Supplementary Table S1. Characteristics of the 75 included studies.

Study	Country	Design	Period	Oncocytic subgroup definition	Bethesda	Test(s)	Tested (n)	Resected (n)	Data reported	Use in this review [overlap note]
Ahmadi 2026	USA	retrospective cohort	Jul 2017 - Dec 2023	Cytology (oncocytic cell >75%, predominance of oncocytic/Hurthle cells, (suspicious for) oncocytic/Hurthle cell neoplasm)	III/IV	GSC	359	106	BCR, 2x2	BCR GSC; DTA-A GSC; DTA-B GSC
Attia 2026	USA	retrospective cohort	Nov 2017 - Jun 2024	Cytology (Hürthle cell (oncocytic) cells present on FNA (HC+), Bethesda III and IV)	III/IV	GSC	45	NR	BCR, 2x2	BCR GSC; Sensitivity analysis
Elsheikh 2026	USA	retrospective cohort	2015-01-01 to 2021-12-31	Cytology (AUS-O (AUS with Hürthle/oncocytic predominance) and FN-O (FN/SFN Hürthle cell/oncocytic type) = oncocytic cell-predominant cytology (OCP))	III/IV	GSC, TSv3, GEC, TSv1, TSv2	80	80	BCR, 2x2, ROM by alteration	DTA-A GSC; DTA-A TSv3; ROM by alteration
Geetha 2026	USA	case series	2019-2022	Cytology (Category III-Oncocytic, Category IV-Oncocytic (TERT-mutated only))	III/IV	TSv3	8	5	PPV, ROM by alteration	Qualitative synthesis only [Overlaps Geetha 2025 (Northwell)]
Khan 2026	USA	conference abstract	2018-2022	Cytology (thyroid FNA with oncocytic cells (Bethesda III/IV))	III/IV	TSv3	332	153	BCR, 2x2	Sensitivity analysis
Lazim 2026	USA	case series	MSKCC 2010-2024; MGH 2016-2025; EUH 2017-2024	Histology	III/IV	TSv3	14	14	ROM by alteration	Qualitative synthesis only [Selected for TP53 mutation; descriptive only]
Stack 2026	USA	retrospective cohort	2015-01 to 2024-12	Cytology (FN/SFN-O (oncocytic follicular neoplasm; aspirates composed almost exclusively of Hurthle cells/oncocytes))	IV	mixed, GEC, GSC, ThyGeNEXT/ThyraMIR	19	47	BCR, 2x2, ROM by alteration	Descriptive: other tests
Alzumaili 2025	USA	case series	MSKCC 2010-2024; MGH 2016-2025	Histology	other	TSv3	21	21	ROM by alteration	Qualitative synthesis only [Selected for TERT mutation; descriptive only]
Bang 2025	South Korea	retrospective cohort	2018-2024	Cytology (AUS-O2 (oncocytic/oncocyte atypia), 2023 TBSRTC subclassification on blinded slide review)	III	single-gene	9	9	BCR, 2x2	Descriptive: other tests
Cocelli 2025	USA	retrospective cohort	Jan 2018 - Mar 2025	Histology	III-V	mixed	65	65	2x2, ROM by alteration	Sens: histology-defined [Histology-defined; includes B-V]
Connelly 2025	USA	retrospective cohort	Jan 2017 - Dec 2022	Histology	III/IV	mixed	17	17	2x2	Sens: histology-defined
Geetha 2025	USA	retrospective cohort	2019-01-01 to 2022-12-31	Cytology (AUS due to oncocyte (Hürthle) predominance)	III	TSv3	66	21	2x2, PPV, ROM by alteration	ROM by alteration
Hsiao 2025	USA	retrospective cohort	2017-01 to 2021-12	Cytology (III-O (AUS with oncocytic cell aspirate; pure/exclusive oncocytic composition))	III	TSv3, TSv2	67	21	BCR, 2x2	BCR TSv3; DTA-A TSv3; DTA-B TSv3
Potonnier 2025	France	retrospective cohort	Dec 2019 - Sep 2022	Histology	III-V	NGS-panel	20	20	2x2, ROM by alteration	Sens: histology-defined

Study	Country	Design	Period	Oncocytic subgroup definition	Bethesda	Test(s)	Tested (n)	Resected (n)	Data reported	Use in this review [overlap note]
Tjendra 2025	USA	conference abstract	2018-01 to 2024-06	Cytology (AUS - predominance of oncocytes (only cases with ThyroSeq KRAS-G12 mutation))	III	TSv3	28	20	PPV, ROM by alteration	Qualitative synthesis only [Overlaps Gajzer 2022 (Miami); abstract]
Ahmadi 2024	USA	retrospective cohort	Jul 2017 - Jun 2021	Cytology (Oncocytic (Hürthle) cell predominance >75% on FNA (WHO criteria) within Bethesda III and IV)	III/IV	GSC	154	56	BCR, 2x2	Qualitative synthesis only [Superseded by Ahmadi 2026 (same UCLA/BWH/UNMC cohort)]
Guzmán-Arocho 2024	USA	retrospective cohort	Jun 2013 - Jul 2021 (GEC 6/2013-11/2017; GSC 12/2017-7/2021)	Cytology (AUS-Onc (oncocytic atypia not meeting criteria for oncocytic FN), on initial FNA; Afirma on repeat FNA)	III	GEC, GSC	57	22	BCR	Qualitative synthesis only [Pooled GEC/GSC; overlaps Onken 2021 (BIDMC)]
Ohori 2024	USA	retrospective cohort	2018-01 to 2019-12	Cytology (ONC (follicular neoplasia, oncocytic type; Bethesda IV))	IV	TSv3	70	34	BCR	Qualitative synthesis only [Overlaps Landau 2021 (UPMC)]
Raghunathan 2024	USA	RCT secondary analysis	Aug 2017 - Jul 2022	Cytology (Hurthle cell >75%, 'predominance of Hurthle cells/Hurthloid features', HCN, SHCN (B-III/IV))	III/IV	GSC, TSv3	149	45	BCR, 2x2, ROM by alteration	BCR TSv3; DTA-A TSv3; DTA-B TSv3; ROM by alteration [UCLA RCT subset]
Yang 2024	Singapore	prospective cohort	Jan 2016 - Oct 2019	Histology	III-V	TSv3	14	14	2x2, ROM by alteration	Sens: histology-defined
de Koster 2024	Netherlands	RCT secondary analysis	Inclusion 2015-07-01 to 2018-10-16; follow-up to 2023-05-01	Cytology (O-FN (oncocytic follicular neoplasm) on central cytology review)	IV	NGS-panel (other)	29	NR	BCR, 2x2	Descriptive: other tests
Kim 2023	USA	retrospective cohort	Nov 2017 - May 2022	Cytology (AUS-HCT, SFN-HCT (Hurthle cell type))	III/IV	TSv3	26	14	BCR, 2x2, ROM by alteration	Sensitivity analysis [Overlaps Raghunathan 2024 (UCLA); sensitivity only]
Tjendra 2023	USA	retrospective cohort	2018-01 to 2022-05	Cytology (OFN (oncocytic follicular neoplasm; aspirates composed exclusively of oncocytic cells), slides re-reviewed)	IV	TSv3	46	26	BCR, 2x2, ROM by alteration	BCR TSv3; DTA-A TSv3; DTA-B TSv3; ROM by alteration
Abi-Raad 2022	USA	retrospective cohort	Oct 2017 - Jan 2021	Cytology (FLUS-HCT (FLUS, Hürthle cell type) and HCN (Bethesda IV Hürthle cell neoplasm))	III/IV	TSv3	66	31	BCR, 2x2, ROM by alteration	BCR TSv3; DTA-A TSv3
Gajzer 2022	USA	retrospective cohort	2018-2020	Cytology (AUS with predominance of Hurthle cells (AUS-PHC))	III	TSv3	88	19	BCR, 2x2, ROM by alteration	BCR TSv3; DTA-A TSv3; DTA-B TSv3; ROM by alteration
Jin 2022	USA	retrospective cohort	Jul 2017 - Jun 2021	Cytology (AUS-HC (AUS with predominance of Hurthle cells), repeat AUS)	III	GSC	18	6	BCR, 2x2	BCR GSC; DTA-A GSC; DTA-B GSC
Spagnuolo 2022	USA	retrospective cohort	2017-2021	Cytology (Bethesda III AUS with Hürthle cells; Bethesda IV suspicious for Hürthle cell neoplasm)	III/IV	TSv3	29	29	BCR, 2x2, ROM by alteration	DTA-A TSv3; ROM by alteration
Yang 2022	USA	retrospective cohort	Nov 2012 - May 2021 (GEC to Jul 2017; GSC Jul 2017 onward)	Histology	III/IV	GEC, GSC	18	18	2x2	Sens: histology-defined
Abdelhakam 2021	USA	retrospective cohort	Jan 2015 - Nov 2019	Cytology (SHCN (suspicious for Hürthle cell neoplasm, Bethesda IV); histology HA/HC also reported)	IV	TSv2, TSv3	20	3	2x2, PPV, ROM by alteration	Qualitative synthesis only [Very small histology-defined subset; descriptive only]

Study	Country	Design	Period	Oncocytic subgroup definition	Bethesda	Test(s)	Tested (n)	Resected (n)	Data reported	Use in this review [overlap note]
Doerfler 2021	USA	retrospective cohort	Pathology series mostly from 2017-11 onward (FFPE cases earlier); CNA-only FNA cohort 2017-11 to 2018-12	Histology	other	TSv3	58	58	2x2, ROM by alteration	Qualitative synthesis only [UPMC; histology-defined]
Gilani 2021	USA	retrospective cohort	Jan 2017 - Mar 2020	Cytology (Hurthle cell neoplasm (HCN / SFN-Hurthle cell type))	IV	TSv3, TSv2, ThyGeNEXT/ThyraMIR, GEC, GSC, Rosetta	85	42	BCR, 2x2, ROM by alteration	BCR ThyGeNEXT; Descriptive: other tests; ROM by alteration [Overlaps Abi-Raad 2022 (Yale)]
Glass 2021	USA	retrospective cohort	2015-01 to 2020-06	Cytology (3H (AUS, Hurthle cell aspirate) - reclassified from report descriptions)	III	GEC, ThyGeNEXT/ThyraMIR, TSv3	43	13	BCR, 2x2, ROM by alteration	BCR GEC; BCR TSv3; BCR ThyGeNEXT; DTA-A GEC; DTA-A TSv3; DTA-B TSv3; ROM by alteration
Landau 2021	USA	retrospective cohort	Nov 2017 - Dec 2020	Cytology (FNHCT (follicular neoplasm, Hürthle cell/oncocytic type))	IV	TSv3	180	79	BCR, 2x2, ROM by alteration	BCR TSv3; DTA-A TSv3; DTA-B TSv3; ROM by alteration
Onken 2021	USA	retrospective cohort	2013-06 to 2017-10 (histology locked Dec 2019)	Cytology (AUS-H (AUS due to Hürthle cells))	III	GEC	32	16	BCR, 2x2, PPV	BCR GEC [Accuracy excluded: overlaps Brauner 2015 (BIDMC)]
Polavarapu 2021	USA	retrospective cohort	Jan 2013 - Dec 2019	Cytology (Bethesda IV Hurthle cell neoplasm (HCN))	IV	GEC, GSC	27	12	BCR	BCR GEC [GSC arm superseded by Ahmadi 2026 (UNMC)]
Zhang 2021	USA	retrospective cohort	GEC Jan 2013-Jul 2017; GSC Jul 2017-Jun 2020	Cytology (Recurrent AUS/FLUS with predominant Hürthle cells)	III	GSC, GEC	31	12	BCR, 2x2	BCR GEC; DTA-A GEC; DTA-B GEC
Arosemena 2020	USA	retrospective cohort	Jan 2012 - Dec 2017	Cytology (Bethesda III with cytology 'consistent with Hürthle cell lesions' (Hürthle cell neoplasm subcategory of B-III))	III	GEC	10	NR	BCR	BCR GEC
Lupo 2020	USA	validation study	FNAs Jan 2013 - Aug 2019	Histology	III-V	ThyGeNEXT/ThyraMIR	41	41	2x2, ROM by alteration	Sens: histology-defined
Ohori 2020	USA	retrospective cohort	Nov 2017 - Oct 2018	Cytology (FNHCT/SFNHCT)	IV	TSv3	31	21	BCR	Qualitative synthesis only [Superseded by Landau 2021 / Ohori 2019 (UPMC)]
Papoian 2020	USA	retrospective cohort	2012 - 2017	Cytology (AUS/FLUS with Hürthle cell type on FNA (cell type 'Hurthle cells'), in patients with histologic Hashimoto thyroiditis)	III	GEC	22	22	BCR	Sensitivity analysis
San Martin 2020	USA	retrospective cohort	2011-12 to 2018-09 (GEC to 2017-07; GSC 2017-07 to 2018-09)	Cytology (Bethesda III/IV with dominant Hurthle cell cytology)	III/IV	GSC, GEC	46	25	BCR, 2x2	BCR GEC; BCR GSC; DTA-A GEC; DTA-B GEC; DTA-B GSC [Cleveland (scenario B/BCR); Elsheikh 2026 used for scenario A]
Angell 2019	USA	retrospective cohort	GEC 2011-01-01 to 2017-07-19; GSC 2017-07-20 to 2018-08-27	Cytology (AUS-H (low cellularity, exclusively Hürthle cells) and SHCN (suspicious for Hürthle cell neoplasm))	III/IV	GSC, GEC	130	NR	BCR	BCR GEC [GSC arm superseded by Ahmadi 2026 (BWH)]
Endo 2019	USA	retrospective cohort	GEC Feb 2011-Jul 2017; GSC Jul 2017-Dec 2018	Cytology (Hürthle cell changes on cytology report: Bethesda III HC+, SFN with HC (SFN-HC+), suspicious for HCN)	III/IV	GSC, GEC	NR	NR	BCR, 2x2, PPV	BCR GSC; DTA-B GEC; DTA-B GSC [Ohio State (supersedes Chaudhary 2016 for scenario B)]
Hao 2019	USA	validation study	NR (validation cohort of Patel 2018)	Histology	III/IV	GSC	26	26	2x2	Qualitative synthesis only [Same cohort as Patel 2018]

Study	Country	Design	Period	Oncocytic subgroup definition	Bethesda	Test(s)	Tested (n)	Resected (n)	Data reported	Use in this review [overlap note]
Harrell 2019	USA	retrospective cohort	GEC Jan 2011 - Jul 2017; GSC Aug 2017 - Jun 2018	Cytology (Oncocyte-dominant Bethesda 3 and 4 FNA)	III/IV	GEC, GSC	138	NR	BCR	BCR GEC; BCR GSC
Ohori 2019	USA	retrospective cohort	Nov 2017 - Jun 2018	Cytology (AUS/FLUS with Hürthle (oncocytic) cell change; FNHCT/SFNHCT)	III/IV	TSv3	43	NR	BCR	BCR TSv3
Parajuli 2019	USA	retrospective cohort	Jun 2012 - Aug 2016	Cytology (AUS/FLUS or SFN/FN with Hurthle cell predominance (>50% Hurthle cells), repeat-indeterminate FNA)	III/IV	GEC, TSv2	56	35	BCR, 2x2	BCR GEC; BCR TSv2; DTA-A GEC; DTA-B GEC; Descriptive: other tests
Schatz-Siemers 2019	USA	retrospective cohort	Jan 2014 - Dec 2017	Cytology (Hürthle cell predominant (>~90% Hürthle cells) AUS/FLUS or FN/SFN)	III/IV	TSv2	188	33	BCR, 2x2, ROM by alteration	BCR TSv2; Descriptive: other tests; ROM by alteration
Steward 2019	USA, Singapore	prospective cohort	Jan 2015 - Dec 2016	Histology	III-V	TSv3	49	49	BCR, 2x2	Sens: histology-defined
Wei 2019	USA	retrospective cohort	Jul 2012 - Jan 2019 (GEC to 2017, GSC 2017-2019)	Cytology ('Oncocytic cytology' within AUS/FLUS or FN/SFN (definition not detailed))	III/IV	GEC, GSC	41	19	BCR, PPV	BCR GEC; BCR GSC
Bellevicine 2018	Italy	prospective cohort	2016-03 to 2017-01	Cytology (AUS/FLUS with Hurthle cell changes (HC qualifier))	III	PCR-panel	46	2	BCR, 2x2, ROM by alteration	Descriptive: other tests
Livhits 2018	USA	RCT secondary analysis	2016-05-01 to 2017-06-30	Cytology (Hürthle cell-predominant (predominant Hürthloid change, predominance of Hürthle cells, suspicion for HCN))	III/IV	GEC, TSv2	22	NR	BCR, 2x2, PPV	BCR GEC; BCR TSv2 [UCLA 2016-17]
Nikiforova 2018	USA	validation study	not stated	Histology	III/IV	TSv3	14	14	2x2	Sens: histology-defined [UPMC; histology-defined]
Patel 2018	USA	validation study	Samples collected 2009-2010 (Alexander 2012 cohort); GSC testing 2016-2017	Histology	III/IV	GSC	26	26	2x2	Sens: histology-defined
Walts 2018	USA	retrospective cohort	NR	Histology	III-V	GEC, Rosetta	28	28	2x2	Sens: histology-defined
Hang 2017	USA	retrospective cohort	2012-02 to 2016-09	Histology	III/IV	GEC	31	31	2x2	Sens: histology-defined
Roychoudhury 2017	USA	retrospective cohort	Jan 2013 - Jun 2015	Cytology (AUS with Hürthle cell features; suspicious for Hürthle cell neoplasm (SHCN))	III/IV	GEC	NR	20	PPV	Qualitative synthesis only [GEC-suspicious nodules only (PPV); descriptive only]
Chaudhary 2016	USA	retrospective cohort	Jul 2012 - Jun 2015 (post-Afirma period)	Cytology (Hürthle cell neoplasm (HCN) / FN Hürthle type)	IV	GEC	13	12	BCR, 2x2, PPV	BCR GEC; DTA-A GEC
Collet 2016	France	retrospective cohort	2011 to 2014	Cytology (Bethesda IV oxyphilic neoplasm (oxyphilic variant))	IV	single-gene	8	8	BCR, 2x2, ROM by alteration	Descriptive: other tests
Giovanella 2016	Switzerland	prospective cohort	2010-01 to 2014-12	Cytology (Bethesda IV Hurthle cell (oncocytic follicular neoplasm, >=50% oncocytes))	IV	PCR-panel	8	8	BCR, 2x2, ROM by alteration	Descriptive: other tests
Samulski 2016	USA	retrospective cohort	2011-01 to 2015-12	Cytology (FNOF (follicular neoplasm with oncocytic features))	IV	GEC	45	31	BCR, 2x2, PPV	Qualitative synthesis only [Superseded by Lastra 2014 (Penn)]

Study	Country	Design	Period	Oncocytic subgroup definition	Bethesda	Test(s)	Tested (n)	Resected (n)	Data reported	Use in this review [overlap note]
Valderrabano 2016	USA	retrospective cohort	miRInform Jul 2012 - Oct 2014 (cytology cohort 2008-2014)	Cytology (HCN (Bethesda IV Hürthle cell neoplasm))	IV	PCR-panel	18	12	BCR, 2x2	Descriptive: other tests
Wu 2016	USA	retrospective cohort	2012-09 to 2015-02 (outcomes updated Feb 2016)	Cytology (Hürthle-cell-predominant nodules (HCN) in AUS/FLUS or SFN/FN per original report)	III/IV	GEC	31	NR	BCR, 2x2	BCR GEC [UCLA 2012-15]
Yang 2016	USA	retrospective cohort	Aug 2012 - Apr 2014	Histology	III/IV	GEC	12	12	2x2	Sens: histology-defined [UCLA; histology-defined]
Brauner 2015	USA	retrospective cohort	AGEC-managed cohort 2011-2014 (BWH 2011-2014; MGH and BIDMC 2013-2014); reference cohorts BWH 2010, MGH 2012	Cytology (SHCN (suspicious for Hürthle cell neoplasm) and AFHCN (AUS/FLUS concerning for Hürthle cell neoplasm))	III/IV	GEC	72	47	BCR, 2x2	DTA-A GEC; DTA-B GEC
Celik 2015	USA	retrospective cohort	Dec 2011 - Jul 2014	Cytology (Bethesda IV 'suspicious for follicular neoplasia/HCN')	IV	GEC	9	6	BCR, PPV	BCR GEC
Eszlinger 2015	Italy	retrospective cohort	2006 - 2013	Histology	III/IV	PCR-panel	28	28	2x2, ROM by alteration	Sens: histology-defined
Harrell 2014	USA	retrospective cohort	Jan 2011 - Apr 2013	Cytology (Hürthle cell-predominant AUS-FLUS (3-HC) and oncocytic FN (4-HC))	III/IV	GEC	21	17	BCR, 2x2, PPV	Qualitative synthesis only [Superseded by Harrell 2019 (same center)]
Lastra 2014	USA	retrospective cohort	2011-02 to 2014-01	Cytology (FNOF (follicular neoplasm with oncocytic features))	IV	GEC	25	15	BCR, 2x2, PPV	BCR GEC; DTA-A GEC; DTA-B GEC
McIver 2014	USA	prospective cohort	2011-05 to 2012-12	Cytology (Suspicious for Hurthle cell neoplasm (SHCN / HCN))	IV	GEC	NR	13	2x2	DTA-A GEC
Park 2014	South Korea	retrospective cohort	Jan 2010 - Dec 2011	Cytology (AUS-HC (predominance of Hürthle cells without nuclear atypia; AUS-NA+HC cases excluded from oncocytic subgroup))	III	single-gene	13	5	BCR, 2x2	Descriptive: other tests
Radkay 2014	USA	retrospective cohort	2008-09 to 2013-08	Cytology (FNHCT (follicular neoplasm, Hurthle cell type) with RAS mutation)	IV	PCR-panel	22	22	PPV, ROM by alteration	ROM by alteration
Alexander 2012	USA	validation study	2009-06 to 2010-12 (19 months)	Histology	III-V	GEC	31	31	2x2	Qualitative synthesis only [Overlaps Patel 2018 (same specimens)]
Keutgen 2012	USA	validation study	Derivation tumour bank 2005-2010; validation period NR	Cytology (Hurthle cell neoplasm (HCN) on FNA (validation set))	IV	miRNA	13	13	2x2	Descriptive: other tests
Lappinga 2010	USA	retrospective cohort	2001-2007	Cytology ('Suspicious for Hurthle cell neoplasm' (pre-Bethesda; equivalent to B-IV HCN))	IV	single-gene	33	33	2x2	Descriptive: other tests

Supplementary Table S2. Search strategies (all searches run on 8 October 2026; 2010 to search date; no language limits)

