2025 City of Hope Multidisciplinary Thyroid Cancer Symposium

Updates on Evaluation & Management of Thyroid Nodules

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Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Access to high quality imaging and advanced tests like molecular testing may be different based on patients' socio-economic status.*
- *Appropriate referrals for evaluation and management regardless of race/gender etc.*

Objectives

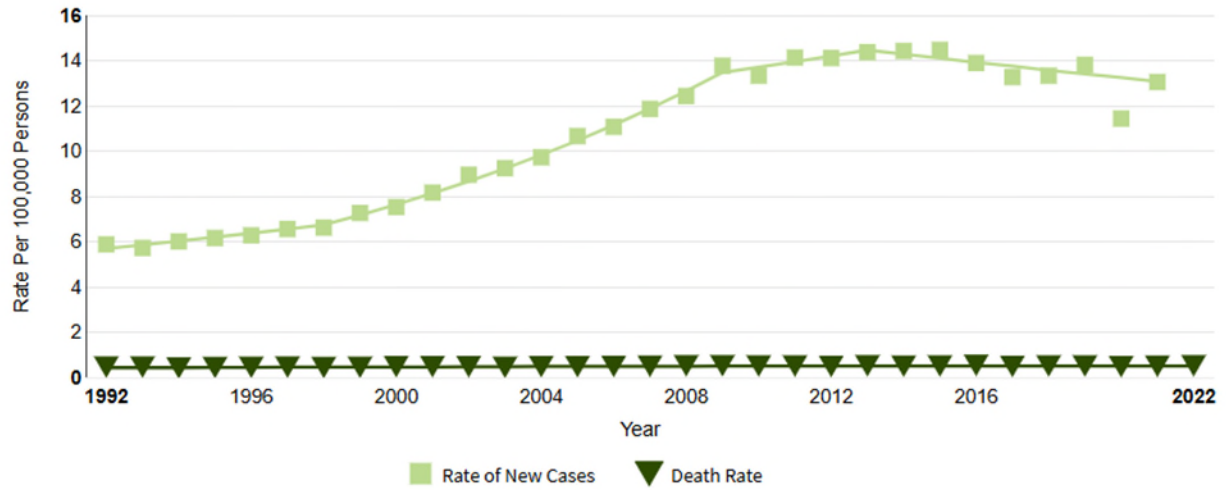
- Review ATA guidelines for thyroid nodule evaluation (Discuss draft guidelines update ATA 2025)
- Brief overview of ATA and TIRADS risk stratification of thyroid nodules
- Review the role of molecular diagnostic testing in thyroid nodule management
- Understand the various commercially available molecular tests
- Review the correct way to incorporate this information into clinical practice
- Future Directions

Incidence of Thyroid Cancer

At a Glance

Estimated New Cases in 2024	44,020
% of All New Cancer Cases	2.2%
Estimated Deaths in 2024	2,170
% of All Cancer Deaths	0.4%

5-Year Relative Survival
98.4%
2014–2020



SEER Cancer Stat Facts: Thyroid Cancer. National Cancer Institute. Bethesda, MD

Rising Incidence

- Increased use and sensitivity of imaging modalities like US, CT, MRI and PET leading to higher detection of “incidentalomas”
- Increase in incidence of palpable thyroid nodules and nodules > 4 cm
- ? Environmental factors associated with true increasing incidence
  - Ionizing radiation (from medical procedures or occupational exposures)
  - Radon exposure
  - Flame retardant/polybrominated diphenyl ethers (PBDEs) exposure

Ukrainski, Melinda B. et al. Increasing Incidence of Thyroid Nodules and Thyroid Cancer: Does Increased Detection of a Subclinical Reservoir Justify the Associated Anxiety and Treatment? Clinical Therapeutics, Volume 38, Issue 4, 976 - 985

Prevalence

- In the adult population, physical examination alone may show a prevalence of 5% to 7%
- Ultrasound shows a prevalence of 20% to 76%
- Autopsy finding with a prevalence close to 50%
- Prevalence of thyroid nodules and risk of malignancy increases with age
- Approx. 4 times more common in women than men
- Occur more often in individuals living in iodine-deficient geographic areas
- In patients with a single palpable nodule, 20 to 48 % had additional nodules detected by ultrasound exam.

