Molecular Markers in Fine Needle Aspirates of Thyroid Nodules

INDEPENDENT CARE HEALTH PLAN

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Medicare Advantage Medical Coverage Policy

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Related Medicare Advantage Medical/Pharmacy Coverage Policies

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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.

Type	Title	ID Number	Jurisdiction Medicare Administrative Contractors (MACs)	Applicable States/Territories
LCD LCA	MolDX: Molecular Diagnostic Tests (MDT) Billing and Coding: MolDX: Afirma™ Assay by Veracyte Update	L36807 A55139	J5 - Wisconsin Physicians Service Insurance Corporation J8 - Wisconsin Physicians Service Insurance Corporation	IA, KS, MO, NE IN, MI
LCD LCA	Thyroid Nodule Molecular Testing Billing and Coding: Thyroid Nodule Molecular Testing	L38968 A58656	J6 - National Government Services, Inc. (Part A/B MAC) JK - National Government Services, Inc. (Part A/B MAC	IL, MN, WI CT, NY, ME, MA, NH, RI, VT
LCD LCA	MolDX: Molecular Diagnostic Tests (MDT) Billing and Coding: MolDX: Afirma™ Assay by Veracyte Update	L36021 A54185	J15 - CGS Administrators, LLC (Part A/B MAC)	KY, OH
LCD LCA	MolDX: Molecular Diagnostic Tests (MDT) Billing and Coding: MolDX: Afirma™ Assay by Veracyte	L35160 A54356	JE - Noridian Healthcare Solutions, LLC	CA, HI, NV, American Samoa, Guam, Northern Mariana Islands
LCD LCA	MolDX: Molecular Diagnostic Tests (MDT) Billing and Coding: MolDX: Afirma™ Assay by Veracyte	L36256 A54358	JF - Noridian Healthcare Solutions, LLC	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
LCD LCA	Biomarkers for Oncology Billing and Coding: Biomarkers for Oncology	L35396 A52896	JH - Novitas Solutions, Inc. (Part A/B MAC)	AR, CO, NM, OK, TX, LA, MS DE, D.C., MD, NJ, PA

			JL - Novitas Solutions, Inc. (Part A/B MAC)	
LCD LCA	MolDX: Molecular Diagnostic Tests (MDT) Billing and Coding: MolDX: Afirma™ Assay by Veracyte Update	L35025 A53098	JJ - Palmetto GBA (Part A/B MAC) JM - Palmetto GBA (Part A/B MAC)	AL, GA, TN NC, SC, VA, WV
LCD LCA	Molecular Pathology Procedures Billing and Coding: Molecular Pathology and Genetic Testing	L34519 A58918	JN - First Coast Service Options, Inc. (Part A/B MAC)	FL, PR, U.S. VI

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 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[18]
    - Family history of thyroid cancer[18]
    - Hoarseness, difficulty swallowing or breathing[18]
    - History of exposure to ionizing radiation[18]
    - Hard nodule compared with rest of gland consistency[18]
    - Presence cervical adenopathy;[18] **AND**
- Indeterminate follicular pathology on fine needle aspiration (Bethesda System for Reporting Thyroid Cytopathology cytologic categories III or IV);[18] **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[11]

ThyraMIR Genomic Classifier (0018U) will be considered medically reasonable and necessary when ThyGeNEXT testing has been performed previously and the results are negative.[18,34]

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;[49] **OR**
- Tests that confirm a diagnosis or known information;[49] **OR**
- Tests to determine risk for developing a disease or condition;[49] **OR**
- Tests performed to measure the quality of a process;[49] **OR**
- Tests without diagnosis specific indications;[49] **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[49]

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[18]
- 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[11]
- 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.[56]

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.[33] 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.[56]

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.[35] 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%.[56]

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%.[56]

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

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	
81479	Unlisted molecular pathology procedure	
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	
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	
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)	
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	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		

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

References

1. American Association of Clinical Endocrinologists (AACE). AACE/ACE/AME Guidelines. American Association of Clinical Endocrinology, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules – 2016 update. https://www.aace.com. Published May 2016. Accessed February 2, 2023.

2. American Association of Clinical Endocrinologists (AACE). White Paper. American Association of Clinical Endocrinology and Associazione Medici Endocrinologi thyroid nodule algorithmic tool. https://www.aace.com. Published 2021. Accessed February 2, 2023.

3. American Association of Endocrine Surgeons (AAES). Original Article. The American Association of Endocrine Surgeons guidelines for the definitive surgical management of thyroid disease in adults. https://www.endocrinesurgery.org. Published 2020. Accessed February 8, 2022.