Database	Records	Search string
PubMed (MEDLINE)	798	(("Thyroid Nodule"[Mesh] OR "Thyroid Neoplasms"[Mesh] OR (thyroid[tiab] AND (nodul*[tiab] OR lesion*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR cytolog*[tiab] OR aspirat*[tiab] OR indeterminate[tiab] OR Bethesda[tiab]))) AND ((Afirma[tiab] OR ThyroSeq[tiab] OR ThyGeNEXT[tiab] OR ThyGenX[tiab] OR ThyraMIR[tiab] OR RosettaGX[tiab] OR "Rosetta GX"[tiab] OR "gene expression classifier*"[tiab] OR "genomic sequencing classifier*"[tiab] OR "genomic classifier*"[tiab] OR "Xpression Atlas"[tiab]) OR (("Oxyphil Cells"[Mesh] OR "Adenoma, Oxyphilic"[Mesh] OR hurthle*[tiab] OR huerthle*[tiab] OR oncocyt*[tiab] OR oxyphil*[tiab]) AND ("Molecular Diagnostic Techniques"[Mesh] OR "Gene Expression Profiling"[Mesh] OR "High-Throughput Nucleotide Sequencing"[Mesh] OR "DNA Copy Number Variations"[Mesh] OR "Mutation"[Mesh] OR molecular[tiab] OR mutation*[tiab] OR "copy number"[tiab] OR haploidi*[tiab] OR "gene expression"[tiab] OR sequencing[tiab] OR NGS[tiab] OR "gene panel*"[tiab])))) AND 2010:2026[dp]
Web of Science Core Collection (SCI-EXPANDED, CPCI-S)	936	TS=(thyroid NEAR/3 (nodul* OR lesion* OR neoplas* OR tumor* OR tumour* OR cancer* OR carcinoma* OR aspirat* OR cytolog*)) AND (TS=(afirma OR thyroseq OR thygenext OR thygenx OR thyramir OR rosettagx OR "rosetta gx" OR "gene expression classifier*" OR "genomic sequencing classifier*" OR "genomic classifier*" OR "xpression atlas") OR (TS=(hurthle* OR huerthle* OR oncocyt* OR oxyphil*) AND TS=(molecular OR mutation* OR "copy number" OR haploidi* OR "gene expression" OR sequencing OR NGS OR "gene panel*"))) AND PY=(2010-2026)
Scopus	1026	TITLE-ABS-KEY(thyroid W/3 (nodul* OR lesion* OR neoplas* OR tumor* OR tumour* OR cancer* OR carcinoma* OR aspirat* OR cytolog*)) AND (TITLE-ABS-KEY(afirma OR thyroseq OR thygenext OR thygenx OR thyramir OR rosettagx OR "rosetta gx" OR "gene expression classifier*" OR "genomic sequencing classifier*" OR "genomic classifier*" OR "xpression atlas") OR (TITLE-ABS-KEY(hurthle* OR huerthle* OR oncocyt* OR oxyphil*) AND TITLE-ABS-KEY(molecular OR mutation* OR "copy number" OR haploidi* OR "gene expression" OR sequencing OR ngs OR "gene panel*"))) AND PUBYEAR > 2009
Cochrane Library (CDSR + CENTRAL)	14	(thyroid NEAR/3 (nodul* OR lesion* OR neoplas* OR tumor* OR tumour* OR cancer* OR carcinoma* OR aspirat* OR cytolog*)):ti,ab,kw AND ((afirma OR thyroseq OR thygenext OR thygenx OR thyramir OR rosettagx OR (gene NEXT expression NEXT classifier*) OR (genomic NEXT sequencing NEXT classifier*) OR (genomic NEXT classifier*)):ti,ab,kw OR ((hurthle* OR huerthle* OR oncocyt* OR oxyphil*):ti,ab,kw AND (molecular OR mutation* OR "copy number" OR "gene expression" OR sequencing):ti,ab,kw))

Supplementary Table S3. Study-level 2×2 data used in each analysis

Notes: Onken 2021 was excluded from the Afirma GEC accuracy analyses because its BIDMC 2013–17 cohort overlaps Brauner 2015 (BIDMC 2013–14); it contributed only to the GEC benign call rate. The histology-defined analysis counts each patient once: Patel 2018 was retained in preference to Alexander 2012 (same FNA specimens), and the GEC arm of Walts 2018 in preference to its RosettaGX Reveal arm (same nodules). for Landau 2021, the benign call rate uses test-negative inferred as no alteration or AFTN-type mutations (TSHR, EZH1, GNAS), whereas its accuracy rows reflect any reportable alteration; its scenario B true-negative count (76) covers only the unoperated nodules with no reported alteration, and 17 further unoperated nodules with AFTN-type mutations that the platform reported as negative were not counted as true negatives, consistent with the any-alteration positivity of the accuracy rows and conservative for scenario B specificity (no resected nodule in Landau 2021 harboured an AFTN-type mutation, so its resected 2×2 is identical under either definition) Spagnuolo 2022: four nodules with only incidental micropapillary carcinoma were counted as benign. Raghunathan 2024: scenario B includes one lost-to-follow-up nodule. Ahmadi 2026: NIFTP classification not reported. Glass 2021: Afirma version not stated (GEC assumed); because the study period (2015–2020) spans the July 2017 GEC-to-GSC transition, the GEC benign call rate and GEC scenario A were repeated excluding Glass 2021 (Supplementary Table S7). Overlap resolution: at the University of Pennsylvania, Lastra 2014 was retained for the GEC analyses although the partially overlapping Samulski 2016 series reported a larger FNOF cohort (45 vs 25), and Samulski 2016 was therefore not entered separately; at Michigan, Jin 2022 was retained for GSC and Zhang 2021 for GEC. At the Cleveland Clinic, scenario A uses the all-resected cohort of Elsheikh 2026 (2015–21) while scenario B and the benign call rate use San Martin 2020 (2017–18), so the two scenarios draw on different cohorts. At Ohio State, Chaudhary 2016 was retained for the GEC benign call rate and scenario A because Endo 2019 reports its GEC benign call rate for oncocytic nodules only as a percentage (25.7%) without an extractable denominator; Endo 2019 contributed to scenario B and the GSC analyses. The GSC counts for Endo 2019 (benign call rate 16 of 18; TP 1, FP 0, FN 0, TN 16) follow the published percentages; the paper's Table 5 lists only 17 GSC-tested oncocytic nodules and is internally inconsistent with its text. Incidental micropapillary carcinomas were counted as malignant in Schatz-Siemers 2019 and Raghunathan 2024 (one KRAS-mutated classic papillary carcinoma smaller than 1 cm) but as benign in Spagnuolo 2022, following each study's published classification. Samulski 2016 reported FNOF accuracy only as percentages (no extractable 2–2); its explicit benign-call data (9 benign of 43 FNOF) were not substituted for Lastra 2014, as both derive from the same institutional series, and substituting them would change the pooled GEC BCR only from 24.7% (20.0–30.1) to 23.8% (19.4–28.9). Resected counts in Table 1 follow each study's reported denominators and may differ by one from the platform-specific totals: Tjendra 2023 included one patient with metastatic oncocytic carcinoma who did not undergo thyroidectomy (counted as malignant), and Brauner 2015 and San Martin 2020 each excluded one nodule from their platform-specific tables. Hsiao 2025 used a mixture of ThyroSeq v2 and v3, and Glass 2021 did not state the ThyroSeq version (v3 assumed).

Analysis	Study	Stratum / test	TP	FP	FN	TN	Note
Scenario A – Afirma GSC	Ahmadi 2026	B-III	8	26	1	15	UCLA/BWH/UNMC; supersedes Ahmadi 2024, Raghunathan 2024 (GSC), Angell 2019, Polavarapu 2021 (GSC)
Scenario A – Afirma GSC	Ahmadi 2026	B-IV	17	17	1	21	
Scenario A – Afirma GSC	Elsheikh 2026	B-III/IV	30	7	6	6	Cleveland Clinic 2015-21; all resected; NIFTP counted malignant by authors
Scenario A – Afirma GSC	Jin 2022	B-III	1	2	0	3	Michigan 2017-21; supersedes Zhang 2021 (GSC)
Scenario A – ThyroSeq v3	Landau 2021	B-IV	27	37	0	15	UPMC; any alteration = positive
Scenario A – ThyroSeq v3	Tjendra 2023	B-IV	7	15	1	4	Miami (B-IV OFN)
Scenario A – ThyroSeq v3	Gajzer 2022	B-III	5	8	0	6	Miami (B-III PHC); non-overlapping category with Tjendra 2023
Scenario A – ThyroSeq v3	Raghunathan 2024	B-III/IV	3	16	0	5	UCLA RCT subset; supersedes Kim 2023
Scenario A – ThyroSeq v3	Elsheikh 2026	B-III/IV	7	2	1	1	Cleveland Clinic; all resected
Scenario A – ThyroSeq v3	Abi-Raad 2022	B-III/IV	8	18	0	5	Yale; any alteration = positive; supersedes Gilani 2021
Scenario A – ThyroSeq v3	Hsiao 2025	B-III	4	8	2	7	Emory; TSv2/v3; positive = intermediate/high POC
Scenario A – ThyroSeq v3	Spagnuolo 2022	B-III/IV	7	15	1	6	Atrius; resected only
Scenario A – ThyroSeq v3	Glass 2021	B-III	0	3	0	2	Dartmouth
Scenario A – Afirma GEC	Brauner 2015	B-III/IV	6	37	0	3	MGH/BWH/BIDMC 2011-14
Scenario A – Afirma GEC	San Martin 2020	B-III/IV	6	12	0	0	Cleveland 2011-17
Scenario A – Afirma GEC	Parajuli 2019	B-III/IV	3	16	0	1	Duke
Scenario A – Afirma GEC	Lastra 2014	B-IV	2	11	0	2	Penn; supersedes Samulski 2016
Scenario A – Afirma GEC	McIver 2014	B-IV	2	10	0	1	Mayo
Scenario A – Afirma GEC	Zhang 2021	B-III	0	6	0	2	Michigan (GEC era)
Scenario A – Afirma GEC	Chaudhary 2016	B-IV	8	4	0	0	Ohio State; no GEC-benign HCN
Scenario A – Afirma GEC	Glass 2021	B-III	0	2	0	2	Dartmouth
Scenario B – Afirma GSC	Ahmadi 2026	B-III	8	26	1	163	
Scenario B – Afirma GSC	Ahmadi 2026	B-IV	17	17	1	114	
Scenario B – Afirma GSC	San Martin 2020	B-III/IV	4	1	1	11	Cleveland (Elsheikh 2026 has no unoperated nodules)
Scenario B – Afirma GSC	Jin 2022	B-III	1	2	0	14	

Analysis	Study	Stratum / test	TP	FP	FN	TN	Note
Scenario B – Afirma GSC	Endo 2019	B-III/IV	1	0	0	16	Ohio State; NIFTP counted malignant
Scenario B – ThyroSeq v3	Landau 2021	B-IV	27	37	0	76	
Scenario B – ThyroSeq v3	Tjendra 2023	B-IV	7	15	1	21	
Scenario B – ThyroSeq v3	Gajzer 2022	B-III	5	8	0	69	
Scenario B – ThyroSeq v3	Raghunathan 2024	B-III/IV	3	16	0	34	
Scenario B – ThyroSeq v3	Hsiao 2025	B-III	4	8	2	48	
Scenario B – ThyroSeq v3	Glass 2021	B-III	0	3	0	11	
Scenario B – Afirma GEC	Brauner 2015	B-III/IV	6	37	0	26	
Scenario B – Afirma GEC	San Martin 2020	B-III/IV	6	12	0	6	
Scenario B – Afirma GEC	Parajuli 2019	B-III/IV	3	16	0	11	
Scenario B – Afirma GEC	Lastra 2014	B-IV	2	11	0	8	
Scenario B – Afirma GEC	Zhang 2021	B-III	0	6	0	4	
Scenario B – Afirma GEC	Endo 2019	B-III/IV	18	23	0	17	NIFTP counted malignant; OSU (supersedes Chaudhary 2016)
Histology-defined (sensitivity)	Patel 2018	GSC	8	7	1	10	
Histology-defined (sensitivity)	Yang 2022 (GSC)	GSC	1	2	0	3	
Histology-defined (sensitivity)	Steward 2019	TSv3	10	13	0	26	may include B-V
Histology-defined (sensitivity)	Nikiforova 2018	TSv3	2	0	0	5	HCC/HCA/HCH only
Histology-defined (sensitivity)	Yang 2024	TSv3	5	3	2	4	includes B-V
Histology-defined (sensitivity)	Hang 2017	GEC	6	24	0	1	
Histology-defined (sensitivity)	Yang 2016	GEC	2	3	0	0	HCA/HCC only
Histology-defined (sensitivity)	Yang 2022 (GEC)	GEC	4	5	2	1	
Histology-defined (sensitivity)	Walts 2018 (GEC)	GEC	2	25	0	1	
Histology-defined (sensitivity)	Lupo 2020	ThyGeNEXT	6	11	2	22	includes B-V
Histology-defined (sensitivity)	Potonnier 2025	NGS panel	1	4	4	11	includes B-V
Histology-defined (sensitivity)	Eszlinger 2015	PCR panel	1	1	4	21	
Histology-defined (sensitivity)	Connelly 2025	Mixed	3	4	3	7	
Histology-defined (sensitivity)	Cocelli 2025	Mixed	27	25	1	12	includes B-V; resected only
Other tests (scenario A)	Schatz-Siemers 2019	TSv2	10	18	0	5	any alteration = positive
Other tests (scenario A)	Parajuli 2019	ThyroSeq (7-gene/v1/v2)	1	1	0	13	
Other tests (scenario B)	de Koster 2024	NGS panel (EfFECTS)	7	11	1	10	prospective RCT; reference incl. borderline tumours
Other tests (scenario A)	Valderrabano 2016	miRInform (PCR panel)	1	0	2	9	
Other tests (scenario A)	Giovanella 2016	PCR/Sanger panel	0	0	5	3	
Other tests (scenario A)	Lappinga 2010	HMGA2 qRT-PCR	4	0	6	23	
Other tests (scenario A)	Keutgen 2012	4-miRNA panel	1	5	0	7	reconstructed (assumption)
Other tests (scenario A)	Bang 2025	BRAF V600E	0	0	2	7	
Other tests (scenario A)	Collet 2016	BRAF V600E	0	0	4	4	
Other tests (scenario A)	Park 2014	BRAF V600E	1	1	0	2	

Analysis	Study	Stratum / test	TP	FP	FN	TN	Note
Other tests (scenario A)	Bellevicine 2018	7-gene PCR panel	0	1	0	1	
Other tests (scenario A)	Stack 2026	Mixed (Afirma/ThyGeNEXT)	4	10	2	3	ad-hoc positivity
Other tests (scenario A)	Gilani 2021	Mixed (all platforms)	8	24	2	8	overlaps Abi-Raad 2022

Supplementary Table S4. Study-level benign call rate data

Notes: Benign call rates use each study's published classifier call. For Landau 2021, test-negative was inferred from the published categories as no alteration or AFTN-type mutations (TSHR, EZH1, GNAS; 93 of 180 nodules), whereas its accuracy rows reflect any reportable alteration. Khan 2026 is a conference abstract; percentages were used to reconstruct the counts. The scenario B accuracy rows for Landau 2021 count only the 76 unoperated nodules with no reported alteration as true negatives (see the notes to Table S3).

Test	Study	Stratum	Benign	Tested	%	Note
GSC	Ahmadi 2026	B-III	164	203	81	
GSC	Ahmadi 2026	B-IV	115	156	74	
GSC	San Martin 2020	B-III/IV	12	19	63	Cleveland
GSC	Jin 2022	B-III	14	18	78	Michigan
GSC	Endo 2019	B-III/IV	16	18	89	Ohio State
GSC	Attia 2026	B-III/IV	28	45	62	Rutgers
GSC	Wei 2019	B-III/IV	8	10	80	Fox Chase
GSC	Harrell 2019	B-III/IV	22	34	65	Memorial (FL)
TSv3	Landau 2021	B-IV	93	180	52	UPMC; incl. 17 reported-negative low-risk alterations
TSv3	Ohori 2019	B-III	17	24	71	UPMC B-III (non-overlapping category with Landau)
TSv3	Tjendra 2023	B-IV	22	46	48	Miami
TSv3	Gajzer 2022	B-III	69	88	78	Miami
TSv3	Raghunathan 2024	B-III/IV	34	61	56	UCLA
TSv3	Hsiao 2025	B-III	50	67	75	Emory
TSv3	Glass 2021	B-III	11	18	61	Dartmouth
TSv3	Abi-Raad 2022	B-III/IV	22	66	33	Yale; 'no alteration' as negative
GEC	Angell 2019	B-III/IV	24	99	24	BWH (supersedes Brauner 2015 for BCR)
GEC	San Martin 2020	B-III/IV	6	27	22	Cleveland
GEC	Parajuli 2019	B-III/IV	11	32	34	Duke
GEC	Onken 2021	B-III	13	32	41	BIDMC
GEC	Lastra 2014	B-IV	8	25	32	Penn
GEC	Zhang 2021	B-III	4	12	33	Michigan
GEC	Harrell 2019	B-III/IV	18	104	17	Memorial (supersedes Harrell 2014)
GEC	Wei 2019	B-III/IV	5	31	16	Fox Chase
GEC	Wu 2016	B-III/IV	7	31	23	UCLA 2012-15
GEC	Livhits 2018	B-III/IV	5	10	50	UCLA 2016-17
GEC	Arosemena 2020	B-III	2	10	20	Miami
GEC	Polavarapu 2021	B-IV	1	7	14	Nebraska
GEC	Celik 2015	B-IV	2	8	25	Mayo Jacksonville
GEC	Chaudhary 2016	B-IV	0	13	0	Ohio State
GEC	Glass 2021	B-III	2	5	40	Dartmouth
ThyGeNEXT/ThyraMIR	Glass 2021	B-III	18	20	90	
ThyGeNEXT/ThyraMIR	Gilani 2021	B-IV	11	21	52	
TSv2/older ThyroSeq	Schatz-Siemers 2019	B-III/IV	115	188	61	
TSv2/older ThyroSeq	Parajuli 2019	B-III/IV	22	24	92	
TSv2/older ThyroSeq	Livhits 2018	B-III/IV	8	12	67	

Supplementary Table S5. Study-level malignancy by molecular alteration class (resected nodules)

Study	Alteration class	Malignant	Benign
Landau 2021	No alteration	0	15
Landau 2021	CNA only	10	19
Landau 2021	RAS-like	10	13
Landau 2021	High-risk (TP53/TERT)	5	2
Landau 2021	BRAF V600E / fusion	2	0
Tjendra 2023	No alteration	1	4
Tjendra 2023	CNA only	2	8
Tjendra 2023	RAS-like	1	4
Tjendra 2023	High-risk (TP53/TERT)	3	0
Gajzer 2022	No alteration	0	6
Gajzer 2022	CNA only	0	2
Gajzer 2022	RAS-like	3	6
Gajzer 2022	High-risk (TP53/TERT)	1	0
Gajzer 2022	BRAF V600E / fusion	1	0
Elsheikh 2026	CNA only	1	0
Elsheikh 2026	RAS-like	13	5
Elsheikh 2026	High-risk (TP53/TERT)	2	0
Elsheikh 2026	BRAF V600E / fusion	2	0
Spagnuolo 2022	No alteration	1	6
Spagnuolo 2022	CNA only	0	6
Spagnuolo 2022	RAS-like	4	8
Spagnuolo 2022	High-risk (TP53/TERT)	1	0
Spagnuolo 2022	BRAF V600E / fusion	1	0
Raghunathan 2024	CNA only	0	2
Raghunathan 2024	RAS-like	1	8
Raghunathan 2024	High-risk (TP53/TERT)	1	3
Gilani 2021	No alteration	2	8
Gilani 2021	CNA only	1	6
Gilani 2021	RAS-like	3	10
Gilani 2021	High-risk (TP53/TERT)	1	0
Geetha 2025	No alteration	0	1
Geetha 2025	CNA only	1	4
Geetha 2025	RAS-like	0	9
Geetha 2025	High-risk (TP53/TERT)	0	3
Schatz-Siemers 2019	No alteration	0	5
Schatz-Siemers 2019	CNA only	0	1
Schatz-Siemers 2019	RAS-like	6	14
Schatz-Siemers 2019	High-risk (TP53/TERT)	3	0
Radkay 2014	RAS-like	12	10
Glass 2021	No alteration	1	4
Glass 2021	CNA only	0	1
Glass 2021	RAS-like	0	4