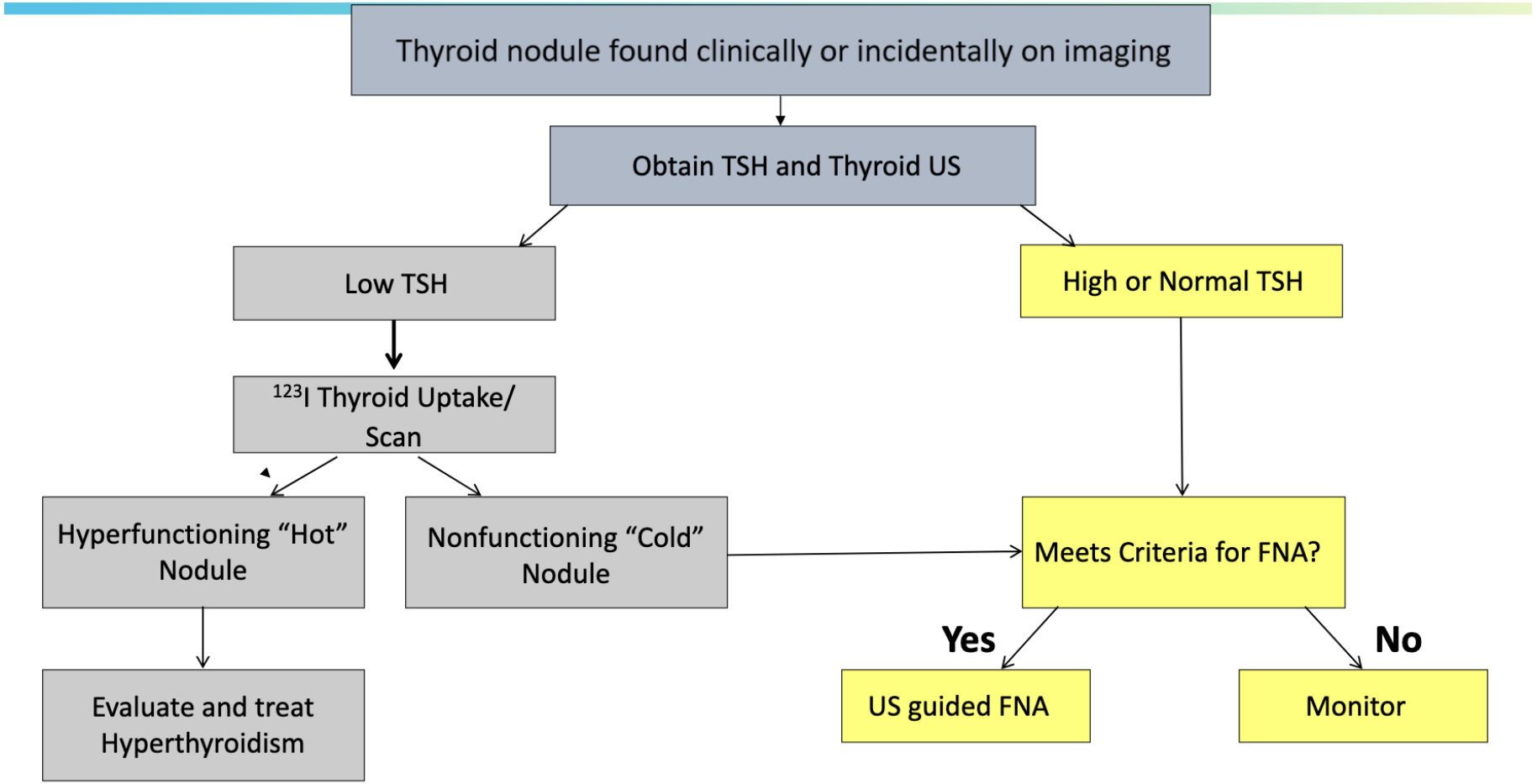
1.Bomeli SR, LeBeau SO, Ferris RL. Evaluation of a thyroid nodule. Otolaryngol. Clin. North Am. 2010 Apr;43(2):229-38
2. Durante C et al. The natural history of benign thyroid nodules. JAMA. 2015 Mar 03;313(9):926-35.
3. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 1997; 126:226.

Risk factors for thyroid nodules

- Radiation exposure
  - History of childhood head and neck radiation therapy
  - Total body radiation for hematopoietic stem cell transplantation
  - Exposure to ionizing radiation from fallout in childhood or adolescence (Chernobyl)

- Family history of thyroid cancer (PTEN hamartoma tumor syndrome [Cowden's disease], FAP, Carney complex, Werner syndrome, or MEN 2, a risk for medullary thyroid cancer [MTC])