4. American Thyroid Association (ATA). American Thyroid Association statement on surgical application of molecular profiling for thyroid nodules: current impact on perioperative decision making. https://www.thyroid.org. Published July 10, 2015. Accessed February 2, 2023.

5. American Thyroid Association (ATA). Special Articles. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. https://www.thyroid.org. Published January 12, 2016. Accessed February 2, 2023.

6. American Thyroid Association (ATA). Special Articles. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. https://www.thyroid.org. Published July 10, 2015. Accessed February 8, 2022.

7. American Thyroid Association (ATA). The 2023 Bethesda System for Reporting Thyroid Cytopathology. https://www.thyroid.org. Published September 13, 2023. Accessed September 27, 2023.

8. Bardet S, Goardon N, Lequesne J, et al. Diagnostic and prognostic value of a 7-panel mutation testing in thyroid nodules with indeterminate cytology: the SWEETMAC study. *Endocrine*. 2021;71(2):407-417. https://www.ncbi.nlm.nih.gov/pmc. Accessed February 7, 2022.

9. Borrelli N, Ugolini C, Giannini R, et al. Role of gene expression profiling in defining indeterminate thyroid nodules in addition to BRAF analysis. *Cancer Cytopathol*. 2016;124(5):340-349.

10. Carr DM, Mastorides S, Stobaugh C, Carlton G, DeLand L, Borkowski A. Molecular testing of atypical thyroid nodules with corresponding surgical correlation: five-year retrospective review in veterans

population. *Cureus*. 2022;14(2):e22536. https://www.ncbi.nlm.nih.gov/pmc. Accessed January 26, 2023.

11. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). Billing and coding: biomarkers for oncology (A52986). https://www.cms.gov. Published October 1, 2015. Updated August 7, 2023. Accessed August 31, 2023.

12. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). Billing and coding: MolDX: Afirma™ Assay by Veracyte (A54356). https://www.cms.gov. Published October 1, 2015. Updated January 1, 2021. Accessed August 31, 2023.

13. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). Billing and coding: MolDX: Afirma™ Assay by Veracyte (A53098). https://www.cms.gov. Published October 1, 2015. Updated January 1, 2021. Accessed August 31, 2023.

14. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). Billing and coding: MolDX: Afirma™ Assay by Veracyte update (A55139). https://www.cms.gov. Published February 16, 2017. Updated April 28, 2022. Accessed August 31, 2023.

15. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). Billing and coding: MolDX: Afirma™ Assay by Veracyte update (A55139). https://www.cms.gov. Published February 16, 2017. Updated April 28, 2022. Accessed August 31, 2023.

16. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). Billing and coding: molecular pathology and genetic testing (A58918). https://www.cms.gov. Published November 8, 2021. Updated July 1, 2023. Accessed August 31, 2023.

17. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). Billing and coding: thyroid nodule molecular testing (A58656). https://www.cms.gov. Published December 1, 2021. Updated January 1, 2022. Accessed August 31, 2023.

18. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). Biomarkers for oncology (L35396). https://www.cms.gov. Published October 1, 2015. Updated December 13, 2020. Accessed August 31, 2023.

19. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). MolDX: molecular diagnostic tests (MDT) (L35160). https://www.cms.gov. Published October 1, 2015. Updated May 4, 2023. Accessed August 31, 2023.

20. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). MolDX: molecular diagnostic tests (MDT) (L36256). https://www.cms.gov. Published October 1, 2015. Updated May 4, 2023. Accessed August 31, 2023.

21. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). MolDX: molecular diagnostic tests (MDT) (L36021). https://www.cms.gov. Published October 1, 2015. Updated May 4, 2023. Accessed August 31, 2023.

22. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). MolDX: molecular diagnostic tests (MDT) (L36807). https://www.cms.gov. Published February 16, 2017. Updated April 27, 2023. Accessed August 31, 2023.

23. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). Molecular pathology procedures (L34519). https://www.cms.gov. Published October 1, 2015. Updated December 12, 2021. Accessed August 31, 2023.

24. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD). Thyroid nodule molecular testing (L38968). https://www.cms.gov. Published December 1, 2021. Accessed August 31, 2023.

25. Ciarletto AM, Narick C, Malchoff CD, et al. Analytical and clinical validation of pairwise microRNA expression analysis to identify medullary thyroid cancer in thyroid fine-needle aspiration samples. *Cancer Cytopathol*. 2021;129(3):239-249. https://www.ncbi.nlm.nih.gov/pmc. Accessed February 7, 2022.

26. ClinicalKey. Clinical Overview. Thyroid nodule. https://www.clinicalkey.com. Updated January 1, 2023. Accessed January 27, 2023.