Supplementary Table S6. QUADAS-2 assessment of the 75 included studies

Study	RoB: patient	RoB: index	RoB: reference	RoB: flow	AC: patient	AC: index	AC: reference	Rationale (P, patient; I, index; R, reference; F, flow)
Ahmadi 2026	low	low	unclear	high	low	low	low	P: All oncocytic-predominant B-III/IV nodules with GSC at 3 sites (reflex at UCLA; some BWH/UNMC patients went straight to surgery).; I: Commercial GSC benign/suspicious.; R: Histology by institutional head and neck pathologists; blinding not stated.; F: Only 16/164 and 22/115 GSC-benign nodules resected; 5 B-III and 7 B-IV suspicious unresected.
Attia 2026	low	low	high	high	low	low	low	P: All Black/Hispanic patients with Bethesda III/IV nodules reflexively tested by GSC at two centers were included (exclusions only for insufficient/no-result samples and other races).; I: Commercial Afirma GSC with predefined benign/suspicious categories.; R: Authors state pathologists were not blinded to GSC results.; F: Only ~29% of nodules resected; unoperated GSC-benign counted as TN and unoperated GSC-suspicious as FP (partial/differential verification).
Elsheikh 2026	high	low	unclear	high	low	low	low	P: Only surgically resected OCP with slides available (173/359), molecular subset 80 not consecutive tested nodules.; I: Commercial GSC/TSv3 with lab-issued categories obtained preoperatively (GEC/TSv2 strata are older tests: applicability high for those).; R: Histology with re-review by an author; blinding to molecular result not stated and NIFTP counted malignant.; F: Only resected nodules analyzed; unresected test-negatives not captured (partial verification).
Geetha 2026	high	low	unclear	high	high	low	low	P: Only TERT-mutated nodules selected from 567 reflexed indeterminate specimens.; I: ThyroSeq reflex testing with standard reporting.; R: Slides reviewed by a pathologist to confirm diagnosis; blinding not stated.; F: 5/8 oncocytic TERT-mutated nodules resected.
Khan 2026	unclear	low	unclear	high	low	low	low	P: All oncocytic FNAs with ThyroSeq over 2018-2022 from an institutional database, but abstract gives no details on consecutiveness or exclusions.; I: ThyroSeq v3 reported with its commercial negative/positive categories.; R: Histology per WHO 2022; blinding to molecular result and NIFTP handling not reported.; F: Only ~20% of test-negative vs 88% of test-positive patients underwent surgery (partial, differential verification).
Lazim 2026	high	low	high	high	high	low	low	P: Only resected nodules preselected for a TP53 mutation (mutation-enriched case series), not a consecutive indeterminate cohort.; I: Commercial ThyroSeq (v3 for 30/32) with predefined reporting, performed preoperatively.; R: Study pathologists re-reviewed histology explicitly unblinded to ThyroSeq results.; F: Only resected TP53-positive nodules analyzed; no test-negative or unresected nodules.
Stack 2026	high	high	unclear	high	low	high	low	P: Only resected Bethesda IV nodules included (selection bias acknowledged by authors); molecular testing by clinician preference.; I: Two platforms (Afirma GEC/GSC and ThyGeNEXT/ThyraMIR) pooled and binned into ad-hoc risk categories; no prespecified positive/negative threshold for the pooled analysis.; R: Surgical histology retrospectively reviewed from reports; blinding to molecular result not stated.; F: Only 19/47 resected FN/SFN-O had molecular testing and unoperated tested nodules are absent (resected-only design).
Alzumaili 2025	high	low	unclear	high	high	low	low	P: Only resected nodules preselected for TERTp mutation (without BRAF V600E).; I: Commercial ThyroSeq GC with predefined reporting performed preoperatively.; R: Benign/low-risk cases re-reviewed blinded by both centers, but blinding of routine diagnoses to ThyroSeq not stated.; F: Only resected TERTp-positive nodules analyzed; no test-negative nodules.
Bang 2025	high	low	unclear	high	low	high	low	P: Only resected AUS nodules with preoperative BRAF results and available slides included.; I: BRAF V600E PCR with fixed mutant/wild-type result; slides re-reviewed blinded.; R: Histology; blinding of surgical pathologists to BRAF result not stated.; F: Surgical cohort only; unresected nodules not included.
Cocelli 2025	high	high	unclear	high	high	high	low	P: Cases identified from resection pathology (histology-defined oncocytic neoplasms) and only those with prior FNA/molecular results analyzed.; I: Three different platforms pooled; positivity partly ad hoc (any reported alteration incl. CNA).; R: Routine final pathology reports; awareness of molecular results not stated.; F: Only resected nodules included; no unresected test-negatives.
Connelly 2025	high	low	unclear	high	high	high	low	P: Only resected nodules with histology-defined oncocytic neoplasm contribute (histology-defined subgroup, enriched by surgical selection).; I: Commercial tests with predefined positive/negative thresholds, but three different platforms (incl. GEC and ThyGenX/ThyGeNEXT versions) pooled.; R: Institutional surgical pathology; blinding to molecular results not stated.; F: Only 16.7% of tested nodules resected; analysis restricted to resected subset.
Geetha 2025	high	low	unclear	high	low	low	low	P: Case-control enriched sampling: 33 consecutive positive and 33 consecutive negative cases chosen.; I: Commercial ThyroSeq (v3 inferred from period/ROM categories; version not stated) with reported categories.; R: Histology from chart review; pathologists' awareness of molecular result not stated.; F: Only 20/33 positives and 1/33 negatives resected.
Hsiao 2025	low	low	unclear	high	low	low	low	P: All AUS/FN with ThyroSeq over 2017-2021 retrieved from database; III-O defined by report comments.; I: Commercial ThyroSeq with predefined POC categories (positive >=30%).; R: Histology from surgical pathology; blinding to ThyroSeq not stated.; F: Only 21/67 III-O resected; most test-negatives unverified (partial verification).
Potonnier 2025	high	high	unclear	high	high	high	low	P: Only resected B-III-V nodules with molecular testing; 65 unoperated patients excluded.; I: In-house general-cancer AmpliSeq panel with lab-defined positivity (incl. VUS); not a thyroid commercial classifier.; R: Histology from reports; cytologist blinded but pathologist blinding to NGS result not stated.; F: Only operated nodules analyzed; unoperated tested nodules excluded.
Tjendra 2025	high	low	unclear	high	high	low	low	P: Only AUS-oncocytic nodules with a positive KRAS-G12 ThyroSeq result were selected (mutation-selected, test-positive only).; I: ThyroSeq v3 commercial assay with predefined calls.; R: Histologic review; blinding to molecular result not reported (abstract).; F: Only test-positive nodules included; 8/28 without surgery; no test-negatives.
Ahmadi 2024	low	low	unclear	high	low	low	low	P: All B-III/IV nodules tested with GSC at 3 centers (general policy of universal testing; UCLA alternating-month allocation); exclusions mainly lost to follow-up.; I: Commercial Afirma GSC with predefined benign/suspicious calls, issued preoperatively.; R: Routine histopathology; blinding to GSC not stated, and NIFTP counted as malignant.; F: Most GSC-benign nodules unresected (assumed benign), 3 B-IV suspicious unresected excluded.
Guzmán-Arocho 2024	low	low	unclear	high	low	high	low	P: All AUS nodules sent for Afirma from a prospective institutional database; testing at clinician discretion after repeat FNA.; I: Commercial Afirma with predefined benign/suspicious calls.; R: Histology from surgical pathology reports; blinding to Afirma not stated.; F: Only 22/58 AUS-Onc resected; unresected Afirma-benign used as low-risk endpoint.

Study	RoB: patient	RoB: index	RoB: reference	RoB: flow	AC: patient	AC: index	AC: reference	Rationale (P, patient; I, index; R, reference; F, flow)
Ohori 2024	low	low	high	high	low	low	low	P: All ONC cases with ThyroSeq v3 over 2 years.; I: ThyroSeq v3 with predefined POC; cytology made blind to molecular results.; R: NIFTP counted as malignant and histology not linked to test result; blinding of pathologists not stated.; F: Only 34/70 resected and histology not reported by test result.
Raghunathan 2024	low	low	high	high	low	low	low	P: All eligible UCLA patients with indeterminate Hurthle-cell FNA in a randomized trial with reflex testing; outside FNAs excluded.; I: Commercial GSC/TSv3 with predefined categories (TSv3 'currently negative' = negative), reflex at FNA before histology.; R: Paper states histopathology reviewers were not blinded to molecular results; one RAS+TERT case adjusted to FLUMP after MDT review.; F: Only 14% (GSC) and 15% (TSv3) of negatives resected; rest assumed benign on surveillance.
Yang 2024	high	low	low	low	high	low	low	P: Only patients proceeding to surgery enrolled; oncocytic subgroup histology-defined; includes Bethesda V; 118/134 FNAs were ex-vivo post-resection.; I: TSv3 with predefined categories; molecular lab blinded to cytology/histology.; R: Central blinded expert pathology panel review.; F: All included nodules had histology (surgical cohort by design).
de Koster 2024	low	high	low	low	low	high	high	P: Prospective trial with consecutive eligible Bethesda III/IV patients; oncocytic subgroup defined by central cytology.; I: Custom NGS (CHS + fusion + CNA-LOH) with study-specific positivity definition (any class 4/5 variant/fusion or suspicious GH-type CNA).; R: Blinded central histopathology, but borderline tumours counted positive and unoperated nodules classified by ultrasound follow-up.; F: 83% operated overall and the rest followed >=1 year with a defined protocol; all nodules analyzed.
Kim 2023	low	high	high	high	low	low	low	P: All HCT AUS/SFN FNAs with ThyroSeq v3 in database search (only adequate material).; I: Positivity defined post hoc as any molecular alteration (incl. CNA-only), not ThyroSeq negative/currently-negative/positive call.; R: Authors state none of the pathologists were blinded to prior cytology/molecular results.; F: Only 14/26 HCT resected; 9 of 10 test-negative unresected.
Tjendra 2023	low	low	low	high	low	low	low	P: All Bethesda IV FNAs with ThyroSeq v3 over the period; OFN assigned on slide re-review.; I: ThyroSeq v3 with predefined negative/currently negative/positive calls.; R: All histology reviewed in-house by two endocrine pathologists; blinding not explicit but slide review standardized (rated low; could be unclear).; F: Only 5/22 test-negative OFN resected versus 22/24 positives (partial verification).
Abi-Raad 2022	low	high	unclear	high	low	low	low	P: All FLUS/FN-HCN FNAs with ThyroSeq v3 results in the period were retrieved.; I: ThyroSeq categorical call not used; positivity defined post hoc as any molecular alteration.; R: Histology reviewed; awareness of ThyroSeq results not stated.; F: Only 31/66 oncocytic nodules resected; unresected nodules not analysable.
Gajzer 2022	low	low	unclear	high	low	low	low	P: All AUS FNAs 2018-2020 reflexed to ThyroSeq v3 (institutional reflex policy).; I: Commercial TSv3 categories (negative/currently negative vs positive).; R: Two pathologists reviewed surgical cases; blinding to molecular results not stated.; F: Only 19/88 PHC nodules resected (13/19 positives, 6/69 negatives).
Jin 2022	low	low	unclear	high	low	low	low	P: Consecutive repeat-AUS nodules with GSC.; I: Commercial GSC benign/suspicious.; R: Histology; blinding to GSC not stated.; F: Only 3/14 benign resected; 1 suspicious declined surgery.
Spagnuolo 2022	high	low	unclear	high	low	low	low	P: Only nodules that underwent surgery (59/133) included.; I: ThyroSeq v3 with commercial risk categories (intermediate/high = positive).; R: Histology from routine reports; blinding to ThyroSeq not stated.; F: Unresected nodules (74/133) excluded; only 29 resected nodules tested.
Yang 2022	high	low	unclear	high	high	high	low	P: Oncocytic subgroup defined only among resected nodules by histology.; I: Commercial Afirma GEC/GSC with predefined calls.; R: In-house surgical pathology; blinding to Afirma not stated.; F: Only resected subset analyzed; most Afirma-benign nodules not resected.
Abdelhakam 2021	low	low	unclear	high	low	high	low	P: All ThyroSeq-tested indeterminate nodules in period included without exclusions.; I: Commercial ThyroSeq GC (v2/v3) with predefined negative/positive categories.; R: Histology by expert pathologists; awareness of GC result not stated.; F: Only 3/20 SHCN resected; GC results of unresected SHCN not reported by cytology.
Doerfler 2021	high	low	high	low	high	low	low	P: Histology-defined series selected from pathology/molecular records (case-control-like); FNA cohort selected by presence of CNA.; I: ThyroSeq v3 with predefined categories (though some tested on FFPE tissue).; R: Pathologists not blinded to FNA molecular results and slides not re-reviewed.; F: All 58 nodules had histology (reference standard applied to all included).
Gilani 2021	unclear	high	unclear	high	low	high	low	P: All HCN cytology cases reviewed, but molecular testing done only at clinician request (30%) and platform chosen by clinician.; I: Mixed platforms pooled with ad-hoc 'any molecular alteration' positivity; ThyroSeq subset uses report negative/positive.; R: Histology from reports with re-review; knowledge of molecular results by pathologists not stated.; F: Only 42/85 tested nodules resected (63% positive vs 29% negative).
Glass 2021	low	low	unclear	high	low	high	low	P: All AUS specimens 2015-2020 included and reclassified retrospectively; molecular testing on a subset.; I: Commercial tests with their own result categories (positivity per vendor categories).; R: Surgical diagnoses taken from reports; blinding not stated.; F: Only 13 of 44 tested 3H nodules resected; most negatives unverified.
Landau 2021	low	high	unclear	high	low	low	low	P: Consecutive FNHCT nodules with TSv3 testing over 37 months.; I: Positivity defined post hoc as any molecular alteration; official TSv3 result category per nodule not reported.; R: Institutional histology; pathologists' knowledge of molecular results not stated (GH-CNA explicitly used as evidence of oncocytic neoplasia).; F: Only 79/180 (44%) resected; most molecularly negative nodules observed.
Onken 2021	low	low	high	high	low	high	low	P: All AUS nodules sent for GEC from a prospective institutional database.; I: Commercial GEC with predefined benign/suspicious categories; AUS-H subclass assigned retrospectively from reports blinded to GEC and histology.; R: Histology reviewed with NIFTP criteria, but unresected GEC-benign nodules use the index test as outcome (incorporation) and NIFTP/cancer composite.; F: Only 16/32 resected; unresected GEC-suspicious excluded.
Polavarapu 2021	high	low	unclear	high	low	high	low	P: Molecular testing by shared decision, not reflexive; 7 HCN patients declined testing during GEC era.; I: Commercial GEC/GSC categories.; R: Histology; blinding not stated; NIFTP counted malignant.; F: GEC 6/7 and GSC 6/20 HCN resected; results of resected nodules not split by test result.
Zhang 2021	low	low	unclear	high	low	low	low	P: Consecutive recurrent AUS/FLUS nodules tested; ND results and those without any follow-up excluded.; I: Commercial Afirma benign/suspicious categories (GEC stratum: applicability high).; R: Histology for resected; blinding not stated; unresected rely on >=6 mo follow-up.; F: Most GSC-benign nodules unresected (14/17).

Study	RoB: patient	RoB: index	RoB: reference	RoB: flow	AC: patient	AC: index	AC: reference	Rationale (P, patient; I, index; R, reference; F, flow)
Arosemena 2020	high	low	high	high	low	high	high	P: Retrospective GEC-tested B-III nodules; 53 lost to follow-up excluded.; I: Commercial Afirma GEC with predefined categories.; R: Mixed reference (histology or ultrasound follow-up), NIFTP counted malignant.; F: 41/126 verified only by follow-up; Hürthle subset 2x2 not reported.
Lupo 2020	high	high	low	high	high	high	low	P: Nonconsecutive archived slides of resected nodules only; non-consensus histology excluded.; I: Mutation-panel-alone 'any mutation' analysis is not the commercial MPTX call; MPTX thresholds being validated.; R: Three blinded pathologists, unanimous consensus.; F: Only consensus cases with adequate nucleic acid analyzed (197/309).
Ohori 2020	low	low	unclear	high	low	low	low	P: All adequate FNHCT/SFNHCT cases with routine ThyroSeq v3 over the period.; I: Commercial TSv3 categories.; R: Histology from surgical pathology; blinding to molecular results not stated; NIFTP counted with malignancy.; F: Only 21/31 resected; no FNHCT breakdown by test result.
Papoian 2020	high	low	unclear	low	high	high	low	P: Surgical cohort restricted to patients with histologic Hashimoto thyroiditis; selection by surgery.; I: Commercial Afirma GEC with predefined calls.; R: Slides reviewed by study pathologist and a blinded second pathologist for HT/cancer, but no oncocytic-specific histology outcome reported.; F: All included patients had surgery (no partial verification within the sample), though no oncocytic 2x2 available.
San Martin 2020	low	low	unclear	high	low	low	low	P: All Bethesda III/IV nodules with Afirma results over the period; 'No Result' excluded.; I: Commercial Afirma GEC/GSC with predefined benign/suspicious calls.; R: Histopathology by subspecialty pathologists; blinding to Afirma result not stated; NIFTP not addressed.; F: Unoperated suspicious nodules excluded and benign-call nodules mostly unverified.
Angell 2019	low	low	unclear	high	low	low	low	P: All Bethesda III/IV nodules >1 cm tested in the clinic; 'No result' excluded.; I: Commercial Afirma categories.; R: No Hürthle-specific histology; blinding not stated.; F: BCR only; verification by histology incomplete and not reported for subgroup.
Endo 2019	low	low	unclear	high	low	low	low	P: All cyto-I nodules with GEC/GSC at a single center (exclusions for missing data/ND).; I: Commercial Afirma categories; cytology read before molecular testing.; R: Histology by academic H&N pathologists; blinding to Afirma not stated; NIFTP counted malignant.; F: Unoperated benign assumed benign; operated-only HC 2x2 not reported.
Hao 2019	high	low	low	low	high	low	low	P: Subset defined by histology within a prospective blinded validation cohort.; I: Locked GSC algorithm; validation samples independent of training.; R: Blinded central histopathology panel in validation study.; F: All validation nodules had histology.
Harrell 2019	low	low	unclear	high	low	high	low	P: All Afirma-tested Bethesda 3/4 FNAs in the practice registry (only non-benign/suspicious results excluded).; I: Commercial Afirma GEC/GSC with predefined calls.; R: Histology rendered by institutional pathologists; blinding not stated.; F: No histologic verification reported for the oncocytic subgroup (BCR only).
Ohori 2019	low	low	unclear	high	low	low	unclear	P: All consecutive AUS/FLUS and FN/SFN cases with ThyroSeq v3 results over 8 months.; I: Commercial ThyroSeq v3 with predefined categories.; R: No histology reported for the oncocytic subset.; F: Only BCR available; no verification by histology for oncocytic cases.
Parajuli 2019	low	low	unclear	high	low	high	low	P: All FNAs sent for molecular testing over the period (repeat-indeterminate nodules, test chosen by clinician).; I: Commercial tests with predefined categories, done preoperatively.; R: Histologic designations from original reports; blinding to molecular result not stated.; F: GEC benign 1/11 and ThyroSeq negative 13/22 resected; partial verification.
Schatz-Siemers 2019	low	high	unclear	high	low	high	low	P: All indeterminate Hürthle-cell-predominant FNAs with successful ThyroSeq over the period.; I: Positivity defined ad hoc as any detectable alteration rather than ThyroSeq reported risk category.; R: Surgical pathology reviewed retrospectively; blinding to ThyroSeq not stated.; F: Only 33/188 (18%) resected; 110 negatives unverified.
Steward 2019	high	low	low	low	high	low	low	P: Only nodules that underwent surgery were enrolled (resected-only design).; I: TSv3 GC with predefined cutoff, lab blinded to cytology/histology.; R: Double-blinded central consensus pathology.; F: All analyzed nodules had histology; 10% inadequate samples excluded.
Wei 2019	low	low	unclear	high	low	high	low	P: All AUS/FLUS and FN/SFN nodules >1 cm submitted for Afirma in the period.; I: Commercial Afirma GEC/GSC with predefined calls.; R: Routine histology; awareness of Afirma result not stated.; F: Only suspicious nodules resected in oncocytic subset; GEC/GSC-benign not verified.
Bellevicine 2018	low	low	unclear	high	low	high	low	P: All consecutive AUS/FLUS FNAs tested prospectively over the period.; I: Prespecified mutation-positive/negative panel result.; R: Histology from surgery (some outside); blinding not stated.; F: Only 2/46 HC cases had histology.
Livhits 2018	low	low	high	high	low	high	low	P: Pragmatic RCT enrolling consecutive eligible indeterminate nodules (94.9% enrolment).; I: Commercial tests with predefined categories.; R: Pathologists explicitly not blinded to molecular results.; F: Negatives largely unoperated (surveillance, some <6 months).
Nikiforova 2018	high	low	unclear	low	high	low	low	P: Case-control style FNA validation set purposely enriched for malignancy (52.6%), resected nodules only.; I: GC cutoff (1.5) set on independent tissue training set and applied to FNA set.; R: Blind histology re-review described for training tissue; not stated for FNA validation set.; F: All FNA validation samples had surgical histology.
Patel 2018	high	low	low	low	high	low	low	P: Prospective multicenter cohort but restricted to resected nodules with residual RNA; subgroup defined by histology.; I: Locked GSC algorithm tested on a blinded independent set.; R: Blinded expert panel histopathology.; F: All included nodules had histology (19/210 excluded for insufficient RNA).
Walts 2018	high	low	unclear	high	high	high	low	P: Only resected nodules with AGEC results, 91% AGEC-suspicious (enriched sampling).; I: Commercial AGEC; Reveal run blinded on archived smears with its predefined categories.; R: Local histology without central review; blinding to AGEC not stated.; F: Only resected cases included; AGEC-benign unoperated nodules absent (partial verification).
Hang 2017	high	low	unclear	high	high	high	low	P: Consecutive GEC-tested nodules but analysis restricted to resected; subgroup selected by histology.; I: GEC commercial categories performed after final cytology diagnosis.; R: Histology; blinding to GEC not stated.; F: Only resected nodules (177/384) analyzed.
Roychoudhury 2017	high	low	unclear	high	low	high	low	P: Only GEC-suspicious nodules were included (case selection on index test result).; I: Commercial Afirma GEC with predefined calls.; R: Histology rendered in routine practice; blinding not stated.; F: No GEC-benign nodules; only resected suspicious subset analyzed.

Study	RoB: patient	RoB: index	RoB: reference	RoB: flow	AC: patient	AC: index	AC: reference	Rationale (P, patient; I, index; R, reference; F, flow)
Chaudhary 2016	low	low	unclear	low	low	high	low	P: All HCN FNAs sent for Afirma (at clinician request) in the post-Afirma period included.; I: Commercial Afirma GEC with predefined calls.; R: Head/neck pathologists; blinding to Afirma not stated.; F: 12/13 HCN resected (near-complete verification).
Collet 2016	high	low	unclear	low	low	high	low	P: Series restricted to nodules with histology (all resected).; I: Prespecified V600E positive/negative result.; R: Histology reference; blinding not stated.; F: All included nodules verified by histology.
Giovanella 2016	low	low	unclear	low	low	high	low	P: Consecutive prospectively enrolled Bethesda IV patients (all operated).; I: Prespecified mutation-positive/negative definition.; R: Histology reference; pathologist blinding to mutation status not stated.; F: All patients underwent surgery.
Samulski 2016	low	low	unclear	high	low	high	low	P: All FNAs with concurrent GEC over 5 years.; I: GEC commercial categories.; R: Histology; blinding not stated.; F: Only 31/45 FNOF resected; most GEC-benign not resected.
Valderrabano 2016	high	low	high	high	low	high	low	P: miRInform used sporadically before Feb 2014 (non-consecutive testing).; I: Commercial miRInform panel with predefined mutation-positive/negative result.; R: Pathologists were aware of cytology and miRInform results.; F: Only 12/18 resected; mutation-positive more likely resected.
Wu 2016	low	low	unclear	high	low	high	low	P: Prospectively maintained database of all reflex-tested Bethesda III/IV nodules; lost to follow-up and insufficient excluded.; I: GEC with commercial categories, reflex-ordered.; R: Histology; blinding not stated; unresected assumed benign.; F: Unknown number resected in HCN; unresected suspicious assumed benign.
Yang 2016	high	low	unclear	high	high	high	low	P: Histology-defined subset among resected GEC-tested nodules only.; I: Commercial GEC with predefined categories.; R: Routine histology; awareness of GEC not stated.; F: Only 73/217 GEC-tested nodules resected.
Brauner 2015	unclear	low	unclear	high	low	high	low	P: HCN patients tested with AGEC at three centers; 21 patients excluded (lost to follow-up, pending results, etc.) and 97 contemporaneous patients managed without AGEC, so selection for testing is unclear.; I: Commercial Afirma GEC with predefined calls.; R: Surgical pathology; blinding to AGEC not stated.; F: 23/26 GEC-benign not resected; Scenario A uses only resected subset.
Celik 2015	low	low	unclear	high	low	high	low	P: All FNAs sent for GEC in the period.; I: Commercial GEC with predefined categories.; R: Routine histology; awareness of GEC result not stated.; F: Only suspicious HCN nodules resected.
Eszlinger 2015	high	low	high	low	high	high	low	P: Consecutive surgical patients only; oncocytic subgroup histology-defined.; I: Predefined mutation panel on archived smears (positive = any mutation detected).; R: Methods state FA/HCA histology re-reviewed by a pathologist aware of molecular results (Discussion claims unawareness - internal inconsistency).; F: All included nodules resected (surgical series).
Harrell 2014	low	low	unclear	high	low	high	low	P: All indeterminate FNAs in a single surgical practice over 27 months sent for GEC.; I: Commercial GEC with predefined categories.; R: Pathology reports issued with external consultation; awareness of GEC not stated.; F: GEC-benign oncocytic nodules not resected.
Lastra 2014	low	low	unclear	high	low	high	low	P: All FNAs with AUS/FN/FNOF and concurrent Afirma in the period.; I: GEC commercial categories.; R: Histology; blinding not stated.; F: Only 2/8 GEC-benign resected.
McIver 2014	high	low	unclear	high	low	high	low	P: Patients at high clinical risk and those choosing surgery were not tested; selection of tested patients.; I: Commercial GEC with benign/suspicious call.; R: Histopathology; blinding to GEC not stated.; F: Most GEC-benign nodules unoperated; analysis only of resected nodules.
Park 2014	high	low	unclear	high	low	high	low	P: Retrospective re-subclassification of AUS; BRAF testing done only in a subset (13/20 AUS-HC).; I: Pyrosequencing with predefined 10% mutant-allele cutoff.; R: Routine histology; blinding not stated.; F: Only 5/20 AUS-HC resected (4 tested and resected).
Radkay 2014	high	low	high	high	high	high	low	P: Only RAS-mutated, resected nodules included (mutation-selected).; I: Prespecified mutation detection.; R: Surgical pathologists knew cytology and molecular results at sign-out; pre-NIFTP FVPTC counted malignant.; F: No RAS-negative nodules; only resected cases (92.5% NRAS, 86% HRAS, 100% KRAS resected overall).
Alexander 2012	low	low	low	high	high	high	low	P: Prospective multicenter collection of consecutive indeterminate aspirates.; I: GEC run blinded to histology with locked classifier.; R: Central blinded histopathology review.; F: Only resected nodules (413/577) analyzed.
Keutgen 2012	high	low	low	low	low	high	low	P: Validation set included only operated indeterminate nodules (derivation set was case-control).; I: Model locked on separate derivation set before applying to independent validation samples.; R: All histology reviewed by an endocrine pathologist after surgery; molecular result unavailable clinically (research assay).; F: All validation nodules resected and verified.
Lappinga 2010	high	high	unclear	low	low	high	low	P: 125 resected cases selected from 1946 FNAs (enriched benign/malignant sampling).; I: Research single-gene assay with ROC-derived cutoff on the same samples.; R: Histology re-reviewed; blinding of histology reviewers to HMGA2 not stated (assay performers were blinded).; F: All included nodules resected; 10/125 RNA failures excluded.