Evaluation of Thyroid Nodules



ATA 2015: Nodule sonographic patterns & risk of malignancy

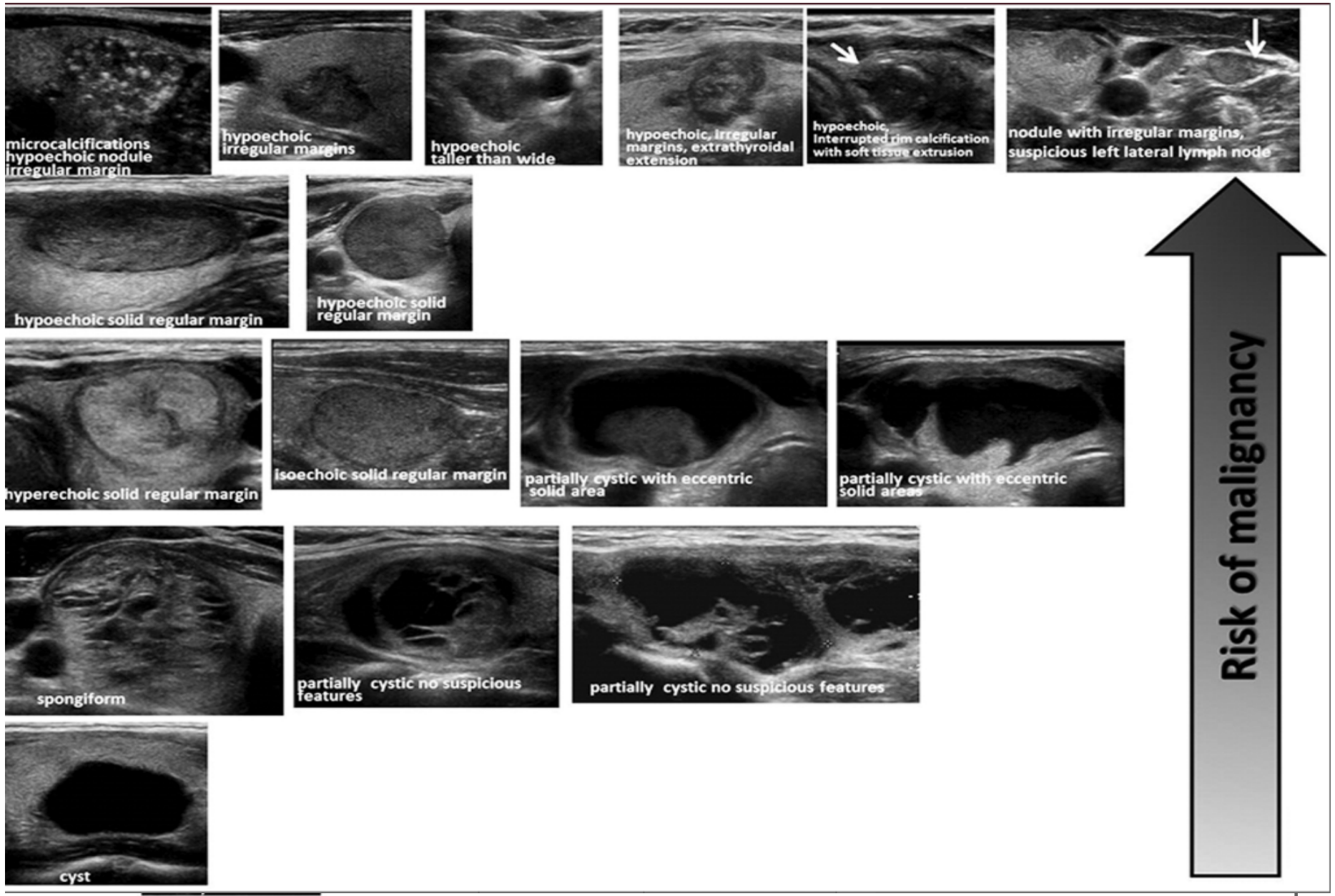
High Suspicion > 70-90%

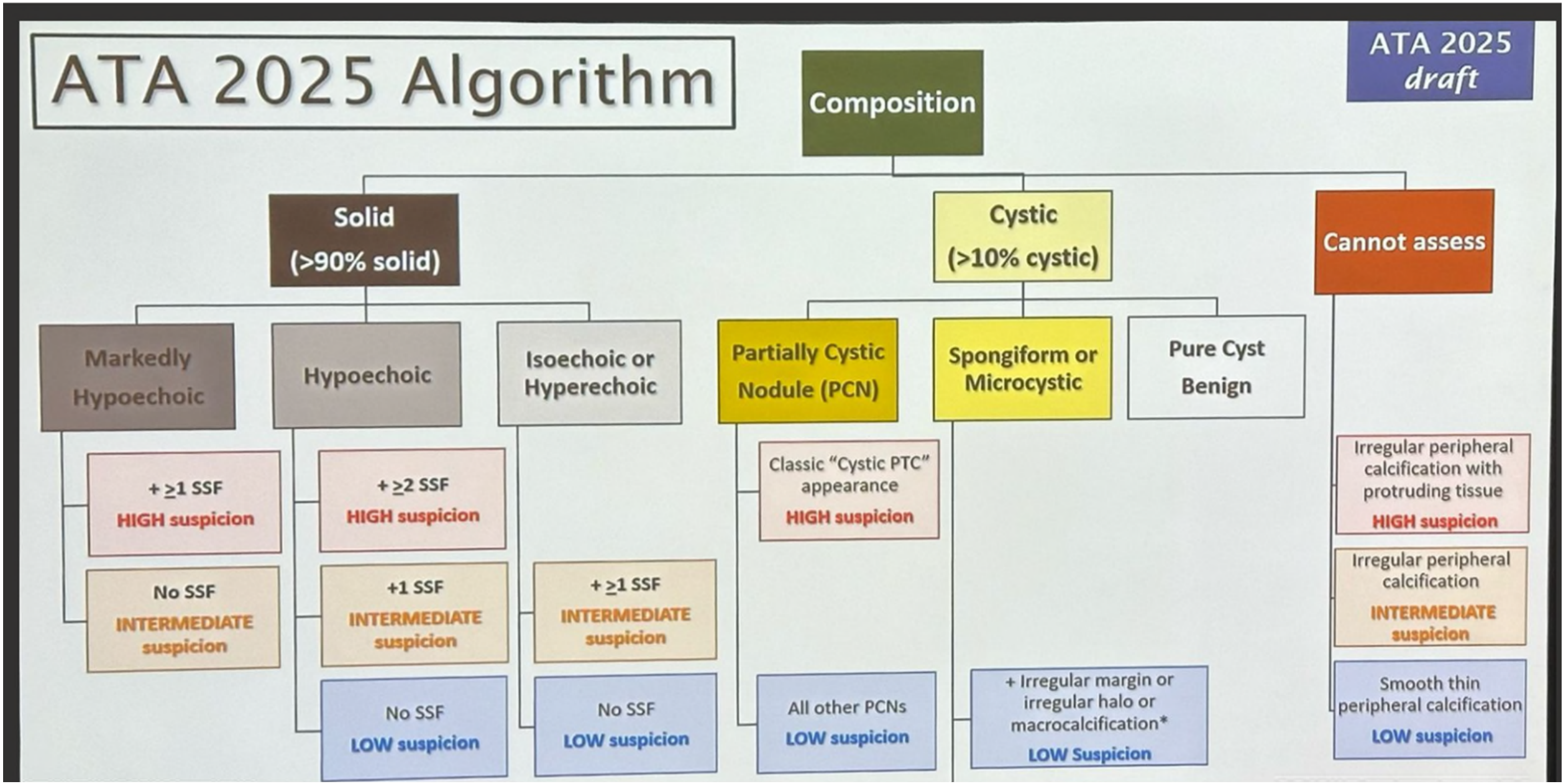
Intermediate Suspicion 10-20%

Low Suspicion 5-10%

Very Low Suspicion <3%

Benign <1%

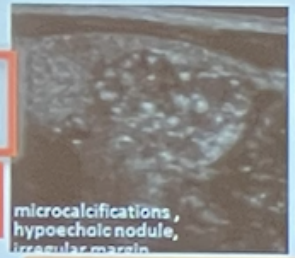


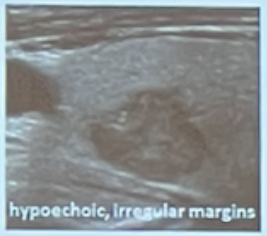

ATA 2025 Algorithm
ATA 2025 draft
Composition
Solid (>90% solid)
Cystic (>10% cystic)
Cannot assess
Markedly Hypoechoic
Hypoechoic
Isoechoic or Hyperechoic
Partially Cystic Nodule (PCN)
Spongiform or Microcystic
Pure Cyst Benign
+ ≥1 SSF HIGH suspicion
No SSF INTERMEDIATE suspicion
+ ≥2 SSF HIGH suspicion
+1 SSF INTERMEDIATE suspicion
No SSF LOW suspicion
+ ≥1 SSF INTERMEDIATE suspicion
No SSF LOW suspicion
Classic "Cystic PTC" appearance HIGH suspicion
All other PCNs LOW suspicion
+ Irregular margin or irregular halo or macrocalcification* LOW Suspicion
Irregular peripheral calcification with protruding tissue HIGH suspicion
Irregular peripheral calcification INTERMEDIATE suspicion
Smooth thin peripheral calcification LOW suspicion

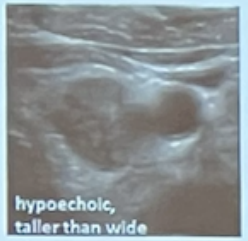
2025 ATA Nodule Sonographic Pattern Risk of Malignancy