27. ECRI Institute. ECRIgene Genetic Test Product Brief. Afirma Genomic Sequencing Classifier (Veracyte, Inc.) for evaluating thyroid nodules of indeterminate cytopathologic diagnosis. https://www.ecri.org. Published February 2020. Accessed January 23, 2023.

28. ECRI Institute. ECRIgene Genetic Test Product Brief. ThyGenX Oncogene Panel Plus ThyraMIR microRNA Classifier (Interpace Diagnostics, LLC) for evaluating cytologically indeterminate thyroid nodules. https://www.ecri.org. Published January 2020. Accessed January 23, 2023.

29. ECRI Institute. ECRIgene Genetic Test Product Brief. ThyroSeq v.3 (University of Pittsburgh Medical Center) for evaluating cytologically indeterminate thyroid nodules. https://www.ecri.org. Published January 2020. Accessed January 23, 2023.

30. Gallant JN, Chen SC, Ortega CA, et al. Evaluation of the molecular landscape of pediatric thyroid nodules and use of a multigene genomic classifier in children. *JAMA Oncol*. 2022;8(9):1323-1327. https://www.ncbi.nlm.nih.gov/pmc. Accessed January 26, 2023.

31. Gargano SM, Badjatia N, Nikolaus Y, Peiper SC, Wang ZX. Characterization and clinical significance of EIF1AX mutations and co-mutations in cytologically indeterminate thyroid nodules: a 5-year retrospective analysis. *Acta Med Acad*. 2021;50(1):4-12. https://www.ama.ba. Accessed January 31, 2023.

32. Gokozan HN, Dilcher TL, Alperstein SA, et al. Combining molecular testing and the Bethesda category III:VI ratio for thyroid fine-needle aspirates: A quality-assurance metric for evaluating diagnostic performance in a cytopathology laboratory. *Cancer Cytopathol*. 2022;130(4):259-274.

33. Hayes, Inc. Molecular Test Assessment. Afirma Genomic Sequencing Classifier (Veracyte Inc.). https://evidence.hayesinc.com. Published April 7, 2021. Updated March 28, 2022. Accessed January 23, 2023.

34. Hayes, Inc. Molecular Test Assessment. ThyGeNEXT and ThyraMIR (Interpace Diagnostics Group Inc). https://evidence.hayesinc.com. Published July 10, 2019. Updated October 21, 2022. Accessed January 23, 2023.

35. Hayes, Inc. Molecular Test Assessment. ThyroSeq v3 (University of Pittsburgh Medical Center, CBLPath). https://evidence.hayesinc.com. Published May 9, 2019. Updated October 19, 2021. Accessed January 23, 2023.

36. Hu C, Jing W, Chang Q, et al. Risk stratification of indeterminate thyroid nodules by novel multigene testing: a study of Asians with a high risk of malignancy. *Mol Oncol*. 2022;16(8):1680-1693. https://www.ncbi.nlm.nih.gov/pmc. Accessed January 26, 2023.

37. Hu MI, Waguespack SG, Dosiou C, et al. Afirma Genomic Sequencing Classifier and Xpression Atlas molecular findings in consecutive Bethesda III-VI thyroid nodules. J *Clin Endocrinol Metab*. 2021;13;106(8):2198-2207. https://www.ncbi.nlm.nih.gov/pmc. Accessed February 7, 2022.

38. Jin X, Lew M, Pantanowitz L, Smola B, Jing X. Performance of Afirma genomic sequencing classifier and histopathological outcome are associated with patterns of atypia in Bethesda category III thyroid nodules. *Cancer Cytopathol*. 2022;130(11):891-898.

39. Kaya C, Dorsaint, P, Mercurio S, et al. Limitations of detecting genetic variants from the RNA sequencing data in tissue and fine-needle aspiration samples. *Thyroid*. 2021;31(4):589-595. https://www.ncbi.nlm.nih.gov/pmc. Accessed February 7, 2022.

40. Kim TH, Jeong DJ, Hahn SY, et al. Triage of patients with AUS/FLUS on thyroid cytopathology: effectiveness of the multimodal diagnostic techniques. *Cancer Med*. 2016;5(5):769-777. https://www.ncbi.nlm.nih.gov/pmc. Accessed May 4, 2017.

41. Labourier E, Fahey TJ. Preoperative molecular testing in thyroid nodules with Bethesda VI cytology: Clinical experience and review of the literature. *Diagn Cytopathol*. 2021;49(4):E175-E180. https://www.ncbi.nlm.nih.gov/pmc. Accessed February 7, 2021.