RoB, risk of bias; AC, applicability concerns. Judgments were drafted with large-language-model assistance and reviewed and finalized by two investigators.

Supplementary Table S7. Sensitivity and subgroup analyses

Note: univariate re-estimates of the four primary models were almost identical to the bivariate results (GSC scenario A 87.5% / 46.5%; ThyroSeq v3 scenario A 93.7% / 29.5%; GSC scenario B 91.2% / 87.4%; ThyroSeq v3 scenario B 95.6% / 76.1%). All models use 150-point (univariate) and 50 × 50-point (bivariate) Gauss–Hermite quadrature, and estimates are stable at higher node counts; the "excluding resected-only cohorts" model has a between-study variance near zero for sensitivity, and its confidence interval is correspondingly wide.

Analysis	Description	k	Nodules	Sensitivity	Specificity	PPV	NPV
ThyroSeq v3, main (scenario A)	Reference	9	246	93.9 (82.9–98.0)	29.9 (23.4–37.5)	35.3 (27.6–43.8)	91.4 (78.1–96.9)
+ Penn conference abstract	Adds Khan 2026 (2x2 reconstructed from percentages)	10	396	92.8 (85.3–96.6)	32.2 (26.3–38.8)	37.7 (29.6–46.4)	88.7 (80.7–93.6)
Excluding 'any alteration' positivity	Excludes studies using 'any alteration' as positive (Landau, Abi-Raad)	7	136	86.8 (72.0–94.4)	31.6 (23.2–41.5)	33.1 (22.1–46.3)	86.1 (70.7–94.1)
Excluding resected-only cohorts	Excludes Elsheikh 2026 and Spagnuolo 2022	7	206	96.8 (81.7–99.5)	30.1 (22.9–38.5)	33.3 (24.7–43.3)	95.1 (72.6–99.3)
Bethesda III only		3	45	81.9 (40.5–96.8)	44.1 (28.6–60.8)	32.1 (17.6–51.1)	88.2 (63.2–97.0)
Bethesda IV only		2	106	97.4 (71.4–99.8)	26.8 (17.8–38.2)	39.5 (29.8–50.2)	95.4 (59.1–99.7)
Afirma GSC, main (scenario A)	Reference	3	161	87.5 (76.9–93.6)	46.5 (36.2–57.1)	49.5 (24.6–74.7)	89.6 (58.9–98.1)
Excluding NIFTP-as-malignant study	Excludes Elsheikh 2026	2	112	92.9 (75.5–98.2)	46.7 (34.7–59.1)	35.9 (20.8–54.3)	95.1 (82.5–98.8)
Afirma GSC, scenario B + Attia 2026	Adds conservative construction (unoperated suspicious = FP)	5	443	90.2 (76.0–96.4)	85.7 (79.3–90.4)	40.2 (25.4–56.9)	98.9 (97.0–99.6)
GEC scenario A excluding Chaudhary 2016	pre-reclassification outcome definition	7	124	100.0 (82.4–100.0)	10.5 (5.9–17.9)	16.8 (11.0–24.9)	100.0 (71.5–100.0)
Histology-defined subgroups, all platforms	one row per patient cohort	14	348	85.8 (62.5–95.7)	49.1 (27.1–71.4)	38.0 (27.5–49.8)	87.3 (77.3–93.2)
Histology-defined, GSC + ThyroSeq v3		5	102	90.2 (72.1–97.0)	65.6 (54.0–75.6)	51.0 (37.5–64.3)	95.8 (70.1–99.5)
Histology-defined, GEC		4	76	92.9 (60.6–99.1)	5.2 (1.5–15.9)	21.3 (10.2–39.4)	60.0 (20.0–90.0)
GSC scenario B excluding Endo 2019	NIFTP counted as malignant by design	4	381	90.9 (75.3–97.0)	86.8 (82.8–90.0)	42.1 (23.8–62.8)	99.0 (97.0–99.7)
GEC scenario B excluding Endo 2019	NIFTP counted as malignant by design	5	154	100.0 (80.5–100.0)	40.1 (32.3–48.6)	17.2 (11.0–25.9)	100.0 (93.5–100.0)
GEC scenario A excluding pre-2016 studies	NIFTP pooled with malignancy (4 studies)	4	50	100.0 (66.4–100.0)	11.9 (3.0–37.4)	19.3 (8.0–39.6)	100.0 (47.8–100.0)
GEC scenario A excluding Glass 2021	Afirma version not stated; period spans the GEC-to-GSC transition	7	132	100.0 (87.2–100.0)	8.6 (4.5–15.7)	21.2 (11.0–36.8)	100.0 (66.4–100.0)
CNA-only ROM including Kim 2023	sensitivity-only study, now reported	11	69				17.8 (7.3–37.5)
GEC BCR including Papoian 2020	sensitivity-only study, now reported	16	468				24.0 (19.5–29.2)
GSC BCR excluding broad-definition studies	Attia 2026, Endo 2019 (oncocytic cells present)	6	440				75.4 (69.2–80.6)
RAS-like ROM excluding Elsheikh 2026	selectively tested alteration classes	10	126				27.9 (17.4–41.6)
GEC BCR excluding Glass 2021	Afirma version not stated (GEC assumed)	14	441				24.4 (19.7–29.9)

Leave-one-study-out (scenario A)

Test	Study omitted	Sensitivity	Specificity
ThyroSeq v3	Abi-Raad 2022	92.7 (80.1–97.5)	31.2 (24.1–39.3)
ThyroSeq v3	Elsheikh 2026	95.1 (78.9–99.0)	29.8 (23.1–37.6)
ThyroSeq v3	Gajzer 2022	93.3 (80.9–97.8)	28.8 (22.1–36.7)
ThyroSeq v3	Glass 2021	93.9 (81.2–98.2)	29.6 (22.8–37.4)
ThyroSeq v3	Hsiao 2025	95.5 (86.9–98.6)	27.8 (21.4–35.3)
ThyroSeq v3	Landau 2021	89.4 (76.4–95.6)	29.8 (22.2–38.8)
ThyroSeq v3	Raghunathan 2024	93.4 (81.4–97.8)	30.9 (23.7–39.1)
ThyroSeq v3	Spagnuolo 2022	95.1 (82.5–98.8)	30.3 (23.1–38.6)
ThyroSeq v3	Tjendra 2023	95.2 (82.4–98.8)	31.3 (24.0–39.7)
Afirma GSC	Elsheikh 2026	92.9 (75.5–98.2)	46.7 (34.7–59.1)
Afirma GSC	Jin 2022	87.3 (76.6–93.5)	45.7 (35.1–56.7)

Benign call rate sensitivity analyses

Analysis	Pooled BCR, % (95% CI)
ThyroSeq v3 BCR + Penn abstract	59.6 (49.9–68.6)
GSC BCR, Bethesda III strata	80.5 (74.8–85.2)
ThyroSeq v3 BCR, Bethesda III strata	74.6 (68.1–80.2)
ThyroSeq v3 BCR, Bethesda IV strata	50.9 (44.4–57.4)
ThyroSeq v3 BCR excluding any-alteration positivity	63.4 (53.7–72.1)

Supplementary Table S8. Reports excluded at full-text review (n = 273) or not retrieved (n = 47)

Study	Title	Journal	DOI	Reason
Angell 2019	Getting more out of molecular testing for indeterminate thyroid nodules	CANCER CYTOPATHOLOGY	10.1002/cncy.22129	Not original research
Daniels 2013	What is the role of molecular markers in the management of 'indeterminate' thyroid nodules?	Cancer Cytopathology	10.1002/cncy.21289	Not original research
Eloy 2022	Preoperative diagnosis of thyroid nodules: An integrated multidisciplinary approach	CANCER CYTOPATHOLOGY	10.1002/cncy.22546	Not original research
Endo 2020	Letter to the Editor: Use of Molecular Diagnostic Tests in Thyroid Nodules with Hürthle Cell-Dominant Cytology.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2020.0021	Not original research
Ladenson 2023	Combined Afirma Genomic Sequencing Classifier and TERT promoter mutation detection in molecular assessment of Bethesda III-VI thyroid nodules.	Cancer cytopathology	10.1002/cncy.22744	Not original research
Tarashchenko 2023	Optimization of diagnosis, surgical treatment and prediction of the course of thyroid tumors and adrenal incidentalomas	Endokrynologia	10.31793/1680-1466.2023.28-2.167	Not original research
Wong 2022	Unraveling Hürthle cell lesions of the thyroid using molecular findings.	Cancer cytopathology	10.1002/cncy.22567	Not original research
Abi-Raad 2024	EIF1AX mutation in thyroid nodules: a histopathologic analysis of 56 cases in the context of institutional practices.	Virchows Archiv : an international journal of pathology	10.1007/s00428-024-03914-5	Case report or <5 oncocytic nodules
Andrioli 2020	Testing for Afirma in Thyroid Nodules with High-Risk Indeterminate Cytology (TIR3B): First Italian Experience.	Endocrine pathology	10.1007/s12022-020-09604-7	Case report or <5 oncocytic nodules
Azaryan 2024	Ultrasound Features and Performance of Afirma Gene Sequencing Classifier in Cytologically Indeterminate Thyroid Nodules.	Journal of the Endocrine Society	10.1210/jendso/bvae010	Case report or <5 oncocytic nodules
Barnes 2022	Molecular Testing for Indeterminate Thyroid Nodules: Association of Negative Predictive Value With Nodule Size.	The American surgeon	10.1177/00031348221109489	Case report or <5 oncocytic nodules
Jones 2023	The histologic outcomes of indeterminate thyroid nodules with rat sarcoma mutations: A case series.	Diagnostic cytopathology	10.1002/dc.25214	Case report or <5 oncocytic nodules
Partyka 2019	Risk of malignancy and neoplasia predicted by three molecular testing platforms in indeterminate thyroid nodules on fine-needle aspiration.	Diagnostic cytopathology	10.1002/dc.24250	Case report or <5 oncocytic nodules
Purgina 2013	Thyroid nodule	JAMA Otolaryngology - Head and Neck Surgery	10.1001/jamaoto.2013.3816	Case report or <5 oncocytic nodules
Townsend 2025	Navigating Diagnostic Uncertainty in Thyroid Nodules: The Critical Role of Cytology and Histology in Oncocytic and Rare Patterned Lesions	Cytopathology	10.1111/cyt.13473	Case report or <5 oncocytic nodules
Wright 2024	Incidental (68)Ga-DOTATATE uptake in thyroid nodules: Is guideline-directed management still appropriate?	Surgery	10.1016/j.surg.2023.04.064	Case report or <5 oncocytic nodules
Xu 2023	A Combination of BRAF and EZH1/SPOP/ZNF148 Three-Gene Mutational Classifier Improves Benign Call Rate in Indeterminate Thyroid Nodules.	Endocrine pathology	10.1007/s12022-023-09782-0	Case report or <5 oncocytic nodules
Young 2018	An academic community hospital experience using commercially available molecular testing in the management of indeterminate thyroid nodules.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2017.09.001	Case report or <5 oncocytic nodules
Zhou 2015	FNA needle rinses preserved in Cytolyt are acceptable specimen type for mutation testing of thyroid nodules.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2015.01.001	Case report or <5 oncocytic nodules
Šamija 2019	HMGA2 Gene Expression in Fine-needle Aspiration Samples of Thyroid Nodules as a Marker for Preoperative Diagnosis of Thyroid Cancer.	Applied immunohistochemistry & molecular morphology : AIMM	10.1097/PAI.0000000000000637	Case report or <5 oncocytic nodules
Belaiche 2024	Molecular Markers in Follicular and Oncocytic Thyroid Carcinomas: Clinical Application of Molecular Genetic Testing.	Current oncology (Toronto, Ont.)	10.3390/curroncol31100441	Wrong population
Cho 2017	Distinguishing parathyroid and thyroid lesions on ultrasound-guided fine-needle aspiration: A correlation of clinical data, ancillary studies, and molecular analysis.	Cancer cytopathology	10.1002/cncy.21888	Wrong population
Gomez-Rueda 2016	A robust biomarker of differential correlations improves the diagnosis of cytologically indeterminate thyroid cancers	INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE	10.3892/ijmm.2016.2534	Wrong population
Hier 2021	Molecular testing for cytologically suspicious and malignant (Bethesda V and VI) thyroid nodules to optimize the extent of surgical intervention: a retrospective chart review.	Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale	10.1186/s40463-021-00500-6	Wrong population
Nikiforova 2013	Targeted next-generation sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer.	The Journal of clinical endocrinology and metabolism	10.1210/jc.2013-2292	Wrong population
Paulson 2015	Molecular Analysis of Oncocytic Thyroid Carcinomas	MODERN PATHOLOGY		Wrong population
Seethala 2017	Clinical and Morphologic Features of ETV6-NTRK3 Translocated Papillary Thyroid Carcinoma in an Adult Population Without Radiation Exposure.	The American journal of surgical pathology	10.1097/PAS.0000000000000814	Wrong population
Skaugen 2022	Performance of a Multigene Genomic Classifier in Thyroid Nodules with Suspicious for Malignancy Cytology.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2022.0282	Wrong population
Starr 2025	Parsing the thyroid cytopathology suspicious for malignancy diagnosis through molecular-derived risk of malignancy and other related parameters: Insights into nodule characteristics and practice patterns.	Cancer cytopathology	10.1002/cncy.22904	Wrong population
Viswanathan 2020	Cytomorphologic features of NTRK-rearranged thyroid carcinoma.	Cancer cytopathology	10.1002/cncy.22374	Wrong population

Study	Title	Journal	DOI	Reason
Abeykoon 2016	The Effect of Implementing Gene Expression Classifier on Outcomes of Thyroid Nodules with Indeterminate Cytology.	Hormones & cancer	10.1007/s12672-016-0263-4	No separable oncocytic subgroup
Aekka 2025	Multiplatform Molecular Testing as an Adjunct to Fine Needle Aspiration in the Evaluation of Pediatric Thyroid Nodules.	The Journal of clinical endocrinology and metabolism	10.1210/clinem/dgaf110	No separable oncocytic subgroup
Ai 2026	Testing insulin-like growth factor messenger RNA-binding protein 3 as a surrogate immunohistochemical marker for indeterminate thyroid nodules with THADA fusion in both cytologic and surgical specimens.	Cancer cytopathology	10.1002/cncy.70076	No separable oncocytic subgroup
Al-Qurayshi 2017	Association of Malignancy Prevalence With Test Properties and Performance of the Gene Expression Classifier in Indeterminate Thyroid Nodules.	JAMA otolaryngology-- head & neck surgery	10.1001/jamaoto.2016.3526	No separable oncocytic subgroup
Alexander 2014	Multicenter clinical experience with the Afirma gene expression classifier.	The Journal of clinical endocrinology and metabolism	10.1210/jc.2013-2482	No separable oncocytic subgroup
Alohali 2023	Effect of Having Concurrent Mutations on the Degree of Aggressiveness in Patients with Thyroid Cancer Positive for TERT Promoter Mutations	Cancers	10.3390/cancers15020413	No separable oncocytic subgroup
Altshuler 2024	Nonoperative, Active Surveillance of Larger Malignant and Suspicious Thyroid Nodules.	The Journal of clinical endocrinology and metabolism	10.1210/clinem/dgae082	No separable oncocytic subgroup
Alzumaili 2023	A Comprehensive Study on the Diagnosis and Management of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features	THYROID	10.1089/thy.2023.0035	No separable oncocytic subgroup
Angell 2015	Afirma Benign Thyroid Nodules Show Similar Growth to Cytologically Benign Nodules During Follow-Up.	The Journal of clinical endocrinology and metabolism	10.1210/jc.2015-2658	No separable oncocytic subgroup
Aragon Han 2014	The impact of molecular testing on the surgical management of patients with thyroid nodules.	Annals of surgical oncology	10.1245/s10434-014-3508-x	No separable oncocytic subgroup
Arnaut Lima 2025	External validation of a microRNA thyroid classifier: a real-world prospective study	European Thyroid Journal	10.1530/ETJ-25-0105	No separable oncocytic subgroup
Assaad 2024	A Preliminary Study Comparing the Performance of Thyroid Molecular Tests to a Deep Learning Algorithm in Predicting Malignancy in Indeterminate Thyroid Fine Needle Aspiration Biopsies	Thyroid	10.1089/thy.2023.0054	No separable oncocytic subgroup
Aydemirli 2021	Yield and costs of molecular diagnostics on thyroid cytology slides in the Netherlands, adapting the Bethesda classification	Endocrinology, Diabetes and Metabolism	10.1002/edm2.293	No separable oncocytic subgroup
Azad 2026	Analysis of PLEKHS2 promoter mutation in preoperative thyroid nodule samples.	Cancer cytopathology	10.1002/cncy.70103	No separable oncocytic subgroup
Azad 2026	Improving Diagnostic Precision in Thyroid Pathology by Synergistic Use of AI and Molecular Markers.	Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists	10.1016/j.eprac.2026.01.750	No separable oncocytic subgroup
Azizi 2018	Shear wave elastography and Afirma™ gene expression classifier in thyroid nodules with indeterminate cytology: a comparison study.	Endocrine	10.1007/s12020-017-1509-9	No separable oncocytic subgroup
Babazadeh 2022	Thyroid nodule molecular profiling: The clinical utility of Afirma Xpression Atlas for nodules with Afirma Genomic Sequencing Classifier-suspicious results.	Surgery	10.1016/j.surg.2021.08.058	No separable oncocytic subgroup
Bakht 2024	Risk of Malignancy and Management of Indeterminate Thyroid Nodules with HRAS/NRAS Mutations	Journal of Clinical and Translational Pathology	10.14218/JCTP.2024.00011	No separable oncocytic subgroup
Bandargal 2022	Prognostic Indicators of EIF1AX-Mutated Thyroid Tumor Malignancy and Cancer Aggressiveness	Cancers	10.3390/cancers14246097	No separable oncocytic subgroup
Bandargal 2023	Characteristics of PTEN Mutation in Thyroid Tumours: A Retrospective Chart Review.	Cancers	10.3390/cancers15051575	No separable oncocytic subgroup
Banizs 2019	The utility of combined mutation analysis and microRNA classification in reclassifying cancer risk of cytologically indeterminate thyroid nodules	DIAGNOSTIC CYTOPATHOLOGY	10.1002/dc.24087	No separable oncocytic subgroup
Brandler 2018	Does Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features (NIFTP) Have a Unique Molecular Profile?	American journal of clinical pathology	10.1093/ajcp/aqy075	No separable oncocytic subgroup
Brandler 2023	Molecular Profiles of Noninvasive, Minimally Invasive, and Invasive Follicular Patterned Thyroid Neoplasms with Papillary Nuclear Features.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2023.0047	No separable oncocytic subgroup
Carty 2020	The Clinical Utility of Molecular Testing in the Management of Thyroid Follicular Neoplasms (Bethesda IV Nodules).	Annals of surgery	10.1097/SLA.0000000000004130	No separable oncocytic subgroup
Castellanos 2026	Afirma genomic sequencing classifier performance in young patients with cytologically indeterminate thyroid nodules.	The Journal of clinical endocrinology and metabolism	10.1210/clinem/dgag059	No separable oncocytic subgroup
Chen 2020	The Role of the ThyroSeq v3 Molecular Test in the Surgical Management of Thyroid Nodules in the Canadian Public Health Care Setting.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2019.0539	No separable oncocytic subgroup
Chiosea 2023	Molecular Profiling of 50 734 Bethesda III-VI Thyroid Nodules by ThyroSeq v3: Implications for Personalized Management.	The Journal of clinical endocrinology and metabolism	10.1210/clinem/dgad220	No separable oncocytic subgroup
Chong 2021	Prevalence and Spectrum of DICER1 Mutations in Adult-onset Thyroid Nodules with Indeterminate Cytology.	The Journal of clinical endocrinology and metabolism	10.1210/clinem/dgab025	No separable oncocytic subgroup