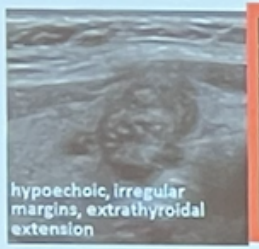
High Suspicion

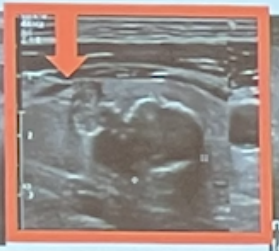
> 50%

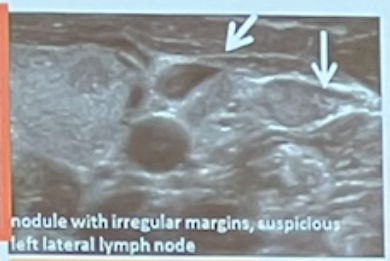


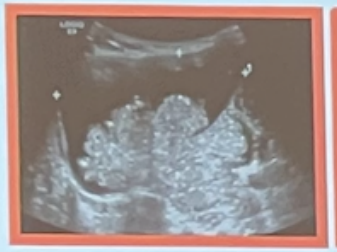








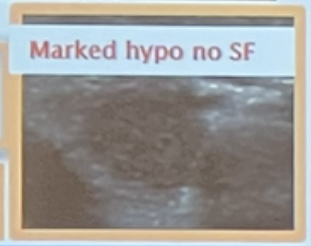


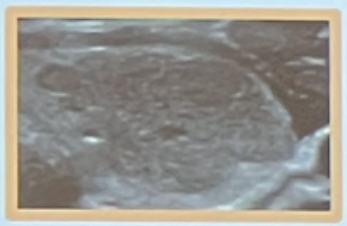


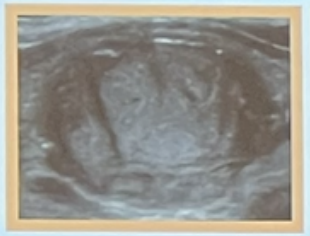
Any nodule w/ ETE or abnl LNS

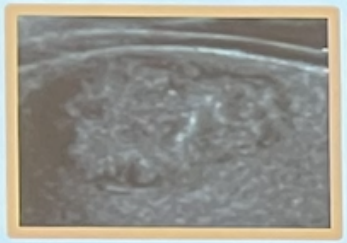
Intermediate Suspicion

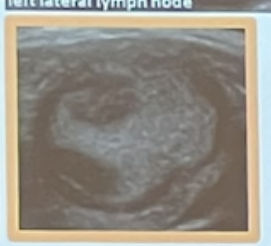
20-50%

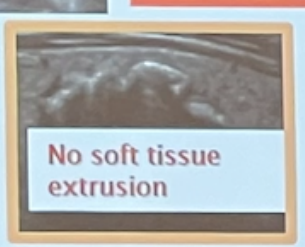






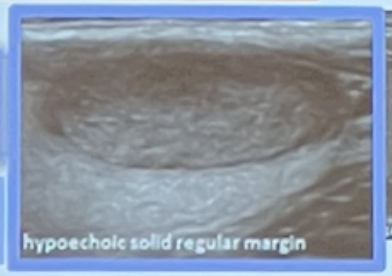


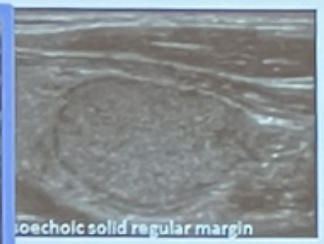


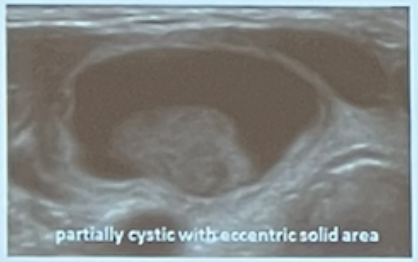