42. Liu Y, Pan B, Xu L, Fang D, Ma X, Lu H. The diagnostic performance of Afirma gene expression classifier for the indeterminate thyroid nodules: a meta-analysis. *Biomed Res Int*. 2019:7150527. https://www.ncbi.nlm.nih.gov/pmc. Accessed June 10, 2020.

43. Lu SY, Chen YC, Zhu CF, et al. A five-gene panel refines differential diagnosis of thyroid nodules. *J Clin Lab Anal*. 2021;35(9):e23920. https://www.ncbi.nlm.nih.gov/pmc. Accessed January 31, 2023.

44. MCG Health. Thyroid nodule gene expression testing. 26th edition. https://www.mcg.com. Accessed January 27, 2023.

45. Napoli F, Rapa I, Mortara U, et al. MicroRNA profiling predicts positive nodal status in papillary thyroid carcinoma in the preoperative setting. *Cancer Cytopathol*. 2022;130(9):695-704.

46. National Comprehensive Cancer Network (NCCN). NCCN Biomarkers Compendium. Thyroid carcinoma: abnormal gene/gene expression profiles. https://www.nccn.org. Updated 2023. Accessed February 2, 2023.

47. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Thyroid carcinoma. https://www.nccn.org. Updated November 1, 2022. Accessed February 2, 2023.

48. O'Conor CJ, Dash RC, Jones CK, Jiang XS. Performance of repeat cytology with reflex ThyroSeq genomic classifier for indeterminant thyroid cytology. *Cancer Cytopathol*. 2022;130(6):469-476.

49. Palmetto GBA. Molecular diagnostic program (MolDX®): coverage, coding, and pricing standards and requirements (M00106). https://www.palmettogba.com/MolDx. Published December 2019. Accessed September 27, 2023.

50. Salameh S, Rajab M, Forest VI, Pusztaszeri M, Payne RJ. Surgical outcomes of thyroid nodules positive for gene expression alterations using ThyroSeq V3 Genomic Classifier. *Cancers (Basel)*. 2022;15(1):49. https://www.ncbi.nlm.nih.gov/pmc. Accessed January 26, 2023.

51. Silaghi CA, Lozovanu V, Georgescu CE, et al. Thyroseq v3, Afirma GSC, and microRNA panels versus previous molecular tests in the preoperative diagnosis of indeterminate thyroid nodules: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2021;12:649522. https://www.ncbi.nlm.nih.gov/pmc. Accessed February 7, 2022.

52. Sistrunk JW, Shifrin A, Frager M, et al. Clinical impact of testing for mutations and microRNAs in thyroid nodules. *Diagn Cytopathol*. 2019;47(8):758-764. https://www.ncbi.nlm.nih.gov/pmc. Accessed January 31, 2023.

53. Skaugen JM, Taneja C, Liu JB, et al. Performance of a multigene genomic classifier in thyroid nodules with suspicious for malignancy cytology. *Thyroid*. 2022;32(12):1500-1508. https://www.ncbi.nlm.nih.gov/pmc. Accessed January 26, 2023.

54. UpToDate, Inc. Atlas of thyroid cytopathology. https://www.uptodate.com. Updated December 2022. Accessed January 26, 2023.

55. UpToDate, Inc. Diagnostic approach to and treatment of thyroid nodules. https://www.uptodate.com. Updated December 2022. Accessed January 26, 2023.

56. UpToDate, Inc. Evaluation and management of thyroid nodules with indeterminate cytology. https://www.uptodate.com. Updated January 24, 2023. Accessed January 26, 2023.

57. UpToDate, Inc. Oncogenes and tumor suppressor genes in thyroid nodules and nonmedullary thyroid cancer. https://www.uptodate.com. Updated December 2022. Accessed January 27, 2023.

58. UpToDate, Inc. Papillary thyroid cancer: clinical features and prognosis. https://www.uptodate.com. Updated December 2022. Accessed January 27, 2023.

59. UpToDate, Inc. Thyroid nodules and cancer in children. https://www.uptodate.com. Updated December 23, 2022. Accessed January 27, 2023.

60. Valderrabano P, Hallanger-Johnson JE, Thapa R, Wang X, McIver B. Comparison of postmarketing findings vs the initial clinical validation findings of a thyroid nodule gene expression classifier: a systematic review and meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2019;e191449.

61. Yip L, Gooding WE, Nikitski A, et al. Risk assessment for distant metastasis in differentiated thyroid cancer using molecular profiling: A matched case-control study. *Cancer*. 2021;127(11):1779-1787. https://www.ncbi.nlm.nih.gov/pmc. Accessed February 7, 2022.

Appendix

Appendix A
Bethesda System Diagnostic Categories for Reporting Thyroid Cytopathology[7]

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

Change Summary

- 01/01/2024 New Policy.