Study	Title	Journal	DOI	Reason
Ciarletto 2021	Analytical and clinical validation of pairwise microRNA expression analysis to identify medullary thyroid cancer in thyroid fine-needle aspiration samples.	Cancer cytopathology	10.1002/cncy.22365	No separable oncocytic subgroup
Cipriani 2022	The Significance of RAS-Like Mutations and MicroRNA Profiling in Predicting Malignancy in Thyroid Biopsy Specimens.	Endocrine pathology	10.1007/s12022-022-09734-0	No separable oncocytic subgroup
Ciregia 2016	Proteomic analysis of fine-needle aspiration in differential diagnosis of thyroid nodules	TRANSLATIONAL RESEARCH	10.1016/j.trsl.2016.04.004	No separable oncocytic subgroup
Cohen 2019	Rethinking Malignancy Risk in Indeterminate Thyroid Nodules with Positive Molecular Studies: Southern California Permanente Experience.	Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery	10.1177/0194599819842859	No separable oncocytic subgroup
Condello 2025	Alterations in gene expression associated with invasion of RAS-mutant thyroid tumors and their potential diagnostic and therapeutic utility	European Thyroid Journal	10.1530/ETJ-25-0022	No separable oncocytic subgroup
Connelly 2023	Interpace, Affirma, and Thyroseq Performance Characteristics in 341 Bethesda Category III/IV Thyroid Nodules	AMERICAN JOURNAL OF CLINICAL PATHOLOGY	10.1093/ajcp/aqad150.051	No separable oncocytic subgroup
Corriveau-Parenteau 2023	Clinical Experience of Cytologically Indeterminate Thyroid Nodules Designated as Negative on Molecular Testing Using ThyroSeq V3: A Retrospective Cohort Study.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2022.0555	No separable oncocytic subgroup
De Leo 2023	Expanding the Spectrum of BRAF Non-V600E Mutations in Thyroid Nodules: Evidence-Based Data from a Tertiary Referral Centre.	International journal of molecular sciences	10.3390/ijms24044057	No separable oncocytic subgroup
Dean 2026	Cytologic atypia is predictive of increased risk of malignancy and BRAF mutations in thyroid follicular neoplasms (Bethesda category IV).	Journal of the American Society of Cytopathology	10.1016/j.jasc.2025.07.003	No separable oncocytic subgroup
Desai 2021	ThyroSeq v3 for Bethesda III and IV: An institutional experience.	Cancer cytopathology	10.1002/cncy.22362	No separable oncocytic subgroup
Dhingra 2016	Office-Based Ultrasound-Guided FNA with Molecular Testing for Thyroid Nodules	OTOLARYNGOLOGY-HEAD AND NECK SURGERY	10.1177/0194599816652378	No separable oncocytic subgroup
Diggans 2015	Machine learning from concept to clinic: reliable detection of BRAF V600E DNA mutations in thyroid nodules using high-dimensional RNA expression data.	Pacific Symposium on Biocomputing. Pacific Symposium on Biocomputing		No separable oncocytic subgroup
Dilli 2025	Managing TBSRTC III thyroid nodules: evaluating repeat FNA, molecular testing, and surgery	Journal of the American Society of Cytopathology	10.1016/j.jasc.2025.05.007	No separable oncocytic subgroup
Domingo 2017	Identification of parathyroid tissue in thyroid fine-needle aspiration: A combined approach using cytology, immunohistochemical, and molecular methods.	Diagnostic cytopathology	10.1002/dc.23711	No separable oncocytic subgroup
Dublin 2022	Predictive Value of a Genomic Classifier in Indeterminate Thyroid Nodules Based on Nodule Size.	JAMA otolaryngology-- head & neck surgery	10.1001/jamaoto.2021.3080	No separable oncocytic subgroup
Duick 2012	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 : official journal of the American Thyroid Association	10.1089/thy.2012.0180	No separable oncocytic subgroup
D'Andréa 2023	Pilot Study on the Use of Untargeted Metabolomic Fingerprinting of Liquid-Cytology Fluids as a Diagnostic Tool of Malignancy for Thyroid Nodules	Metabolites	10.3390/metabo13070782	No separable oncocytic subgroup
Elsheikh 2026	Molecular testing and other metrics in thyroid cytology as quality-assurance measures in evaluating variation among pathologists in the diagnosis of atypia of undetermined significance.	Cancer cytopathology	10.1002/cncy.70074	No separable oncocytic subgroup
Fazeli 2020	ThyroSeq v2 Testing: Impact on Cytologic Diagnosis, Management, and Cost of Care in Patients with Thyroid Nodule.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2019.0191	No separable oncocytic subgroup
Figge 2021	Do Ultrasound Patterns and Clinical Parameters Inform the Probability of Thyroid Cancer Predicted by Molecular Testing in Nodules with Indeterminate Cytology?	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2021.0119	No separable oncocytic subgroup
Gallant 2022	Evaluation of the Molecular Landscape of Pediatric Thyroid Nodules and Use of a Multigene Genomic Classifier in Children.	JAMA oncology	10.1001/jamaoncol.2022.1655	No separable oncocytic subgroup
Garrett 2024	Monitoring Outcomes of Indeterminate Thyroid Nodules and Predictive Capabilities of Molecular Testing.	The Annals of otology, rhinology, and laryngology	10.1177/00034894241264380	No separable oncocytic subgroup
Gilani 2022	RAS mutation and associated risk of malignancy in the thyroid gland: An FNA study with cytology-histology correlation.	Cancer cytopathology	10.1002/cncy.22537	No separable oncocytic subgroup
Gill 2015	Local molecular analysis of indeterminate thyroid nodules Poliquin Resident Research Competition 2015	Journal of Otolaryngology - Head and Neck Surgery	10.1186/s40463-015-0106-2	No separable oncocytic subgroup
Gokozan 2022	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 Cytopathology	10.1002/cncy.22542	No separable oncocytic subgroup
Gomes-Lima 2020	A Novel Risk Stratification System for Thyroid Nodules With Indeterminate Cytology-A Pilot Cohort Study.	Frontiers in endocrinology	10.3389/fendo.2020.00053	No separable oncocytic subgroup
Gortakowski 2021	Single Institution Experience with Afirma and Thyroseq Testing in Indeterminate Thyroid Nodules.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2020.0801	No separable oncocytic subgroup
Guan 2020	The real-world performance of ThyroSeqV.2 to diagnose thyroid "neoplasm requiring surgery".	American journal of cancer research		No separable oncocytic subgroup
Guan 2020	Utilities of RAS Mutations in Preoperative Fine Needle Biopsies for Decision Making for Thyroid Nodule Management: Results from a Single-Center Prospective Cohort.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2019.0116	No separable oncocytic subgroup

Study	Title	Journal	DOI	Reason
Guarnotta 2023	Ultrasound Parameters Can Accurately Predict the Risk of Malignancy in Patients with “Indeterminate TIR3b” Cytology Nodules: A Prospective Study	International Journal of Molecular Sciences	10.3390/ijms24098296	No separable oncocytic subgroup
Gubbiotti 2023	THADA-IGF2BP3 fusions detected in fine-needle aspiration specimens of thyroid nodules: An institutional experience.	Diagnostic cytopathology	10.1002/dc.25113	No separable oncocytic subgroup
Hall 2023	Risk stratification of cytologically indeterminate thyroid nodules with nondiagnostic or benign cytology on repeat FNA: Implications for molecular testing and surveillance.	Cancer cytopathology	10.1002/cncy.22684	No separable oncocytic subgroup
Hamada 2026	Thyroid nodules of uncertain malignant potential non-conforming to World Health Organization diagnostic criteria - clinicopathologic and molecular characterization of 39 cases.	Human pathology	10.1016/j.humpath.2026.106239	No separable oncocytic subgroup
Harrell 2018	COMMUNITY ENDOCRINE SURGICAL EXPERIENCE WITH FALSE-NEGATIVE AFIRMA GEC(®) RESULTS: 2011-2017.	Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists	10.4158/EP-2017-0263	No separable oncocytic subgroup
Harrison 2017	Evaluation of the Afirma Gene Expression Classifier in Repeat Indeterminate Thyroid Nodules.	Archives of pathology & laboratory medicine	10.5858/arpa.2016-0328-OA	No separable oncocytic subgroup
Heider 2019	Malignant risk of indeterminate pediatric thyroid nodules-An institutional experience.	Diagnostic cytopathology	10.1002/dc.24266	No separable oncocytic subgroup
Hu 2021	Afirma Genomic Sequencing Classifier and Xpression Atlas Molecular Findings in Consecutive Bethesda III-VI Thyroid Nodules.	The Journal of clinical endocrinology and metabolism	10.1210/clinem/dgab304	No separable oncocytic subgroup
Hu 2022	The Effect Modification of Ultrasound Risk Classification on Molecular Testing in Predicting the Risk of Malignancy in Cytologically Indeterminate Thyroid Nodules.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2021.0659	No separable oncocytic subgroup
Hudson 2023	Does the likelihood of malignancy in thyroid nodules with RAS mutations increase in direct proportion with the allele frequency percentage?	Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale	10.1186/s40463-022-00611-8	No separable oncocytic subgroup
Jackson 2020	Incremental utility of expanded mutation panel when used in combination with microRNA classification in indeterminate thyroid nodules.	Diagnostic cytopathology	10.1002/dc.24328	No separable oncocytic subgroup
Jiang 2016	Young Investigator Challenge: Molecular testing in noninvasive follicular thyroid neoplasm with papillary-like nuclear features.	Cancer cytopathology	10.1002/cncy.21802	No separable oncocytic subgroup
Jin 2023	Performance of Afirma genomic sequencing classifier and histopathological outcome in Bethesda category III thyroid nodules: Initial versus repeat fine-needle aspiration.	Diagnostic cytopathology	10.1002/dc.25203	No separable oncocytic subgroup
Jin 2025	Performance of Afirma Genomic Sequencing Classifier in Binary Subcategories of Atypia of Undetermined Significance Thyroid Nodules: Single Versus Repeat Diagnosis.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2024.0277	No separable oncocytic subgroup
Jin 2026	Combining Thyroid Imaging Report and Data System (TIRADS) and Afirma Genomic Sequencing Classifier (GSC) for potential improvement of malignant risk stratification of Bethesda III thyroid nodules.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2026.01.001	No separable oncocytic subgroup
Jitpasutham 2024	Thyroid nodules with DICER1 mutation or PTEN alteration: A comparative cytologic, clinical, and molecular study of 117 FNA cases.	Cancer cytopathology	10.1002/cncy.22811	No separable oncocytic subgroup
Jug 2018	Molecular testing for indeterminate thyroid nodules: Performance of the Afirma gene expression classifier and ThyroSeq panel.	Cancer cytopathology	10.1002/cncy.21993	No separable oncocytic subgroup
Jug 2019	Negative Results on Thyroid Molecular Testing Decrease Rates of Surgery for Indeterminate Thyroid Nodules.	Endocrine pathology	10.1007/s12022-019-9571-x	No separable oncocytic subgroup
Jug 2020	High-risk and intermediate-high-risk results from the ThyroSeq v2 and v3 thyroid genomic classifier are associated with neoplasia: Independent performance assessment at an academic institution.	Cancer cytopathology	10.1002/cncy.22283	No separable oncocytic subgroup
Kandil 2023	Diagnostic Performance of Afirma and Interpace Diagnostics Genetic Testing in Indeterminate Thyroid Nodules: A Single Center Study.	Cancers	10.3390/cancers15072098	No separable oncocytic subgroup
Karimkhan 2025	DICER1 mutations in Bethesda III/IV thyroid cytology samples: A multicenter observational study.	Cancer cytopathology	10.1002/cncy.70045	No separable oncocytic subgroup
Karunamurthy 2016	Prevalence and phenotypic correlations of EIF1AX mutations in thyroid nodules.	Endocrine-related cancer	10.1530/ERC-16-0043	No separable oncocytic subgroup
Kay-Rivest 2017	The first Canadian experience with the Afirma® gene expression classifier test.	Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale	10.1186/s40463-017-0201-7	No separable oncocytic subgroup
Kerr 2022	Thyroid nodules of indeterminate cytology in Hispanic/Latinx patients.	Head & neck	10.1002/hed.27100	No separable oncocytic subgroup
Kim 2023	Bethesda III and IV Thyroid Nodules Managed Nonoperatively After Molecular Testing With Afirma GSC or Thyroseq v3.	The Journal of clinical endocrinology and metabolism	10.1210/clinem/dgad181	No separable oncocytic subgroup
Kloos 2013	Does addition of BRAF V600E mutation testing modify sensitivity or specificity of the Afirma Gene Expression Classifier in cytologically indeterminate thyroid nodules?	The Journal of clinical endocrinology and metabolism	10.1210/jc.2012-3762	No separable oncocytic subgroup
Kostek 2025	Molecular Testing in Thyroid Nodules: How Much Does It Change Clinical Practice?	Biomedicines	10.3390/biomedicines13081947	No separable oncocytic subgroup

Study	Title	Journal	DOI	Reason
Krasner 2019	Molecular mutations as a possible factor for determining extent of thyroid surgery.	Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale	10.1186/s40463-019-0372-5	No separable oncocytic subgroup
Labourier 2015	Molecular Testing for miRNA, mRNA, and DNA on Fine-Needle Aspiration Improves the Preoperative Diagnosis of Thyroid Nodules With Indeterminate Cytology.	The Journal of clinical endocrinology and metabolism	10.1210/jc.2015-1158	No separable oncocytic subgroup
Lastra 2018	Preoperative cytologic interpretation of noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a 1-year multi-institutional experience.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2017.12.004	No separable oncocytic subgroup
Lee 2022	An institutional experience with DICER1 mutated thyroid nodules-evaluating the cytomorphology and molecular phenotype.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2022.07.002	No separable oncocytic subgroup
Lee 2025	Validation of preoperative BRAF V600E testing by ThyroSCAN PanelChip in thyroid nodules	Endocrine Connections	10.1530/EC-24-0718	No separable oncocytic subgroup
Lefebvre 2025	High RAS Allele Frequency Signals Increased Risk of TERT Promoter Mutations in Thyroid Tumors.	Cancers	10.3390/cancers17172851	No separable oncocytic subgroup
Leng 2026	Expected, unexpected, and unintended consequences of the Afirma gene sequencing classifier.	Surgery	10.1016/j.surg.2026.110619	No separable oncocytic subgroup
Li 2021	The utility of ThyroSeq(®) in the management of indeterminate thyroid nodules by fine-needle aspiration.	Cytopathology : official journal of the British Society for Clinical Cytology	10.1111/cyt.12981	No separable oncocytic subgroup
Lin 2024	The value of Korean, American, and Chinese ultrasound risk stratification systems combined with BRAF(V600E) mutation for detecting papillary thyroid carcinoma in cytologically indeterminate thyroid nodules	Endocrine	10.1007/s12020-023-03586-2	No separable oncocytic subgroup
Livhits 2017	A pragmatic randomized clinical trial comparing molecular markers for indeterminate thyroid nodules: an interim analysis	Thyroid	10.1089/thy.2017.29046.abstracts	No separable oncocytic subgroup
Livhits 2018	Genomic sequencing classifier versus thyroseq V3 in the management of indeterminate thyroid nodules: a randomized clinical trial	Thyroid	10.1089/thy.2018.29071.sc.abstracts	No separable oncocytic subgroup
Luniewski 2026	Trends in thyroid Bethesda category III in the era of molecular testing: a single-center study.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2026.06.002	No separable oncocytic subgroup
Lynch 2022	Thyroid nodules >4 cm with atypia of undetermined significance cytology independently associate with malignant pathology.	Surgery	10.1016/j.surg.2021.08.017	No separable oncocytic subgroup
Lyon 2026	Positive predictive value of the Afirma gene sequencing classifier for evaluation of the indeterminate thyroid nodule: An institutional experience.	American journal of surgery	10.1016/j.amjsurg.2025.116759	No separable oncocytic subgroup
Lévesque 2025	Publicly Funded Molecular Testing of Indeterminate Thyroid Nodules: Canada's Experience.	The Journal of clinical endocrinology and metabolism	10.1210/clinem/dgae355	No separable oncocytic subgroup
Marcadis 2019	Interinstitutional variation in predictive value of the ThyroSeq v2 genomic classifier for cytologically indeterminate thyroid nodules.	Surgery	10.1016/j.surg.2018.04.062	No separable oncocytic subgroup
Marti 2015	Wide Inter-institutional Variation in Performance of a Molecular Classifier for Indeterminate Thyroid Nodules.	Annals of surgical oncology	10.1245/s10434-015-4486-3	No separable oncocytic subgroup
Matos 2024	Comparative Cyto-Histological Genetic Profile in a Series of Differentiated Thyroid Carcinomas	Diagnostics	10.3390/diagnostics14030278	No separable oncocytic subgroup
McCoy 2012	Intraoperative pathologic examination in the era of molecular testing for differentiated thyroid cancer	Journal of the American College of Surgeons	10.1016/j.jamcollsurg.2012.05.027	No separable oncocytic subgroup
Mohammed 2025	False negative rate and concordance of ThyGeNEXT®+ThyraMIR® testing with post-thyroidectomy histopathology.	Journal of clinical & translational endocrinology	10.1016/j.jcte.2025.100396	No separable oncocytic subgroup
Monti 2015	BRAF Mutations in an Italian Regional Population: Implications for the Therapy of Thyroid Cancer.	International journal of endocrinology	10.1155/2015/138734	No separable oncocytic subgroup
Morand 2024	Molecular Profiling for Bethesda III to VI Nodules: Results of a Multicenter International Retrospective Study.	Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists	10.1016/j.eprac.2024.01.002	No separable oncocytic subgroup
Morariu 2021	Clinicopathologic Characteristics of Thyroid Nodules Positive for the THADA-IGF2BP3 Fusion on Preoperative Molecular Analysis.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2020.0589	No separable oncocytic subgroup
Mostoufi-Moab 2018	Molecular Testing for Oncogenic Gene Alterations in Pediatric Thyroid Lesions.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2017.0059	No separable oncocytic subgroup
Munoz-Zuluaga 2024	Use of the Afirma Xpression Atlas for cytologically indeterminate, Afirma Genomic Sequencing Classifier suspicious thyroid nodules: Clinicopathologic analysis with postoperative molecular testing.	American journal of clinical pathology	10.1093/ajcp/aqad169	No separable oncocytic subgroup
Nikiforov 2015	Impact of the Multi-Gene ThyroSeq Next-Generation Sequencing Assay on Cancer Diagnosis in Thyroid Nodules with Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance Cytology.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2015.0305	No separable oncocytic subgroup
Nikitski 2021	Can TP53-mutant follicular adenoma be a precursor of anaplastic thyroid carcinoma?	Endocrine-related cancer	10.1530/ERC-21-0095	No separable oncocytic subgroup

Study	Title	Journal	DOI	Reason
Nishino 2021	Repeat Fine Needle Aspiration Cytology Refines the Selection of Thyroid Nodules for Afirma Gene Expression Classifier Testing.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2020.0969	No separable oncocytic subgroup
Noureldine 2015	Effect of Gene Expression Classifier Molecular Testing on the Surgical Decision-Making Process for Patients With Thyroid Nodules.	JAMA otolaryngology-- head & neck surgery	10.1001/jamaoto.2015.2708	No separable oncocytic subgroup
O'Conor 2022	Performance of repeat cytology with reflex ThyroSeq genomic classifier for indeterminant thyroid cytology.	Cancer cytopathology	10.1002/cncy.22552	No separable oncocytic subgroup
Oh 2024	Small Multi-Gene DNA Panel Can Aid in Reducing the Surgical Resection Rate and Predicting the Malignancy Risk of Thyroid Nodules	ENDOCRINOLOGY AND METABOLISM	10.3803/EnM.2024.2034	No separable oncocytic subgroup
Olmos 2023	ThyroidPrint®: clinical utility for indeterminate thyroid cytology.	Endocrine-related cancer	10.1530/ERC-22-0409	No separable oncocytic subgroup
Pagan 2016	The diagnostic application of RNA sequencing in patients with thyroid cancer: an analysis of 851 variants and 133 fusions in 524 genes.	BMC bioinformatics	10.1186/s12859-015-0849-9	No separable oncocytic subgroup
Papazian 2023	Repeat Fine-Needle Aspiration With Molecular Analysis in Management of Indeterminate Thyroid Nodules.	Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery	10.1177/01945998221093527	No separable oncocytic subgroup
Partyka 2018	Utilization of direct smears of thyroid fine-needle aspirates for ancillary molecular testing: A comparison of two proprietary testing platforms.	Diagnostic cytopathology	10.1002/dc.23902	No separable oncocytic subgroup
Patel 2017	Preoperative detection of RAS mutation may guide extent of thyroidectomy	SURGERY	10.1016/j.surg.2016.04.054	No separable oncocytic subgroup
Payne 2024	Molecular Mutations and Clinical Behavior in Bethesda III and IV Thyroid Nodules: A Comparative Study.	Cancers	10.3390/cancers16244249	No separable oncocytic subgroup
Peng 2026	Afirma Xpression Atlas Alteration Status Is Associated with Malignancy Risk in Indeterminate Thyroid Nodules.	Thyroid : official journal of the American Thyroid Association	10.1177/10507256261484715	No separable oncocytic subgroup
Perry 2024	The negative outlook: Long-term follow up of ThyroSeq negative and low-risk nodules.	Cancer cytopathology	10.1002/cncy.22875	No separable oncocytic subgroup
Perumal 2023	Utility of the Growth Differentiation Factor-15 in the Differential Diagnosis of Follicular-Patterned Lesions of the Thyroid on Cytopathologic and Histopathologic Samples.	Cureus	10.7759/cureus.46206	No separable oncocytic subgroup
Randolph 2022	Preoperative Identification of Medullary Thyroid Carcinoma (MTC): Clinical Validation of the Afirma MTC RNA-Sequencing Classifier.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2022.0189	No separable oncocytic subgroup
Remer 2023	Chronic Lymphocytic Thyroiditis May Limit the Utility of Molecular Testing in AUS/FLUS Thyroid Nodules.	The Journal of surgical research	10.1016/j.jss.2023.03.034	No separable oncocytic subgroup
Renshaw 2024	Modified Bethesda criteria for thyroid aspirates significantly decrease nondiagnostic rates without decreasing sensitivity.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2024.04.005	No separable oncocytic subgroup
Renshaw 2026	Higher adequacy rates for thyroid aspirates: impact of long-term implementation of modified Bethesda adequacy criteria on aspiration and Afirma performance.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2026.07.006	No separable oncocytic subgroup
Rivas 2018	ThyroSeq(®)V2.0 Molecular Testing: A Cost-Effective Approach for the Evaluation of Indeterminate Thyroid Nodules.	Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists	10.4158/EP-2018-0212	No separable oncocytic subgroup
Sacks 2016	Impact of Afirma gene expression classifier on cytopathology diagnosis and rate of thyroidectomy.	Cancer cytopathology	10.1002/cncy.21749	No separable oncocytic subgroup
Sahli 2019	The association between the ultrasonography TIRADS classification system and surgical pathology among indeterminate thyroid nodules.	Surgery	10.1016/j.surg.2018.04.094	No separable oncocytic subgroup
Salameh 2022	Surgical Outcomes of Thyroid Nodules Positive for Gene Expression Alterations Using ThyroSeq V3 Genomic Classifier.	Cancers	10.3390/cancers15010049	No separable oncocytic subgroup
Scola 2021	Molecular Testing Has Limited Utility in the Surgical Evaluation of Bethesda III Thyroid Nodules.	The Journal of surgical research	10.1016/j.jss.2021.06.026	No separable oncocytic subgroup
Selvaggi 2021	The role of ThyroSeq V3 testing in the management of patients with indeterminate thyroid nodules on fine needle aspiration.	Diagnostic cytopathology	10.1002/dc.24751	No separable oncocytic subgroup
Seo 2025	Histopathologic and Clinical Features of Bethesda III-VI Nodules Harboring Isolated RAS Mutations.	Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists	10.1016/j.eprac.2024.12.001	No separable oncocytic subgroup
Shen 2012	MicroRNA signature in thyroid fine needle aspiration cytology applied to "atypia of undetermined significance" cases	Thyroid	10.1089/thy.2011.0081	No separable oncocytic subgroup
Shrestha 2016	Correlation Between Histological Diagnosis and Mutational Panel Testing of Thyroid Nodules: A Two-Year Institutional Experience.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2016.0048	No separable oncocytic subgroup