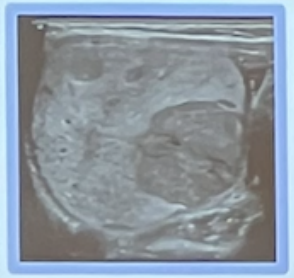
Low Suspicion

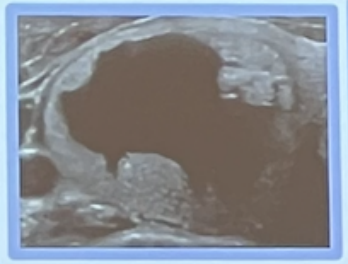
3-20%

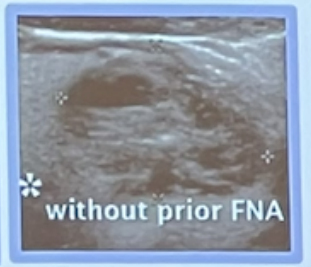


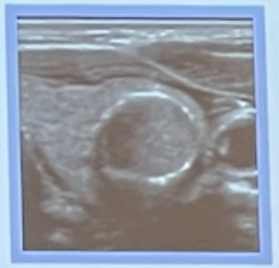






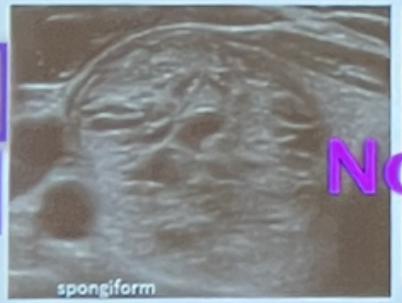




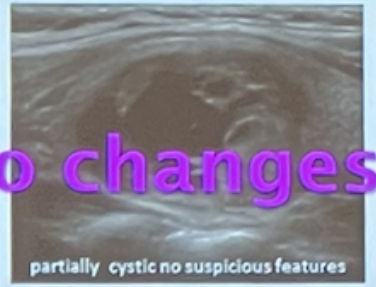


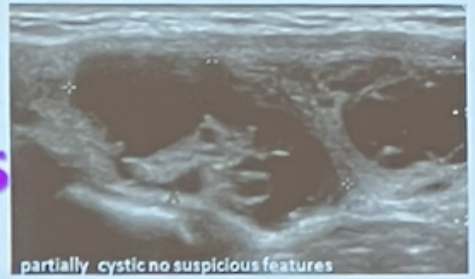
Very low Suspicion

< 3%



No changes

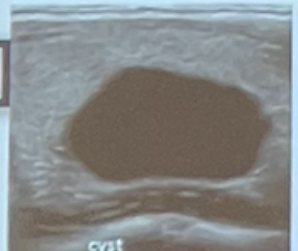




ATA 2025 *draft*

Benign

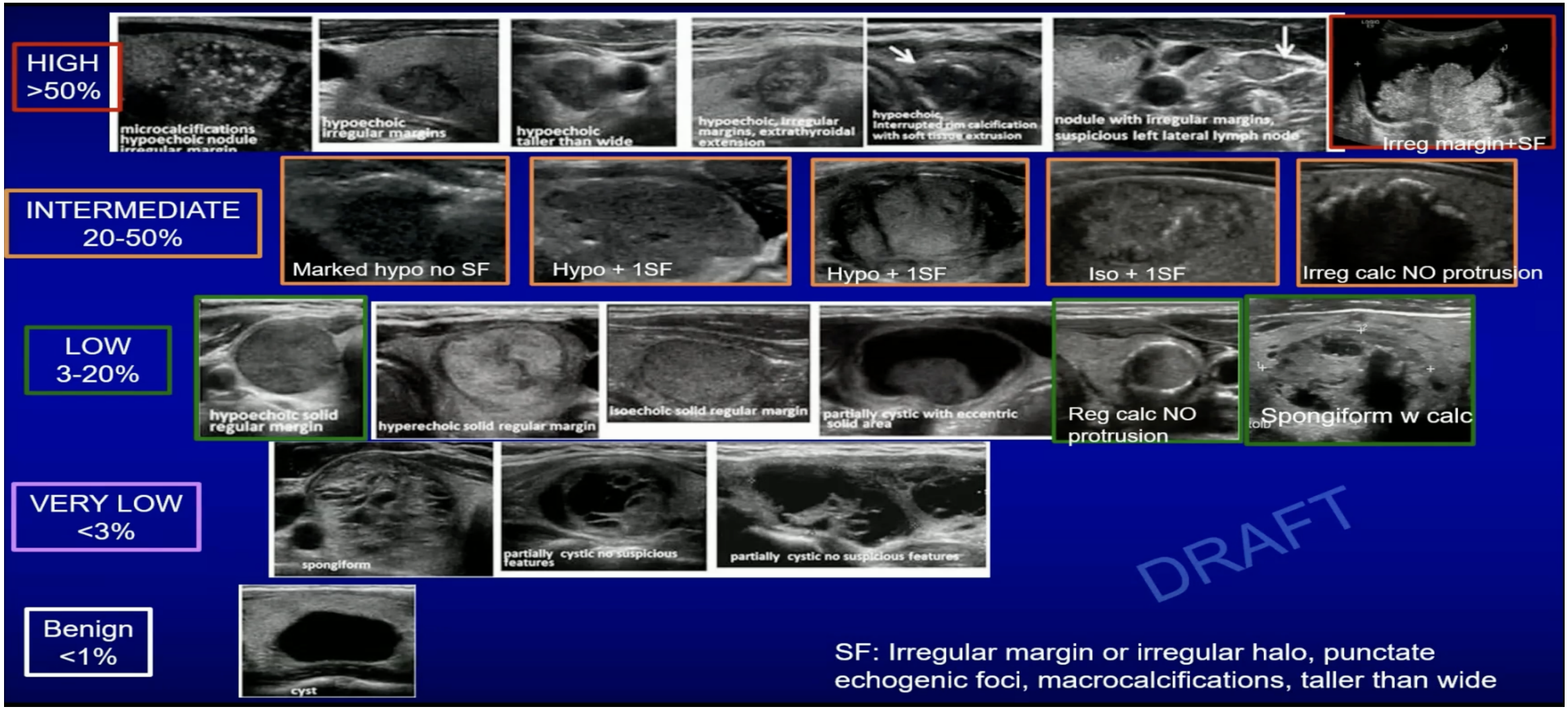
Near 0



No changes

Solid nodule Suspicious Features (SSF)—irregular margin or irregular halo, punctate echogenic foci, taller than wide shape, macrocalcifications

