses a proprietary genomic classifier based on the algorithmic analysis of all detected genetic alterations to provide the test result as positive or negative**.**

References

Related Policies, Processes and Other Documents
N/A

Non-Regulatory references
Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med. 2012 Aug 23;367(8):705-15.

Bernet V, Hupart KH, Parangi S, et al. AACE/ACE disease state commentary: molecular diagnostic testing of thyroid nodules with indeterminate cytopathology. Endocr Pract. 2014 Apr;20(4):360-3.

Duick DS, Klopper JP, Diggans JC, et al. The impact of benign gene expression classifier test results on the endocrinologist-patient decision to operate on patients with thyroid nodules with indeterminate fine-needle aspiration cytopathology. Thyroid. 2012 Oct;22(10):996-1001.

Livhits MJ, Zhu CY, Kuo EJ et al. Effectiveness of Molecular Testing Techniques for Diagnosis of Indeterminate Thyroid Nodules: A Randomized Clinical Trial. JAMA Oncol. 2021 Jan 1;7(1):70-77.

National Comprehensive Cancer Network (NCCN) [web site]. Thyroid Cancer. Version 2.2026 — June 2, 2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
Accessed July 8, 2026.

Ross DS, Evaluation and management of thyroid nodules with indeterminate cytology. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed on July 8, 2026.

Symplr, Inc., Molecular Test Assessment Afirma™ Genomic Sequencing Classifier (Veracyte). Houston, TX: April 2021.

Regulatory References
Centers for Medicare and Medicaid (CMS) [web site]. LCD - Thyroid Nodule Molecular Testing (L38968). Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=38968&ver=4
Accessed July 8, 2026.

Centers for Medicare and Medicaid (CMS) [web site]. Local Coverage Article Billing and Coding: MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules A59509 Available at:https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=59509&ver=5&
Accessed July 8, 2026.

Centers for Medicare and Medicaid (CMS) [web site]. Local Coverage Determination MolDX: Molecular Testing for Risk Stratification of Thyroid Nodules L39682. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39682&ver=8&bc=0 Accessed July 8, 2026.

Centers for Medicare and Medicaid (CMS) [web site]. Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT) (A57772). Available at: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=57772&ver=78&bc=0Accessed July 8, 2026.

Centers for Medicare and Medicaid (CMS) [web site]. Local Coverage Determination (LCD) MolDX: Molecular Diagnostic Tests (MDT) (L36807) . Available at https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=36807&ver=45&keyword=L36807&keywordType=starts&areaId=s66&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1
Accessed on July 8, 2026.

This policy contains medical necessity criteria that apply for this service. Please note that payment for covered services is subject to eligibility criteria, contract exclusions and the limitations noted in the member's contract at the time the services are rendered.

Version Control

Signature / Approval on File? Yes ☒ No☐

Revision Date	Owner	Notes
9/1/2026	Health Care Services	Revised
10/1/2025	Health Care Services	Revised- Formatting Only
10/4/2024	Health Care Services	Reviewed
10/1/2023	Health Care Services	Reviewed
10/1/2022	Health Care Services	Revised
3/1/2022	Health Care Services	Revised
1/1/2022	Health Care Services	Reviewed
2/1/2021	Health Care Services	Revised
8/1/2020	Health Care Services	Revised
9/1/2019	Medical Management	Revised
10/1/2018	Medical Management	Revised
11/1/2017	Medical Management	Revised