Study	Title	Journal	DOI	Reason
Sipos 2016	LONG-TERM NONOPERATIVE RATE OF THYROID NODULES WITH BENIGN RESULTS ON THE AFIRMA GENE EXPRESSION CLASSIFIER.	Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists	10.4158/EP151006.OR	No separable oncocytic subgroup
Sirotnikov 2024	ThyroSeq overview on indeterminate thyroid nodules: An institutional experience.	Diagnostic cytopathology	10.1002/dc.25311	No separable oncocytic subgroup
Sistrunk 2019	Clinical impact of testing for mutations and microRNAs in thyroid nodules	DIAGNOSTIC CYTOPATHOLOGY	10.1002/dc.24190	No separable oncocytic subgroup
Sistrunk 2020	Clinical performance of multiplatform mutation panel and microRNA risk classifier in indeterminate thyroid nodules.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2020.02.002	No separable oncocytic subgroup
Song 2017	Pre-operative features of non-invasive follicular thyroid neoplasms with papillary-like nuclear features: An analysis of their cytological, Gene Expression Classifier and sonographic findings.	Cytopathology : official journal of the British Society for Clinical Cytology	10.1111/cyt.12501	No separable oncocytic subgroup
Song 2025	Performance of molecular testing for indeterminate thyroid nodules in Black patients.	American journal of surgery	10.1016/j.amjsurg.2025.116569	No separable oncocytic subgroup
Steinmetz 2022	How Effective is the Use of Molecular Testing in Preoperative Decision Making for Management of Indeterminate Thyroid Nodules?	World journal of surgery	10.1007/s00268-022-06744-1	No separable oncocytic subgroup
Stillman 2024	Molecular Testing for Bethesda III Thyroid Nodules: Trends in Implementation, Cytopathology Call Rates, Surgery Rates, and Malignancy Yield at a Single Institution	THYROID	10.1089/thy.2023.0664	No separable oncocytic subgroup
Sultan 2020	UTILITY OF AFIRMA GENE EXPRESSION CLASSIFIER FOR EVALUATION OF INDETERMINATE THYROID NODULES AND CORRELATION WITH ULTRASOUND RISK ASSESSMENT: SINGLE INSTITUTIONAL EXPERIENCE.	Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists	10.4158/EP-2019-0350	No separable oncocytic subgroup
Swaminathan 2026	Diagnostic value of molecular testing for evaluating thyroid nodules greater than 4 centimeters.	American journal of surgery	10.1016/j.amjsurg.2025.116755	No separable oncocytic subgroup
Talmor 2022	Association of patient characteristics, ultrasound features, and molecular testing with malignancy risk in Bethesda III-V thyroid nodules	LARYNGOSCOPE INVESTIGATIVE OTOLARYNGOLOGY	10.1002/lio2.847	No separable oncocytic subgroup
Taye 2018	Clinical performance of a next-generation sequencing assay (ThyroSeq v2) in the evaluation of indeterminate thyroid nodules.	Surgery	10.1016/j.surg.2017.07.032	No separable oncocytic subgroup
Titov 2019	Combined quantitation of HMGA2 mRNA, microRNAs, and mitochondrial-DNA content enables the identification and typing of thyroid tumors in fine-needle aspiration smears.	BMC cancer	10.1186/s12885-019-6154-7	No separable oncocytic subgroup
Titov 2021	Preoperative Typing of Thyroid and Parathyroid Tumors with a Combined Molecular Classifier.	Cancers	10.3390/cancers13020237	No separable oncocytic subgroup
Torrecillas 2022	Utility of mutational analysis for risk stratification of indeterminate thyroid nodules in a real-world setting.	Clinical endocrinology	10.1111/cen.14601	No separable oncocytic subgroup
Tumati 2024	Clinical utility of a microRNA classifier in cytologically indeterminate thyroid nodules with RAS mutations: A multi-institutional study.	Surgery	10.1016/j.surg.2023.07.042	No separable oncocytic subgroup
Tumati 2025	Evaluating the clinical performance of an updated microRNA classifier in indeterminate and RAS-mutated thyroid nodule management: A multi-institutional study.	Surgery	10.1016/j.surg.2024.07.076	No separable oncocytic subgroup
Valderrabano 2017	Evaluation of ThyroSeq v2 performance in thyroid nodules with indeterminate cytology.	Endocrine-related cancer	10.1530/ERC-16-0512	No separable oncocytic subgroup
Valderrabano 2018	Impact of oncogene panel results on surgical management of cytologically indeterminate thyroid nodules	Head and Neck	10.1002/hed.25165	No separable oncocytic subgroup
VanderLaan 2022	Molecular testing results as a quality metric for evaluating cytopathologists' utilization of the atypia of undetermined significance category for thyroid nodule fine-needle aspirations.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2021.10.001	No separable oncocytic subgroup
Velez Torres 2024	Exploring the atypia of undetermined significance: Malignant ratio, ThyroSeq v3 positive call rate, molecular-derived risk of malignancy, and risk of malignancy as possible quality metric tools in thyroid cytology.	Cancer cytopathology	10.1002/cncy.22820	No separable oncocytic subgroup
Verma 2024	The role of the ThyGeNEXT oncogene panel used in combination with the expanded miRNA panel ThyraMIRv2 in Indeterminate thyroid nodules: A large, blinded, real-world, observational study.	Cancer cytopathology	10.1002/cncy.22829	No separable oncocytic subgroup
Vielh 2020	DNA FISH Diagnostic Assay on Cytological Samples of Thyroid Follicular Neoplasms	CANCERS	10.3390/cancers12092529	No separable oncocytic subgroup
Villabona 2016	UTILITY OF ULTRASOUND VERSUS GENE EXPRESSION CLASSIFIER IN THYROID NODULES WITH ATYPIA OF UNDETERMINED SIGNIFICANCE.	Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists	10.4158/EP161231.OR	No separable oncocytic subgroup
Vora 2020	Long-Term Outcomes of Thyroid Nodule AFIRMA GEC Testing and Literature Review: An Institutional Experience.	Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery	10.1177/0194599820911718	No separable oncocytic subgroup
Vriens 2012	MicroRNA expression profiling is a potential diagnostic tool for thyroid cancer.	Cancer	10.1002/cncr.26587	No separable oncocytic subgroup

Study	Title	Journal	DOI	Reason
Wang 2016	A panel of four genes accurately differentiates benign from malignant thyroid nodules	JOURNAL OF EXPERIMENTAL & CLINICAL CANCER RESEARCH	10.1186/s13046-016-0447-3	No separable oncocytic subgroup
Wang 2020	Diagnostic Value of Molecular Testing in Sonographically Suspicious Thyroid Nodules.	Journal of the Endocrine Society	10.1210/jendso/bvaa081	No separable oncocytic subgroup
Wang 2021	Retrospective analysis of cancer-specific gene expression panel for thyroid fine needle aspiration specimens	Journal of Cancer Research and Clinical Oncology	10.1007/s00432-021-03706-3	No separable oncocytic subgroup
Wang 2026	Diagnostic accuracy in BRAF V600E-negative papillary thyroid cancer via 5-gene expression profiling of residual nucleic acids from mutation testing: a retrospective study.	BMC cancer	10.1186/s12885-026-15818-5	No separable oncocytic subgroup
Whitmer 2022	Risk of malignancy in cytologically indeterminate thyroid nodules harboring thyroid stimulating hormone receptor mutations.	Frontiers in endocrinology	10.3389/fendo.2022.1073592	No separable oncocytic subgroup
Wiseman 2013	Whole-transcriptome profiling of thyroid nodules identifies expression-based signatures for accurate thyroid cancer diagnosis.	The Journal of clinical endocrinology and metabolism	10.1210/jc.2013-1991	No separable oncocytic subgroup
Witt 2015	Surgeon-performed ultrasound-guided FNAC with on-site cytopathology improves adequacy and accuracy.	The Laryngoscope	10.1002/lary.25214	No separable oncocytic subgroup
Witt 2016	Outcome of thyroid gene expression classifier testing in clinical practice.	The Laryngoscope	10.1002/lary.25607	No separable oncocytic subgroup
Wong 2016	Noninvasive Follicular Variant of Papillary Thyroid Carcinoma and the Afirma Gene-Expression Classifier.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2015.0644	No separable oncocytic subgroup
Wong 2026	Impact of Co-Mutations and Genetic Variations on Malignancy Risk in RAS-Positive Indeterminate Thyroid Nodules: an Institutional Experience	Endocrine Pathology	10.1007/s12022-026-09910-6	No separable oncocytic subgroup
Wright 2023	The clinical significance of the American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS) category 5 thyroid nodules: Not as risky as we think?	Surgery	10.1016/j.surg.2022.06.055	No separable oncocytic subgroup
Wu 2016	Effect of malignancy rates on cost-effectiveness of routine gene expression classifier testing for indeterminate thyroid nodules.	Surgery	10.1016/j.surg.2015.05.035	No separable oncocytic subgroup
Wu 2019	American College of Radiology thyroid imaging report and data system combined with K-RAS mutation improves the management of cytologically indeterminate thyroid nodules	PLoS ONE	10.1371/journal.pone.0219383	No separable oncocytic subgroup
Wylie 2016	Molecular classification of thyroid lesions by combined testing for miRNA gene expression and somatic gene alterations.	The journal of pathology. Clinical research	10.1002/cjp2.38	No separable oncocytic subgroup
Xia 2022	Do ACR TI-RADS scores demonstrate unique thyroid molecular profiles?	Ultrasonography (Seoul, Korea)	10.14366/usg.21130	No separable oncocytic subgroup
Xu 2024	Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): Prevalence, cyto-histo correlation, and molecular and ultrasonographic profile.	Annals of diagnostic pathology	10.1016/j.anndiagpath.2024.152390	No separable oncocytic subgroup
Yang 2025	Molecular Testing Using ThyGeNEXT/ThyraMIR in Thyroid Nodules With Indeterminate Cytology: A Single Medical Institute Experience.	Diagnostic cytopathology	10.1002/dc.25474	No separable oncocytic subgroup
Yip 2014	A clinical algorithm for fine-needle aspiration molecular testing effectively guides the appropriate extent of initial thyroidectomy.	Annals of surgery	10.1097/SLA.0000000000000215	No separable oncocytic subgroup
Zand 2024	THADA-IGF2BP3 gene fusions in thyroid fine needle aspiration is involved in the pathway to "noninvasive follicular thyroid neoplasm with papillary-like nuclear features".	Diagnostic cytopathology	10.1002/dc.25373	No separable oncocytic subgroup
Zhang 2026	Application Value of Multi-Gene Testing in the Evaluation of Benign and Malignant Thyroid Nodules	Iranian Journal of Biotechnology	10.30498/ijb.2026.564985.4327	No separable oncocytic subgroup
Zhao 2020	Risk Stratification Study of Indeterminate Thyroid Nodules with a next-generation Sequencing Assay with Residual ThinPrep® Material.	Journal of Cancer	10.7150/jca.46086	No separable oncocytic subgroup
Zheng 2023	Molecular Testing Results for Indeterminate Thyroid Nodules and Social Habits.	The Journal of surgical research	10.1016/j.jss.2022.11.042	No separable oncocytic subgroup
Zhu 2015	Relationship Between Sonographic Characteristics and Afirma Gene Expression Classifier Results in Thyroid Nodules With Indeterminate Fine-Needle Aspiration Cytopathology.	AJR. American journal of roentgenology	10.2214/AJR.14.13984	No separable oncocytic subgroup
Zhu 2021	Outcomes of Indeterminate Thyroid Nodules Managed Nonoperatively after Molecular Testing.	The Journal of clinical endocrinology and metabolism	10.1210/clinem/dgaa887	No separable oncocytic subgroup
Bim 2021	Molecular Signature Expands the Landscape of Driver Negative Thyroid Cancers.	Cancers	10.3390/cancers13205184	No molecular test on FNA
Davis 2015	Indeterminate thyroid nodule: Knowing what we do not know	American Surgeon		No molecular test on FNA
Dutta 2023	Detection of driver mutations in plasma cell-free nucleic acids in differentiated thyroid neoplasm	European Journal of Endocrinology	10.1093/ejendo/lvac018	No molecular test on FNA
Larcher de Almeida 2021	Combining the American Thyroid Association's Ultrasound Classification with Cytological Subcategorization Improves the Assessment of Malignancy Risk in Indeterminate Thyroid Nodules.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2019.0575	No molecular test on FNA
Li 2018	CHL1 expression differentiates Hürthle cell carcinoma from benign Hürthle cell nodules.	Journal of surgical oncology	10.1002/jso.25214	No molecular test on FNA
Yazgan 2016	Thyroid FNAC containing hürthle cells and hürthle-like cells: A study of 128 cases.	Journal of cytology	10.4103/0970-9371.190447	No molecular test on FNA
Abi-Raad 2025	TERT promoter mutations and additional molecular alterations in thyroid fine-needle aspiration specimens: A multi-institutional study with histopathologic follow-up.	American journal of clinical pathology	10.1093/ajcp/aqae117	Oncocytic subgroup without extractable data

Study	Title	Journal	DOI	Reason
Alzumaili 2026	Thyroid Tumors of Uncertain Malignant Potential (UMP)- Clinicopathologic and Molecular Characterization of 324 Cases.	Endocrine pathology	10.1007/s12022-026-09915-1	Oncocytic subgroup without extractable data
Andrianus 2023	Unraveling the significance of TSHR mutations in indeterminate thyroid cytology specimens.	Diagnostic cytopathology	10.1002/dc.25138	Oncocytic subgroup without extractable data
Baca 2017	Qualifiers of atypia in the cytologic diagnosis of thyroid nodules are associated with different Afirma gene expression classifier results and clinical outcomes.	Cancer cytopathology	10.1002/cncy.21827	Oncocytic subgroup without extractable data
Bardet 2021	Diagnostic and prognostic value of a 7-panel mutation testing in thyroid nodules with indeterminate cytology: the SWEETMAC study	Endocrine	10.1007/s12020-020-02411-4	Oncocytic subgroup without extractable data
Bourque 2026	Malignancy Risk, Molecular Mutations, and Surgical Outcomes of Thyroid Nodules Classified as Atypia of Undetermined Significance in the Bethesda System: A Comprehensive Analysis.	Cytopathology : official journal of the British Society for Clinical Cytology	10.1111/cyt.13503	Oncocytic subgroup without extractable data
Calcaterra 2025	Disease-Specific and Histological Outcomes of Preoperative TERT Promoter Mutation Detected in Isolation or in Combination with Other Mutations in Thyroid Neoplasms.	Thyroid : official journal of the American Thyroid Association	10.1177/10507256251370304	Oncocytic subgroup without extractable data
Chin 2020	Correlation of ThyroSeq Results with Surgical Histopathology in Cytologically Indeterminate Thyroid Nodules.	Endocrine pathology	10.1007/s12022-020-09641-2	Oncocytic subgroup without extractable data
Deaver 2018	Outcomes of Bethesda categories III and IV thyroid nodules over 5 years and performance of the Afirma gene expression classifier: A single-institution study.	Clinical endocrinology	10.1111/cen.13747	Oncocytic subgroup without extractable data
Endo 2020	Features of Cytologically Indeterminate Molecularly Benign Nodules Treated With Surgery.	The Journal of clinical endocrinology and metabolism	10.1210/clinem/dgaa506	Oncocytic subgroup without extractable data
Endo 2021	Prevalence of cancer and the benign call rate of afirma gene classifier in (18) F-Fluorodeoxyglucose positron emission tomography positive cytologically indeterminate thyroid nodules.	Cancer medicine	10.1002/cam4.3704	Oncocytic subgroup without extractable data
Finkelstein 2022	A Retrospective Evaluation of the Diagnostic Performance of an Interdependent Pairwise MicroRNA Expression Analysis with a Mutation Panel in Indeterminate Thyroid Nodules.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2022.0124	Oncocytic subgroup without extractable data
Geng 2021	Comparison of Afirma Gene Expression Classifier with Gene Sequencing Classifier in indeterminate thyroid nodules: A single-institutional experience.	Cytopathology : official journal of the British Society for Clinical Cytology	10.1111/cyt.12920	Oncocytic subgroup without extractable data
Glass 2022	Using molecular testing to improve the management of thyroid nodules with indeterminate cytology: an institutional experience with review of molecular alterations.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2021.08.004	Oncocytic subgroup without extractable data
Hu 2022	Risk stratification of indeterminate thyroid nodules by novel multigene testing: a study of Asians with a high risk of malignancy.	Molecular oncology	10.1002/1878-0261.13205	Oncocytic subgroup without extractable data
Ixchel Sanchez 2025	Pediatric thyroid nodules: A comprehensive study of cytology, histology, molecular findings, and risk of malignancy with emphasis on atypia of undetermined significance category.	American journal of clinical pathology	10.1093/ajcp/aqaf034	Oncocytic subgroup without extractable data
Jin 2011	HMGA2 expression analysis in cytological and paraffin-embedded tissue specimens of thyroid tumors by relative quantitative RT-PCR.	Diagnostic molecular pathology : the American journal of surgical pathology, part B	10.1097/PDM.0b013e3181ed784d	Oncocytic subgroup without extractable data
Jin 2015	The Diagnostic Utility of Combination of HMGA2 and IMP3 qRT-PCR Testing in Thyroid Neoplasms	APPLIED IMMUNOHISTOCHEMISTRY & MOLECULAR MORPHOLOGY	10.1097/PAI.0000000000000031	Oncocytic subgroup without extractable data
Lithwick-Yanai 2017	Multicenter validation of a microRNA-based assay for diagnosing indeterminate thyroid nodules utilising fine needle aspirate smears.	Journal of clinical pathology	10.1136/jclinpath-2016-204089	Oncocytic subgroup without extractable data
Lončar 2023	European experience with the Afirma Gene Expression Classifier for indeterminate thyroid nodules: A clinical utility study in the Netherlands.	Head & neck	10.1002/hed.27472	Oncocytic subgroup without extractable data
Martinez Coconubo 2023	Use of molecular testing results to analyze the overuse of atypia of undetermined significance in thyroid cytology.	Journal of the American Society of Cytopathology	10.1016/j.jasc.2023.09.002	Oncocytic subgroup without extractable data
Nachum 2025	Thyroid Nodules with Indeterminate Cytology and Negative Molecular Profile: Prevalence of Malignancy and Practice Paradigms for Surveillance.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2024.0455	Oncocytic subgroup without extractable data
Nikiforov 2014	Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v2 next-generation sequencing assay.	Cancer	10.1002/cncr.29038	Oncocytic subgroup without extractable data
Rajab 2022	Coexisting Molecular Alterations Increase the Risk of Malignancy in Thyroid Nodules with Copy Number Alterations.	Cancers	10.3390/cancers14246149	Oncocytic subgroup without extractable data
Savoia 2026	Clinicopathological, Molecular, and Economic Outcomes of Bethesda III and IV Thyroid Nodules Following Implementation of a Publicly Funded ThyroSeq v3 Program: A Retrospective Two-Center Cohort Study.	Cancers	10.3390/cancers18162695	Oncocytic subgroup without extractable data
Sfreddo 2024	RAS-Mutated Cytologically Indeterminate Thyroid Nodules: Prevalence of Malignancy and Behavior Under Active Surveillance.	Thyroid : official journal of the American Thyroid Association	10.1089/thy.2023.0544	Oncocytic subgroup without extractable data
Shahi 2019	Semiquantitative assessment of cytomorphologic features can predict mutation status of thyroid nodules with indeterminate cytologic diagnosis.	Human pathology	10.1016/j.humpath.2019.08.010	Oncocytic subgroup without extractable data
Titov 2022	Validation of preoperative diagnosis of malignant thyroid tumors using a molecular classifier	Voprosy Onkologii	10.37469/0507-3758-2022-68-6-741-751	Oncocytic subgroup without extractable data
Wharry 2014	Thyroid Nodules (≥4 cm): Can Ultrasound and Cytology Reliably Exclude Cancer?	WORLD JOURNAL OF SURGERY	10.1007/s00268-013-2261-9	Oncocytic subgroup without extractable data
de Koster 2023	A clinically applicable molecular classification of oncocytic cell thyroid nodules.	Endocrine-related cancer	10.1530/ERC-23-0047	Oncocytic subgroup without extractable data