ATA 2025 Thyroid Nodule Guidelines Draft (ATA 2024 Conference)



ATA 2025 Thyroid Nodule Guidelines Draft(Shared at ATA 2024 Conference)

Size Thresholds for FNA

ATA Sonographic Pattern	RoM range	Threshold range for FNA	Strength of recommendation	Quality of evidence
High Suspicion	>50%	1.0 – 1.5cm	Strong	Moderate
Intermediate Suspicion	21 – 50%	1.0 – 2.0cm	Conditional	Moderate
Low Suspicion	4 –20%	1.5 – 2.5cm	Conditional	Moderate
Very Low Suspicion	≤3%	No FNA	Strong	Moderate
		Consider FNA if ≥2.5cm	Conditional	Low
Benign	<1%	No FNA	Strong	High

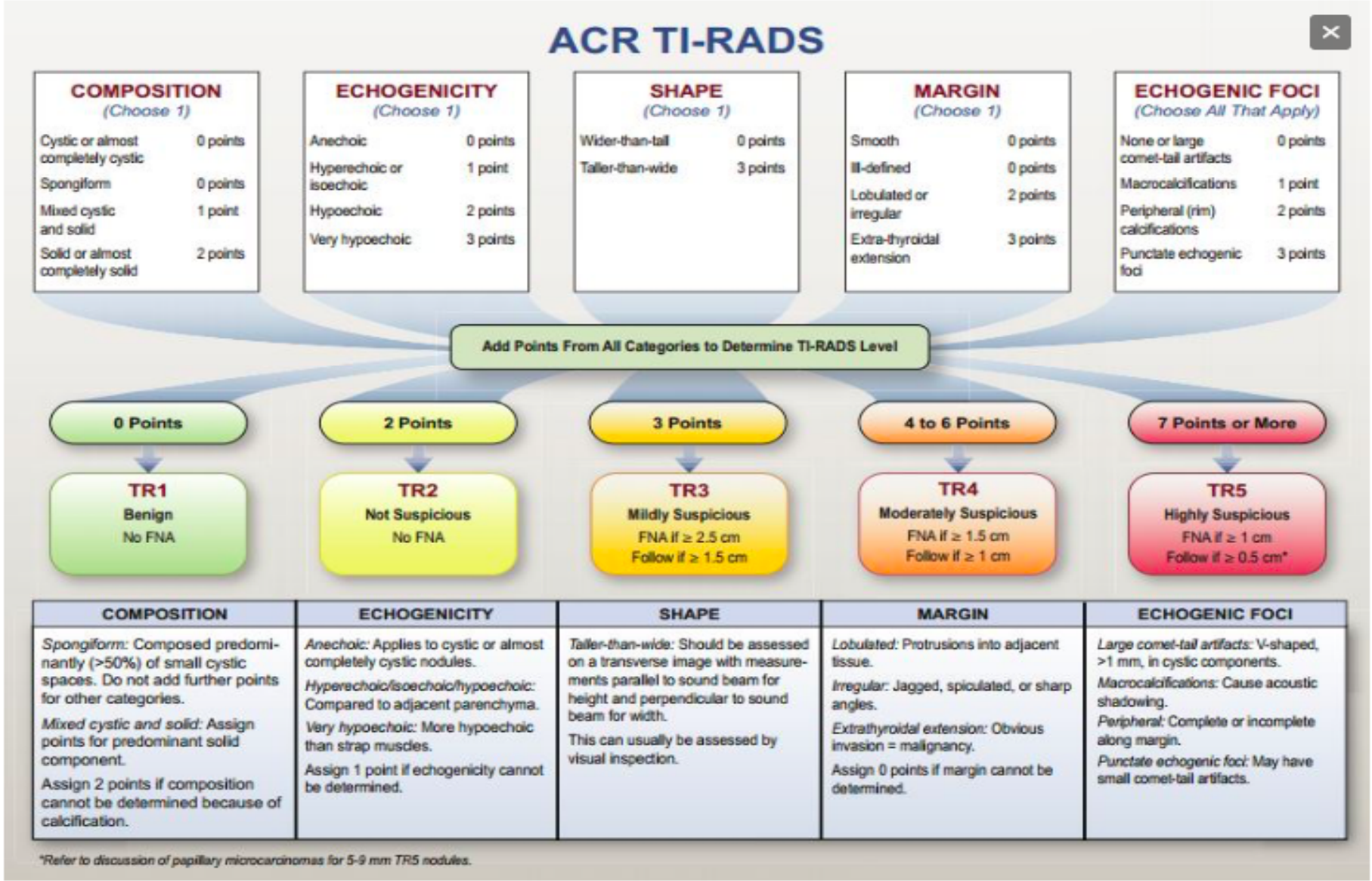
Consider FNA <1cm with abnormal lymph nodes, extrathyroidal extension, posterior location, or personal risk factors