Study	Title	Journal	DOI	Reason
Šamija 2020	Quantitative analysis of galectin-3 expression in benign and malignant thyroid nodules	Acta Clinica Croatica	10.20471/acc.2020.59.s1.03	Oncocytic subgroup without extractable data
Dettmer 2013	MicroRNA expression array identifies novel diagnostic markers for conventional and oncocytic follicular thyroid carcinomas.	The Journal of clinical endocrinology and metabolism	10.1210/jc.2012-2694	Unsuitable design
Nikiforova 2021	Thyroid cytology smear slides: An untapped resource for ThyroSeq testing.	Cancer cytopathology	10.1002/cncy.22331	Unsuitable design
Livhits 2021	Effectiveness of Molecular Testing Techniques for Diagnosis of Indeterminate Thyroid Nodules: A Randomized Clinical Trial.	JAMA oncology	10.1001/jamaoncol.2020.5935	Duplicate report
Abi-Raad 2022	Are Copy Number Variations Identified in Thyroid Fine Needle Aspiration Specimens Associated with Hurthle Cell Morphology?	LABORATORY INVESTIGATION		Conference abstract (full paper available or insufficient data)
Belovarac 2019	Molecular Features of Thyroid Hurthle Cell Lesions: Can pre-surgical Molecular Analysis by ThyroSeq and Afirma differentiate Benign vs. Malignant Hurthle cell nodules?	MODERN PATHOLOGY		Conference abstract (full paper available or insufficient data)
Chen 2021	Utilization of ThyGenX/ThyraMIR Molecular Test on FNA of Indeterminate Thyroid NodulesA Single Institution's Experience	MODERN PATHOLOGY		Conference abstract (full paper available or insufficient data)
Cocelli 2024	Variable Molecular Alterations Observed in Both Benign and Malignant Oncocytic (Hurthle cell) Neoplasms of the Thyroid	LABORATORY INVESTIGATION		Conference abstract (full paper available or insufficient data)
Elsheikh 2026	Inter-observer Variation among Cytopathologists in the Evaluation of Oncocytic Cell-Predominant Thyroid Fine Needle Aspiration Cytology and Correlation with Molecular Testing: A Validation Study of 173 Cases with Surgical Followup	LABORATORY INVESTIGATION	10.1016/j.labinv.2025.104570	Conference abstract (full paper available or insufficient data)
Holmes 2015	Performance of the Afirma Gene Expression Classifier in Hurthle Cell Thyroid Nodules	LABORATORY INVESTIGATION		Conference abstract (full paper available or insufficient data)
Hsiao 2023	Risk Stratification of Thyroseq Results in Bethesda III Thyroid Lesions: Clinicopathologic Correlation with Cytologic Findings in 532 Cases	LABORATORY INVESTIGATION		Conference abstract (full paper available or insufficient data)
Jin 2022	Performance of Afirma Genomic Sequencing Classifier and Histopathological Outcome Are Associated with Subtype of Atypia in Bethesda Category III Thyroid Nodules	MODERN PATHOLOGY		Conference abstract (full paper available or insufficient data)
Jin 2023	Performance of Afirma Genomic Sequencing Classifier and Histopathological Outcome in Bethesda Category III Thyroid Nodules: A Comparison Between Single and Repeat Fine Needle Aspiration	LABORATORY INVESTIGATION		Conference abstract (full paper available or insufficient data)
Jin 2024	Performance of Afirma Genomic Sequencing Classifier and Histopathological Outcome in Bethesda Category III Thyroid Nodules subcategorized by Nuclear Atypia and Other: A Comparison Between Single and Repeat Fine Needle Aspiration	LABORATORY INVESTIGATION		Conference abstract (full paper available or insufficient data)
Kim 2023	"Copy Number Alteration" as the Sole Molecular Finding of a Thyroseq Test is More Commonly Seen in Hurthle Cell Lesions of the Thyroid with Benign Nature	LABORATORY INVESTIGATION		Conference abstract (full paper available or insufficient data)
Landau 2020	Oncocytic or Oncocytoid? Mimics and Markers of Oncocytic Differentiation as Revealed by Molecular Profiling of Thyroid Fine Needle Aspirates Diagnosed as Oncocytic Follicular Neoplasm	MODERN PATHOLOGY		Conference abstract (full paper available or insufficient data)
Lastra 2014	Implications of a Suspicious AFIRMA® Test Result in Thyroid Fine Needle Aspiration Cytology	MODERN PATHOLOGY		Conference abstract (full paper available or insufficient data)
Schatz-Siemers 2018	Molecular and Histologic Correlation of Hurthle Cell Lesions on Thyroid Fine Needle Aspiration Biopsies	MODERN PATHOLOGY		Conference abstract (full paper available or insufficient data)
Song 2018	Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features: Correlation Between Preoperative Fine-Needle Aspiration Diagnoses and Gene Expression Classifier Results	AMERICAN JOURNAL OF CLINICAL PATHOLOGY	10.1093/ajcp/aqx117.090	Conference abstract (full paper available or insufficient data)
Zhang 2021	Performance of the Afirma Genomic Sequencing Classifier versus Gene Expression Classifier in Bethesda Category III Thyroid Nodules: An Institutional Experience	MODERN PATHOLOGY		Conference abstract (full paper available or insufficient data)
Aguilar-Jakthong 2019	Comparative Test Performance of ThyroSeq® and Afirma®, Including Their Newer Versions, in Indeterminate Thyroid Fine-Needle Aspiration	MODERN PATHOLOGY		Report not retrieved
Arkin 2015	Evaluation of the Afirma Gene Expression Classifier in Cytologically Indeterminate Thyroid Nodules: A Pilot Study of 45 Fine Needle Aspiration Cases	LABORATORY INVESTIGATION		Report not retrieved
Baldassarri 2016	Suspicious AFIRMA® Gene Expression Classifier Test Result in Thyroid Fine Needle Aspiration Cytology: Implications for Patient Management	LABORATORY INVESTIGATION		Report not retrieved

Study	Title	Journal	DOI	Reason
Bose 2016	Indeterminate Thyroid Nodules: Does Asuragen Testing Improve the Specificity of Afirma Test Results?	MODERN PATHOLOGY		Report not retrieved
Buonocore 2019	Negative ThyroSeq® genomic testing for indeterminate thyroid nodules: the Memorial Sloan Kettering Cancer Center experience	VIRCHOWS ARCHIV		Report not retrieved
Buonocore 2019	Surgical follow-up of ThyroSeq® positive thyroid nodules: the Memorial Sloan Kettering Cancer Center experience	VIRCHOWS ARCHIV		Report not retrieved
Chen 2021	Utilization of ThyGenX/ThyraMIR Molecular Test on FNA of Indeterminate Thyroid Nodules-A Single Institution's Experience	LABORATORY INVESTIGATION		Report not retrieved
Darras 2017	ThyroSeq Testing for Indeterminate Thyroid Nodules: An Institutional Experience	LABORATORY INVESTIGATION		Report not retrieved
Fazeli 2018	Cost Impact of ThyroSeq v2 Testing in Thyroid Nodules Interpreted as Atypical Cells of Undetermined Significance (AUS)/ Follicular Lesion of Undetermined Significance (FLUS) and Follicular Neoplasm (FN) /Suspicious for Follicular Neoplasm (SFN)	LABORATORY INVESTIGATION		Report not retrieved
Foster 2020	The Afirma Gene Sequencing Classifier in Cytologically Indeterminate Thyroid Nodules - Experience of a Single Institution	LABORATORY INVESTIGATION		Report not retrieved
Freeman 2022	Identifying metastatic renal cell carcinoma in thyroid fine-needle aspirates by molecular testing.	Endocrine-related cancer	10.1530/ERC-22-0195	Report not retrieved
Gaddam 2023	The Diagnostic Performance of Afirma Genomic Sequencing Classifier (GSC) for Indeterminate Thyroid Nodules: A Single Teaching Institution Experience	LABORATORY INVESTIGATION		Report not retrieved
Gomez 2015	Utility of Afirma Testing on Thyroid Fine Needle Aspiration (FNA) Specimens: "Suspicious" Results With Clinicopathologic Follow-Up	MODERN PATHOLOGY		Report not retrieved
Guerrero 2019	Correlation Between Cytologic, ThyroSeq Next Generation Sequencing Assay, and Definitive Surgical Histopathologic Diagnosis In Thyroid Nodules--A Multi-Institutional Experience	LABORATORY INVESTIGATION		Report not retrieved
Hitscherich 2020	DETECTING THYROID CANCER: COMPARATIVE ANALYSIS OF AFIRMA GENOMIC SEQUENCE CLASSIFIER VERSUS THYROSEQ V3 GENOMIC CLASSIFIER	BRITISH JOURNAL OF SURGERY		Report not retrieved
Huenerberg 2019	Impact of Thyroseq® Performance on Indeterminate Thyroid nodules: An Institutional Experience	LABORATORY INVESTIGATION		Report not retrieved
Jin 2026	Afirma Genomic Sequencing Classifier (GSC) and mRNA Expression Features in Bethesda III Thyroid Nodules: Comparative Analysis of Nuclear Versus Other Atypia and Correlation with Histology	LABORATORY INVESTIGATION	10.1016/j.labinv.2025.104589	Report not retrieved
Karagiannis 2026	Positive Predictive Value (PPV) of a Bethesda Category III (Indeterminate Result) Thyroid Cytology Finding with and Without Ancillary Molecular Testing (Afirma, Veracyte) in the Detection of Thyroid Malignancy	LABORATORY INVESTIGATION	10.1016/j.labinv.2025.104630	Report not retrieved
Karslioglu French 2022	Clinicopathological features and outcomes of thyroid nodules with EIF1AX mutations.	Endocrine-related cancer	10.1530/ERC-22-0041	Report not retrieved
Lai 2020	ThyroSeq Next-Generation Sequencing in Cytologically Indeterminate Thyroid Nodules - Experience of a Single Institution	MODERN PATHOLOGY		Report not retrieved
Laklouk 2017	Diagnostic Implication of ThyroSeq Sequencing Assay on Thyroid Nodules with FNA Cytology Diagnosis of Bethesda III: Atypia of Undetermined Significance versus Follicular Lesion of Undetermined Significance	LABORATORY INVESTIGATION		Report not retrieved
Laklouk 2017	Predictive accuracy of thyroseq v2 formalignant thyroid nodules among Bethesda-III cytology subcategories: Atypia of undetermined significance (AUS) and follicular lesion of undetermined significance (FLUS)	VIRCHOWS ARCHIV		Report not retrieved
Laklouk 2018	Impact of Racial and Ethnic Differences on the Accurate Classifiction of Thyroid Nodules Using ThyroSeq NextGeneration Sequencing	LABORATORY INVESTIGATION		Report not retrieved
Lan 2023	Diagnostic Value and Challenges of BRAF V600E Molecular Testing and Thyroid Fine-Needle Aspiration Cytology: A Retrospective Study from a Tertiary Institution in Southern Hunan Province, China.	Acta cytologica	10.1159/000534138	Report not retrieved
Lastra 2014	Implications of a Suspicious AFIRMA®Test Result in Thyroid Fine Needle Aspiration Cytology	LABORATORY INVESTIGATION		Report not retrieved
Lewis 2016	Performance of the Afirma Gene Expression Classifier in the Evaluation of Cytologically Indeterminate Thyroid Nodules: An Institutional Experience	MODERN PATHOLOGY		Report not retrieved
Lin 2019	Comparison of Diagnostic Accuracy between ThyroSeq v2 and ThyroSeq v3 Molecular Test for Indeterminate Thyroid Nodules	LABORATORY INVESTIGATION		Report not retrieved
Munoz-Zuluaga 2023	Deploying Afirma Xpression Atlas for Cytologically Indeterminate, Afirma GSC Suspicious Thyroid Nodules: A Single Institution Study with Clinicopathologic and Molecular Outcomes	LABORATORY INVESTIGATION		Report not retrieved
Murphy 2017	Malignancy Rate of Thyroid Nodules and Role of Gene Expression Classifier Testing at an Academic Institution	ANNALS OF SURGICAL ONCOLOGY		Report not retrieved
NCT02681328 2016	Randomized Trial Comparing Performance of Molecular Markers for Indeterminate Thyroid Nodules	https://clinicaltrials.gov/study/NCT02681328		Report not retrieved
Nikiforova 2014	Next-Generation Sequencing Panel (ThyroSeq) in Extended Mutational Profiling of Thyroid Cancer	MODERN PATHOLOGY		Report not retrieved

Study	Title	Journal	DOI	Reason
Piazza 2017	The Correlation of Afirma® Gene Expression Classifier Results with Follow-Up Findings for Thyroid Fine Needle Aspiration Specimens	LABORATORY INVESTIGATION		Report not retrieved
Piñero 2024	AUS: Malignant Ratio and ThyroSeq v3 Molecular Testing Outcomes: A Potential Quality Metric Tool in Thyroid Cytology?	LABORATORY INVESTIGATION		Report not retrieved
Quaytman 2022	Clinicopathologic features of thyroid nodules with PTEN mutations on preoperative testing.	Endocrine-related cancer	10.1530/ERC-22-0061	Report not retrieved
Ren 2023	Afirma Genomic Sequencing Classifier with Afirma Xpression Atlas Results on Thyroid Nodules	LABORATORY INVESTIGATION		Report not retrieved
Saxena 2016	Applying Strict Cytomorphologic Criteria and Minimizing Interobserver Variability in Diagnosing "Atypia of Uncertain Significance" Increases the Positive Predictive Value of the Afirma GEC Assay in Thyroid Fine Needle Aspiration	LABORATORY INVESTIGATION		Report not retrieved
Trabzonlu 2025	From Smear to Sequence: Using Thyroid Cytology Smear Slides for ThyroSeq Molecular Analysis and Clinicopathologic Insights From 61 Tested Nodules.	Archives of pathology & laboratory medicine	10.5858/arpa.2025-0115-OA	Report not retrieved
Wald 2013	Targeted NGS Panel (ThyroSeq) for Diagnosis of Thyroid Cancer	JOURNAL OF MOLECULAR DIAGNOSTICS		Report not retrieved
Witt 2016	Targeted Next Generation Sequencing with ThyroSeq v2.1 for Indeterminate Thyroid Nodules in Clinical Practice.	Delaware medical journal		Report not retrieved
Wong 2016	Non-Invasive Follicular Variant of Papillary Thyroid Carcinoma and the Afirma Gene-Expression Classifier	MODERN PATHOLOGY		Report not retrieved
Wyble 2022	High-Risk Ultrasound Findings Are Superior to Afirma Molecular Profiling for Prediction of Malignancy in Resected Thyroid Nodules: An Institutional Experience	JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS	10.1097/01.XCS.0000893400.95190.cb	Report not retrieved
Xing 2026	Impact of ThyroSeq Implementation for Bethesda V on Thyroid Cytology Distribution and Risk Stratification	LABORATORY INVESTIGATION	10.1016/j.labinv.2025.104637	Report not retrieved
Xu 2018	Risk Stratification of Thyroid Nodules in Bethesda System Category III Cytopathology (AUS/FLUS) Using Subclassification and Gene Expression Classifier (GEC): A Single Aspirator's Experience	LABORATORY INVESTIGATION		Report not retrieved
Yang 2015	The Utility of Gene Expression Classifier (Afirma, Veracyte, Inc.) Testing in Indeterminate Thyroid Nodules: A Follow-Up Study	LABORATORY INVESTIGATION		Report not retrieved
Yang 2020	Afirma Testing in Thyroid Nodules with Indeterminate Cytology: A single Medical Institute Experience	AMERICAN JOURNAL OF CLINICAL PATHOLOGY		Report not retrieved
Ye 2026	Practice Pattern Changes After Implementation of ThyroSeq Molecular Testing for Indeterminate Thyroid Fine Needle Aspiration Biopsies: A Single Institution Experience	LABORATORY INVESTIGATION	10.1016/j.labinv.2025.104638	Report not retrieved
Zeiger 2018	Clinical performance of a next-generation sequencing assay (ThyroSeq v2) in the evaluation of indeterminate thyroid nodules Discussion	SURGERY		Report not retrieved
Dowell 2025	Comparing the diagnostic accuracy of Afirma GSC to ThyroSeq V3 in cytologically indeterminate thyroid nodules	European Thyroid Journal	10.1530/ETJ-25-0296	Not original research (E1): systematic review and meta-analysis; flagged for reference-list mining; full-text check during revision confirmed no oncocytic-specific analysis (added in revision)

Supplementary Table S9. Funding sources and declared conflicts of interest for the 75 included studies

Ties to test manufacturers were classified as Veracyte (Afirma GEC/GSC), Interpace (ThyGeNEXT/ThyraMIR) or UPMC/ThyroSeq (CBLPath, Sonic Healthcare). “None” indicates an explicit no-conflict statement in the publication; “—” indicates that no funding or conflict-of-interest statement was present. Statements are quoted or summarized from the source publications; conference abstracts report per-author disclosures.

Study	Platform(s)	Test-manufacturer tie	Funding	Declared conflicts of interest
Ahmadi 2026	GSC	Veracyte (Afirma)	-	S.A. received research funding from Veracyte to comply with BWH institutional guidelines that require industry to support research-related administrative activities. The remaining authors have nothing to disclose.
Attia 2026	GSC	None	Funding source: None.	Competing interests: None.
Elsheikh 2026	GSC, TSv3, GEC, TSv1, TSv2	None	-	The authors declare no conflicts of interest.
Geetha 2026	TSv3	None	The authors received no financial support for the research, authorship, and/or publication of this article.	The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Khan 2026	TSv3	None	-	Disclosures: Niaz Khan: None; Zubair Baloch: None.
Lazim 2026	TSv3	None	Supported in part by the Cancer Center Support Grant of the NIH/NCI under award number P30CA008748 to Memorial Sloan-Kettering Cancer Center.	The authors have no conflicts of interest to disclose.
Stack 2026	mixed, GEC, GSC, ThyGeNEXT/ThyraMIR	None	The authors have nothing to report.	The authors declare no conflicts of interest.
Alzumaili 2025	TSv3	None	R.I., A.A., M.R.T., B.X., L.G.T.M., and R.A.G. receive funding from Cancer Center Support Grant of the NIH/NCI.	The authors have no conflicts of interest to disclose.
Bang 2025	single-gene	None	This paper was written as part of Konkuk University's research support program for its faculty on sabbatical leave in 2023.	The authors declare no competing interests.
Cocelli 2025	mixed	None	FUNDING: Not applicable.	The authors declare no conflicts of interest.
Connelly 2025	mixed	None	-	The authors made no disclosures.
Geetha 2025	TSv3	None	-	The authors declare no conflicts of interest.
Hsiao 2025	TSv3, TSv2	None	Acknowledges Anthea Hammond, medical writer at Emory University, for proofreading (no funding stated).	The authors declare no conflicts of interest.
Potonnier 2025	NGS-panel	None	This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sectors.	The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work.
Tjendra 2025	TSv3	None	-	Disclosures: Youley Tjendra: None; Porshya Curnow Pinero: None; Yesica Miltos: None; Yiqin Zuo: None; Manuel Lora Gonzalez: None; Merce Jorda: None; Elena Brachtel: None; Monica Garcia-Buitrago: None; Carmen Gomez-Fernandez: None; Roberto Ruiz-Cordero: None; Jaylou Velez Torres: None.
Ahmadi 2024	GSC	Veracyte (Afirma)	-	S.A. received research funding from Veracyte to comply with BWH institutional guidelines that require industry to support research-related administrative activities. The remaining authors have nothing to disclose.
Guzmán-Arocho 2024	GEC, GSC	None (other industry ties; see COI)	-	P.V.L. has received consulting fees from Gala Therapeutics, Galvanize Therapeutics, and Ruby Robotics, unrelated to the content of this manuscript. M.N. has received consulting and/or contractor fees from EBIX/Oakstone CME, unrelated to the content of this manuscript. [Y.G.A.: unrelated disclosures only]
Ohori 2024	TSv3	UPMC/ThyroSeq	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.	Yuri E. Nikiforov owns intellectual property related to ThyroSeq for which he receives royalties, and he serves as a consultant for Sonic Healthcare USA outside the submitted work. The remaining authors disclosed no conflicts of interest.
Raghunathan 2024	GSC, TSv3	None	This research did not receive any specific funding from any agencies in the public, commercial, or not-for-profit areas.	The authors have no conflicts of interests or disclosures to report.
Yang 2024	TSv3	UPMC/ThyroSeq	Endocrine and Metabolic Society of Singapore; National University Healthcare System Clinician Scientist Program (abstract page).	Simion I. Chiosea reports personal/consulting fees from Sonic Healthcare USA outside the submitted work. Keng Hua Lim reports personal/consulting fees from ENT Sinus and Allergy PTE LTD. Chwee Ming Lim reports grants from the National Medical Research Council. [others unrelated]
de Koster 2024	NGS-panel (other)	None	The EfFECTS trial was supported by a project grant from the Dutch Cancer Society (KUN 2014-6514).	The authors have no conflicts of interest to declare that are relevant to the content of this article.
Kim 2023	TSv3	None	-	No conflict of interest declared.
Tjendra 2023	TSv3	None	-	The authors have no conflict of interest to disclose.
Abi-Raad 2022	TSv3	None	No specific funding was disclosed.	The authors made no disclosures.
Gajzer 2022	TSv3	None	-	The authors made no disclosures.
Jin 2022	GSC	None	-	The authors made no disclosures.
Spagnuolo 2022	TSv3	None	-	The authors have no multiplicity of interest to disclose.
Yang 2022	GEC, GSC	None	Funding source: None.	Disclosures: None.
Abdelhakam 2021	TSv2, TSv3	None	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.	Conflict of interest: None.
Doerfler 2021	TSv3	UPMC/ThyroSeq	This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.	Y E N and M N N own intellectual property related to ThyroSeq and receive royalty; they serve as consultants for Sonic Healthcare USA. All other authors have no financial interests to disclose.
Gilani 2021	TSv3, TSv2, ThyGeNEXT/ThyraMIR, GEC,	None	No specific funding was disclosed.	The authors made no disclosures.

Study	Platform(s)	Test-manufacturer tie	Funding	Declared conflicts of interest
	GSC, Rosetta			
Glass 2021	GEC, ThyGeNEXT/ThyraMIR, TSv3	None	No specific funding was disclosed.	The authors made no disclosures.
Landau 2021	TSv3	UPMC/ThyroSeq	This study was supported by departmental funds.	Yuri E. Nikiforov owns IP related to ThyroSeq and receives royalties; he serves as consultant for Sonic Healthcare USA. The other authors made no disclosures.
Onken 2021	GEC	Veracyte (Afirma)	No specific funding was disclosed.	James V. Hennessey reports other support from Veracyte to Beth Israel Deaconess Medical Center during the conduct of the study. Paul A. VanderLaan reports personal fees from Gala Therapeutics, Intuitive Surgical, and Galvanize Therapeutics outside the submitted work. Allison M. Onken, Pamela Hartzband, and Michiya Nishino made no disclosures.
Polavarapu 2021	GEC, GSC	None (other industry ties; see COI)	-	V.S.: Site principal investigator for multicenter trials for NovoNordisk, Eli Lilly, and Kowa Pharmaceuticals. W.G.: Site principal investigator for Roche and Siemens. All other authors have nothing to disclose.
Zhang 2021	GSC, GEC	None	-	All authors have no conflict of interest.
Arosemena 2020	GEC	None	The authors received no financial support for the research, authorship, and/or publication of this article.	No competing financial interests exist.
Lupo 2020	ThyGeNEXT/ThyraMIR	Interpace	Funding information: Interpace Diagnostics. Acknowledgment: The study was sponsored by Interpace Diagnostics Corporation.	J. Woody Sistrunk, Nicole Massoll, Ryan Campbell, Ann E. Walts, and Shikha Bose received institutional research funding from Interpace Diagnostics. Mark A. Lupo has received research funding from Interpace Diagnostics. J. Woody Sistrunk and Nicole Massoll are consultants for Interpace Diagnostics. Histopathology review by Thomas J. Giordano and Peter M. Sadow was funded by Interpace Diagnostics. Sara A. Jackson, Christina M. Narick, Nicole Toney, Sydney D. Finkelstein, Alidad Mireskandari, Gyanendra Kumar are employees of Interpace Diagnostics.
Ohori 2020	TSv3	None	No specific funding was disclosed.	The authors made no disclosures.
Papoian 2020	GEC	None	-	None of the authors declare any conflicts of interest.
San Martin 2020	GSC, GEC	None	-	The authors have nothing to disclose.
Angell 2019	GSC, GEC	None	Funding: None.	Statement: All authors have no financial disclosures.
Endo 2019	GSC, GEC	None	-	No competing financial interests exist.
Hao 2019	GSC	Veracyte (Afirma)	Funding for the publication of this article was provided by Veracyte, Inc.	YH, RTK, JB, SYK, GF, PSW, JH, and GCK are employed by Veracyte, Inc.
Harrell 2019	GEC, GSC	-	-	-
Ohori 2019	TSv3	UPMC/ThyroSeq	No specific funding was disclosed.	Marina N. Nikiforova and Yuri E. Nikiforov own intellectual property rights related to ThyroSeq from University of Pittsburgh Medical Center/ThyroSeq/CBLPath Inc for work performed as part of the current study and have a patent licensed for ThyroSeq.
Parajuli 2019	GEC, TSv2	None	-	The authors declare no potential conflict of interest.
Schatz-Siemers 2019	TSv2	None	-	The authors have no disclosures to report.
Steward 2019	TSv3	Veracyte; UPMC/ThyroSeq	Supported in part by the P50CA097190 Head and Neck Cancer SPORE grant to University of Pittsburgh and P50CA168505 Thyroid Cancer SPORE grant to The Ohio State University. The funders had no role in the design and conduct of the study.	Drs Carty, Ferris, McCoy, Seethala, and Yip are employees of University of Pittsburgh Physicians, an affiliate of UPMC. UPMC has granted CBLPath Inc. a license to market ThyroSeq for commercial use. Dr Chiosea receives compensation from his employer (UPMC) in connection with ThyroSeq analyses. Dr Mayson previously received research support from Rosetta Genomics. Dr Nikiforov and Dr Nikiforova have intellectual property rights related to ThyroSeq and will receive royalties associated with commercial use of ThyroSeq. Dr Sipos received an honorarium for speaking for Veracyte and Genzyme. Dr Steward received research funding from Rosetta, Veracyte, and GeneproDX. [Burman: institutional trial grants AstraZeneca, Eisai, IBSA, Bayer, Loxo; Sosa: DMC member of industry-supported registry]
Wei 2019	GEC, GSC	Veracyte (Afirma)	No specific funding was disclosed.	Colleen Veloski has acted as a paid member of the Speaker's Bureau for Sanofi-Genzyme and has received other support to her research study site from Veracyte for work performed outside of the current study. The other authors made no disclosures.
Bellevicine 2018	PCR-panel	None	This study was supported by a grant from the Regione Campania for the investigation of the molecular biology of thyroid cancer (LR n.24 29/12/2005).	The authors made no disclosures.
Livhits 2018	GEC, TSv2	None	Not reported	Disclosures: The authors have nothing to disclose. (Acknowledgment: ClinicalTrials.gov no. NCT02681328.)
Nikiforova 2018	TSv3	UPMC/ThyroSeq	This work was supported in part by the P50CA097190 Head and Neck Cancer SPORE grant. Sample collection was supported in part by the UPCI Tissue and Research Pathology/Health Sciences Tissue Bank shared resource supported in part by award P30CA047904 and by a generous gift from William and Susan Johnson.	COI statement: Dr. Nikiforov and Dr. Nikiforova report IP related to ThyroSeq; they receive compensation from their employer (UPMC) in connection with ThyroSeq test offered through CBLPath, Inc. All other authors have nothing to disclose.
Patel 2018	GSC	Veracyte (Afirma)	-	Drs Patel, Blevins, Shanik, and Ladenson have received speaker's honoraria from Veracyte Inc. Drs Ghossein, LiVolsi, Sadow, and Ladenson serve as consultants for Veracyte Inc. Drs Blevins, Shanik, and Ladenson have received institutional research support from Veracyte Inc. Drs Babiarz, Barth, Huang, Kennedy, Kim, Kloos, and Whitney and Mr

Study	Platform(s)	Test-manufacturer tie	Funding	Declared conflicts of interest
				Walsh are employees of Veracyte Inc.
Walts 2018	GEC, Rosetta	-	Acknowledgment only (case contribution).	No COI or funding statement present in article.
Hang 2017	GEC	None	No specific funding was disclosed.	The authors made no disclosures.
Roychoudhury 2017	GEC	None	-	None of the authors declare any conflicts of interest.
Chaudhary 2016	GEC	None	-	The authors have no financial conflicts of interest to disclose.
Collet 2016	single-gene	-	-	-
Giovanella 2016	PCR-panel	None	This study was supported by a grant from the Advisory Board of Research-Ente Ospedaliero Cantonale, Bellinzona, Switzerland.	Conflicts of interest: None.
Samulski 2016	GEC	Veracyte (Afirma)	The authors have no grants or funding to disclose.	One author is a consultant for Veracyte, Inc.
Valderrabano 2016	PCR-panel	Veracyte; Asuragen; UPMC/ThyroSeq (CBLPath); Rosetta	-	Dr McIver reports receiving payments for scientific consulting services from Veracyte, Asuragen, and CBLPath (manufacturers or sellers of Afirma, miRInform, and ThyroSeq V2, respectively) between 2011 and 2014. Dr Leon has received sponsored research funding from Rosetta Genomics. No other conflicts of interest exist.
Wu 2016	GEC	Veracyte (Afirma)	H. H. Lee Research Award (Dr. James Wu).	Dr. Michael Yeh is a consultant to Veracyte, Inc. The other authors have no conflicts of interest to disclose.
Yang 2016	GEC	None	No specific funding was disclosed.	The authors made no disclosures.
Brauner 2015	GEC	Veracyte (Afirma)	Eran Brauner is sponsored by a grant from the Clair and Emanuel G. Rosenblatt Fund and American Healthcare Professionals and Friends for Medicine in Israel (APF).	James V. Hennessey has served as a onetime consultant to Veracyte in 2014. No competing financial interests exist for the other authors.
Celik 2015	GEC	None	-	Conflict of interest: None.
Eszlinger 2015	PCR-panel	None	This research was supported by a Deutsche Krebshilfe grant (109994) to Markus Eszlinger.	All authors have nothing to declare. No competing financial interests exist.
Harrell 2014	GEC	None (other industry ties; see COI)	-	Dr. Harrell is a member of the LabCorp Endocrine Advisory Board. Dr. Bimston has no multiplicity of interest to disclose.
Lastra 2014	GEC	Veracyte (Afirma)	No specific funding was disclosed.	Dr. LiVolsi previously worked as a histology consultant for Veracyte Inc.
McIver 2014	GEC	Veracyte (Afirma)	No formal funding section; the authors acknowledge Ms Heidi Gautier of Veracyte Inc, who developed the 'Enabled Model' and assisted with the manuscript.	B.M. has received speaker honoraria and scientific consulting fees from Veracyte Inc and Asuragen Inc. No other author has any relevant financial conflict of interest.
Park 2014	single-gene	None	This work was funded by the Seoul National University Bundang Hospital, Seongnam, Korea (02-2011-022).	The authors made no disclosures.
Radkay 2014	PCR-panel	None (other industry ties; see COI)	No specific funding was disclosed.	Dr. Nikiforov has acted as a paid consultant for Quest Diagnostics for work performed outside of the current study. Dr. Carty: consultant editor for UpToDate and book chapter author (outside study).
Alexander 2012	GEC	Veracyte (Afirma)	Supported by research grants to the individual study institutions from Veracyte. (Funded by Veracyte.)	Disclosure forms provided by the authors are available at NEJM.org. Author affiliations list Veracyte, South San Francisco, CA (G.C.K., D.C., J.D., L.F., P.S.W., J.I.W., R.B.L.).
Keutgen 2012	miRNA	None	This study was supported by Dancer's Care Foundation.	No potential conflicts of interest were disclosed.
Lappinga 2010	single-gene	None	-	The authors made no disclosures.

Supplementary Table S10a. Verification sample of excluded records: design

Stage	Stratum (original exclusion basis)	Excluded (N)	Sampled (n)	Fraction
Title/abstract	E1 Not primary research	388	125	32.2%
Title/abstract	E2 Case report	85	28	32.9%
Title/abstract	E3 Population not matched	189	61	32.3%
Title/abstract	E5 No FNA molecular test	222	72	32.4%
Title/abstract	E8 Design not matched	44	14	31.8%
Title/abstract	Subtotal	928	300	32.3%
Full text	Case report or <5 oncocytic nodules	13	5	38.5%
Full text	Conference abstract	16	6	37.5%
Full text	Duplicate report	1	0	0%
Full text	No molecular test on FNA	6	2	33.3%
Full text	No separable oncocytic subgroup	187	68	36.4%
Full text	Not original research	7	3	42.9%
Full text	Oncocytic subgroup without extractable data	31	11	35.5%
Full text	Unsuitable design	2	1	50%
Full text	Wrong population	10	4	40%
Full text	Subtotal	273	100	36.6%
Stratified random sampling, proportional allocation (numpy default_rng, seed 20261114). Sampled records re-adjudicated against the written criteria (I1-I5 / E1-E11) without access to the original decisions.				

Supplementary Table S10b. Verification sample of excluded records: results

Stage	Re-adjudicated (n)	Falsely excluded (n)	False-negative rate (exact 95% CI)	Notes
Title/abstract	300	0	0.0% (0.0-1.2%)	50 abstracts with oncocytic and/or molecular signals individually adjudicated (reviews; case reports; medullary/parathyroid/pediatric populations; analytical-validity and cost-effectiveness designs; one modelled-NPV analysis using published estimates; one narrative review); all confirmed the original codes.
Full text - documents verified	95	0	0.0% (0.0-3.8%)	89 re-procured full-length articles + 1 open-access article downloaded during revision + the ATA-2017 supplement containing the Livhits interim-analysis abstract + corresponding full papers of 4 conference-abstract records. Seven studies contained a recognizable oncocytic subgroup or subgroup characteristic, each confirmed ineligible (Barnes 2022: n=1, below minimum; Loncar 2023 and Hu 2022: basel
Full text - record-level closures	5	0	-	Conference-abstract records with no retrievable abstract text: two corresponding full papers are included studies in this review (Abi-Rad 2022; Landau 2021); two corresponding full papers were obtained and verified during this check (Jin, Diagn Cytopathol 2023; Jin 2025) - neither has a separable oncocytic subgroup; one (Belovarac 2019) has no full-length counterpart in the screening database.
Total	400	0	0/300 and 0/100	Complementary audit: all 149 FT-stage 'full text not available'

				exclusions reviewed; the 15 provisionally carried from the pilot-round inclusion list are all present in the final 74/75-study included set.

Supplementary Table S11. Scenario B datasets: composition and follow-up of unoperated test-negative nodules.

Test	Dataset (study)	Scenario B nodules	TN	Unoperated assumed-benign (share of TN)	Verification basis for unoperated	Minimum follow-up	Losses to follow-up	Cancers during observation
GSC	Ahmadi 2026, B-III	198	163	148 (91%)	Ultrasound surveillance; benign call required >=1 y stability (median 24 mo, range 9-76)	>= 1 y	Study exclusions mainly LTFU	None reported
GSC	Ahmadi 2026, B-IV	149	114	93 (82%)	Same as above	>= 1 y	Same as above	None reported
GSC	San Martin 2020	17	11	11 (100%)	GSC-benign offered US follow-up in lieu of surgery	NR	NR	None reported
GSC	Jin 2022	17	14	11 (79%)	Clinical/US stability required for unoperated benign	>= 6 mo	NR	None reported
GSC	Endo 2019	17	16	16 (100%)	Unoperated benign assumed benign (paper's design)	median 7.5 mo	NR	None reported
TSv3	Landau 2021	140	76	61 (80%)	Observed without surgery; no systematic serial imaging reported	NR	NR	None reported
TSv3	Tjendra 2023	44	21	17 (81%)	Observed; no systematic imaging reported	NR	2 MT-positive LTFU	None reported
TSv3	Gajzer 2022	82	69	63 (91%)	Observed; no systematic imaging reported	NR	NR	None reported
TSv3	Raghunathan 2024	53	34	29 (85%)	Randomized-trial cohort; annual	1 y (protocol)	5 GSC-arm / 1 TSv3-arm	None reported

					ultrasound (96% stable at 1 y)			
TSv3	Hsiao 2025	62	48	41 (85%)	Observed; no systematic imaging reported	NR	NR	None reported
TSv3	Glass 2021	14	11	9 (82%)	Observed; no systematic imaging reported	NR	NR	None reported
GEC	Brauner 2015	69	26	23 (88%)	GEC-benign unoperated; observation	NR	21 excluded at outset incl. LTFU	None reported
GEC	San Martin 2020 (GEC)	19	6	6 (100%)	Benign-call nodules mostly unverified	NR	NR	None reported
GEC	Parajuli 2019	31	11	10 (91%)	Observed; no systematic imaging reported	NR	NR	None reported
GEC	Lastra 2014	21	8	6 (75%)	Observed; no systematic imaging reported	NR	NR	None reported
GEC	Zhang 2021	10	4	2 (50%)	Unresected verified by >=6-month follow-up	>= 6 mo	ND/no-follow-up excluded at outset	None reported
GEC	Endo 2019 (GEC)	58	17	17 (100%)	Unoperated benign assumed benign	median 7.5 mo	NR	None reported
Total	17 datasets	1006	649	563 (GSC 279 / TSv3 220 / GEC 64)	4 of 17 datasets specify a minimum follow-up duration			0 cancers in any dataset
Nodules per dataset = scenario B 2x2 totals (DTA_2x2 sheet); unoperated = scenario B TN minus scenario A TN. NR = not reported. AFTN-signature nodules in Landau 2021								

(TSHR/EZH1/GNAS, n=17 unoperated) are counted negative per protocol.								

Supplementary Table S12. Alteration-level detail underlying the alteration-class analysis.

Study (oncocytic cohort)	Variant / finding	Total	Resected	Malignant	Benign	NIFTP	Class in Table 3	Source / note
Landau 2021 (FNHCT, 180 nodules, 79 resected)	GH-CNA alone	42	29	10	19	incl.	CNA only	Table 1; class M/B from extraction (CNA 10/19)
Landau 2021	HRAS/KRAS/NRAS/GEA	20	18	10*	13*	incl.	RAS-like	*class-level (RAS-like incl. EIF1AX/PAX8::PPARG per hierarchy)
Landau 2021	TP53 and/or TERT (6 of 7 with GH-CNA)	7	6	5	2	incl.	High-risk	class 5/2
Landau 2021	TP53 + KRAS	1	1	in HR 5/2			High-risk	counted in high-risk by hierarchy
Landau 2021	EIF1AX (1 splice-site + GH-CNA; 1 splice-site + HRAS)	8	5	in RAS 10/13			RAS-like	variant-level outcome in paper suppl.
Landau 2021	PAX8::PPARG	4	2	in RAS 10/13			RAS-like	
Landau 2021	BRAF V600E	3	2	2	0		BRAF/fusion	
Landau 2021	PAX8::GLIS3	1	1	in BRAF/F 2/0			BRAF/fusion	
Landau 2021	AFTN signature (TSHR 12, EZH1 4, GNAS 1)	17	0	-	-	-	Negative	all unoperated; test-negative per protocol
Schatz-Siemers 2019 (Hürthle FNA, 188; 33 resected)	NRAS	22	8	3	3	2	RAS-like	Table 2
Schatz-Siemers 2019	KRAS	10	6	1	3	2	RAS-like	
Schatz-Siemers 2019	HRAS	7	2	1	0	1	RAS-like	
Schatz-Siemers 2019	PAX8::PPARG	7	3	1	0	2	RAS-like	
Schatz-Siemers 2019	TSHR	7	1	0	1	0	Negative	
Schatz-Siemers 2019	EIF1AX	5	1	0	1	0	RAS-like	
Schatz-Siemers 2019	MET	4	2	0	1	1	RAS-like	
Schatz-Siemers	Clonal CNA	3	1	0	1	0	CNA only	

2019								
Schatz-Siemers 2019	TERT (2 secondary, with NRAS)	2	2	2	0	0	High-risk	
Schatz-Siemers 2019	TP53	1	1	1	0	0	High-risk	
Schatz-Siemers 2019	PIK3CA / GNAS / PTEN	1/1/3	1/0/0	1/0/0	0/0/0	0	RAS-like / Negative / RAS-like	
Schatz-Siemers 2019	Negative	115	5	0	5	0	Negative	
Gajzer 2022 (AUS-PHC, 88; 19 positive, resected)	RAS total (KRAS 6, NRAS 3, HRAS 0)	9	9	3*	6*	incl.	RAS-like	Tables 1-2; *class-level 3/6; RAS-type split from Table 2
Gajzer 2022	CNA	4	4	0	2	incl.	CNA only	class 0/2
Gajzer 2022	TP53	1	1	1	0		High-risk	class 1/0
Gajzer 2022	BRAF K601E / DICER1 / EIF1AX / GEA	1 each (col. order partly unparseable)	-	-	-		RAS-like etc.	see paper Table 1 PHC column
Tjendra 2023 (B-IV OFN, 46; 27 resected)	Isolated chromosomal CNA	12	-	2*	8*	incl.	CNA only	class 2/8; *includes CNA-combination rows
Tjendra 2023	Isolated RAS	3	-	1*	4*	incl.	RAS-like	class 1/4 (incl. RAS+GEA 1)
Tjendra 2023	EZH1	2	-	-	-		Negative	
Tjendra 2023	CNA + TERT	2	-	in HR 3/0			High-risk	
Tjendra 2023	BRAF V600E + TERT	1	-	in HR 3/0			High-risk	hierarchy: TP53/TERT first
Tjendra 2023	TP53 + CNA	1	-	in HR 3/0			High-risk	
Tjendra 2023	BRAF G466R + CNA	1	-	-	-		RAS-like (non-V600E)	angioinvasive OCA on follow-up
Tjendra 2023	RAS + GEA / GEA	2	-	-	-		RAS-like / Negative	
Radkay 2014 (RAS+ nodules with oncocytic features)	KRAS	18 of 24 oncocytic-feature cases	-	-	-		RAS-like	Table 2: oncocytic features KRAS 75.0% vs NRAS 15.4% vs HRAS 4.5%; oncocytic-subset outcome 12M/10B overall
Radkay 2014	NRAS / HRAS	21 / 2 with oncocytic features	-	-	-		RAS-like	class-level 12/10 used in Table 3
Gilani 2021	TERT + EIF1AX	1	1	1	0		High-risk	Table 5 (case-level)

(HCN FNA, 85; 42 resected, 28 malignant)								
Gilani 2021	NRAS	1	1	1	0		RAS-like	class RAS 3/10
Gilani 2021	EIF1AX	1	1	1	0		RAS-like	
Gilani 2021	CNA (limited)	1	1	1	0		CNA only	class 1/6
Gilani 2021	Molecular 'suspicious' (unspecified)	3	3	3	0		per hierarchy	Table 5 HCC rows
Gilani 2021	KRAS (follicular carcinoma)	1	1	1	0		RAS-like	
Gilani 2021	No alteration (malignant: PTC 5, PDC 2)	7	7	7	1		Negative	class 2/8
Geetha 2025 (oncocytic-feature indeterminate, 33 MT-positive)	KRAS 7 / NRAS 7 / HRAS 2	7/7/2	-	0*	9*	incl.	RAS-like	Tables 3-6; *class RAS 0/9 - KRAS+ nodules were NIFTP/oncocytic adenoma
Geetha 2025	CNA (incl. 2 GH/Hürthle-type CNA)	8	-	1	4	incl.	CNA only	class 1/4
Geetha 2025	TERT (1), TERT+CNA (1), TERT+EIF1AX (1)	3	3	0	3	0	High-risk	class 0/3 - all three non-malignant (FND/WDT-UMP grouped benign); main heterogeneity driver of the high-risk class
Geetha 2025	EIF1AX / EZH1 / THADA::IGF2BP3 / GEA	1/1/1/3	-	-	-		RAS-like / Negative	
Elsheikh 2026 (Cleveland resected cohort)	NRAS or KRAS	14	14	10	4	(NIFTP counted malignant by authors)	RAS-like	main text; per-variant tables in suppl. S4-S5; class RAS 13/5
Elsheikh 2026	High-risk (TP53/TERT) / BRAF V600E / fusion / CNA	-	-	malignant: HR 2, BRAF/F 2, CNA 1			High-risk / BRAF / CNA	class HR 2/0, BRAF/F 2/0, CNA 1/0
Spagnuolo 2022 (Hürthle-predominant B-III/IV, resected)	Variant-level split (NRAS/HRAS/KRAS etc.) not extractable - full text paywalled (Elsevier), not in PMC, re-procurement attempted 2026-11-15	29 ThyroSeq-tested	29	8*	21*		class-level	*class totals as used in Table 3 (Neg 1/6, RAS 4/8, CNA 0/6, HR 1/0, BRAF/F 1/0). Abstract cross-check: 22/29 positive, 7 of the positive malignant; 7 negative (1 malignant).

								Abstract-page PDF re-checked.
Glass 2021 (AUS-3H, Dartmouth)	Variant-level not extractable (small dataset)	-	-	0*	4*		RAS-like 0/4; Neg 1/4; CNA 0/1	*class-level as used in Table 3
Raghunathan 2024 (UCLA RCT Hürthle subset, TSv3 arm; 27 positive all resected: 3M/24B)	RAS (incl. KRAS)	10	10	1	9	0	RAS-like	malignant one = KRAS (PTC); paper narrative + Suppl. S1-S2
Raghunathan 2024	TERT (1) / RAS+TERT (1) / EIF1AX+TERT (1)	3	3	0	3	0	High-risk	all benign; the RAS+TERT case was reclassified FLUMP after MDT review
Raghunathan 2024	TP53 + EIF1AX	1	1	1	0	0	High-risk	malignant (PTC) - the only malignant high-risk case; class HR 1/3 matches Table 3 exactly
Raghunathan 2024	CNA + low-level TP53	1	1	0	1	0	CNA only	low-level variant counted negative per protocol
Raghunathan 2024	EIF1AX (1) / TTF1 (1) / MET (1)	3	3	0	3	0	RAS-like / other	within the 24 benign
Raghunathan 2024	GEA or chromosomal CNA	9	9	1	8	0	CNA only / Negative	malignant one = multiple GEA (HCC)
Raghunathan 2024	Test-negative (unoperated)	34	0	-	-	-	Negative	28 with ultrasound surveillance at 1 y, 96% stable; 1 lost to follow-up
Class-level malignant/benign counts are those used in the meta-analysis (Table 3); variant-level columns reproduce the source papers. Coverage: variant-level detail for 10 of 11 contributing								

studies; Spagnuolo 2022 and Glass 2021 class-level only (full texts not re-procurable; Spagnuolo cross-checked against its published abstract). The high-risk class divergence (crude 17/25, 68% vs random-effect								

Supplementary Table S13. Case mix of platform datasets underlying the indirect between-platform comparisons

.

Characteristic	Afirma GSC	ThyroSeq v3	Afirma GEC	Note
Datasets (studies), scenario A	4 (3)	9 (9)	8 (8)	Table 2
Resected-nodule malignancy prevalence (scenario A)	40%	30%	20%	manuscript Results
Benign call rate, pooled	74.2% (67.9-79.6); k=8 datasets	59.6% (48.4-69.9); k=8	24.7% (20.0-30.1); k=15	any-alteration positivity rule in 2 TSv3 datasets (Landau, Abi-Rad) - exclusion SA narrows difference
Bethesda composition of accuracy datasets	III: Ahmadi, Jin; III/IV: Elsheikh	III: Gajzer, Hsiao, Glass; IV: Landau, Tjendra; III/IV: Raghunathan, Elsheikh, Abi-Rad, Spagnuolo	mostly III/IV and IV	
Periods	2015-2026	2014-2024	2010-2018	
Within-population comparison	Raghunathan 2024 (RCT, same patients): BCR 84% (66/79) vs 56% (34/61); Elsheikh 2026 (same centre, both platforms)			only direct comparative evidence
External head-to-head (all-comer ITN)	Dowell 2025 (Eur Thyroid J): no significant difference between platforms			cited in Discussion; no oncocytic subgroup