Factors influencing decision making for nodule FNA ATA 2025 DRAFT

Factors	Favors smaller size	Favors larger size
Age (~60 yrs)	Younger	Older
Personal risk factors for thyroid cancer(e.g. XRT as child, genetic syndrome)	Present	Absent
Comorbidities	Absent	Present
Evidence for sonographic pattern ROM	Strong	Weak
FDG or Ga-68 Dotatate avidity (Focal)	Present	Absent
Symptoms	Present	Absent
Nodule location	Isthmus, posterior	Other
Patient preference		

Surveillance of unsampled nodules ATA 2025 DRAFT

ATA sonographic pattern	Surveillance US time interval (months)	Action	Strength of recommendation/Quality of Evidence
High Suspicion	6-9	FNA if growth or abnormal LNs	Strong/Moderate
Intermediate Suspicion	9-18	Growth→FNA, stable→ increase surveillance interval	Conditional/Low-Moderate
Low Suspicion	12-24	Growth→FNA, stable→ increase surveillance interval	Conditional/Low-Moderate
Very Low suspicion/Benign	Not indicated	Not applicable	Strong/Moderate
Growth =50% volume increase or 20% increase in 2 dimensions			



ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee
Tessler, Franklin N. et al. Journal of the American College of Radiology, Volume 14, Issue 5, 587 – 595.2017

Size Threshold for FNA Biopsy Proposed by the Five Sonographic Classification Systems

AACE/ACE/AME	ACR TIRADS	ATA	K-TIRADS	EU-TIRADS
High	TR5	High suspicion	TR5	TR5
FNA >10 mm	FNA ≥10 mm	FNA ≥10 mm	FNA ≥10 mm	FNA >10 mm
ROM 50%–90%	ROM ≥20%	ROM 70%–90%	ROM >60%	ROM 26%–87%
Intermediate	TR4	Intermediate suspicion	TR4	TR4
FNA >20 mm	FNA ≥15 mm	FNA ≥***10*** mm	FNA ≥***10*** mm	FNA >15 mm
ROM 5%–15%	ROM 5%–20%	ROM 10%–20%	ROM 15%–50%	ROM 6%–17%
	TR3	Low suspicion	TR3	TR3
	FNA ≥25 mm	FNA ≥***15*** mm	FNA ≥***15*** mm	FNA >***20*** mm
	ROM 5%	ROM 5%–10%	ROM 3%–15%	ROM 2%–4%
Low	TR2	Very low suspicion	TR2	TR2
FNA >20 mm	No FNA	FNA ≥***20*** mm	FNA ≥***20*** mm	No FNA
ROM ≈1%	ROM 2%	ROM <3%	ROM 1%–3%	ROM 0%
	TR1	Benign	—	—
	No FNA	No FNA		
	ROM 2%	ROM < 1%		

Grani, G. et al (2018). Reducing the Number of Unnecessary Thyroid Biopsies While Improving Diagnostic Accuracy: Toward the "Right" TIRADS. *The Journal of Clinical Endocrinology & Metabolism, 104*, 95–102.

Real- world comparison of ATA and TIRADS

Table 5
Comparison of the Diagnostic Performance of ATA and ACR TI-RADS Classification

	ATA classification	ACR TI-RADS classification
Sensitivity, (95% CI)	77.3 (68.5-86.0)	78.4 (69.8-87.0)
Specificity, (95% CI)	76.6 (71.2-82.0)	73.2 (67.5-78.9)
Positive predictive value, (95% CI)	55.3 (46.5-64.1)	52.3 (43.7-60.8)
Negative predictive value, (95% CI)	90.0 (85.8-94.8)	90.1 (85.8-94.3)
AUC (*P* = .18)	0.77	0.76
Kappa statistics (95% CI)	0.93 (88.8-97.0)	

Abbreviations: ACR TI-RADS = American College of Radiology Thyroid Imaging Reporting and Data System; ATA = American Thyroid Association; AUC = area under the curve; CI = confidence interval.
ATA and ACR TI-RADS:

- ATA Benign/very low/low suspicion are negative.
- ATA intermediate/high are positive.
- ACR TI-RADS 1/2/3 are negative.
- ACR TI-RADS 4/5 are positive.

Table 6
Malignancy Rate Within Each ATA and ACR TI-RADS

ACR TI-RADS classification	Total nodules	Malignant nodules (%)
5	32	29 (90.6)
4	100	40 (40)
3	159	16 (10.1)
2	26	3(11.5)
1	6	0 (0.0)
ATA classification		
High	52	44 (84.6)
Intermediate	71	24 (33.8)
Low	179	19 (10.6)
Very low	16	1 (6.3)
Benign	5	0 (0.0)

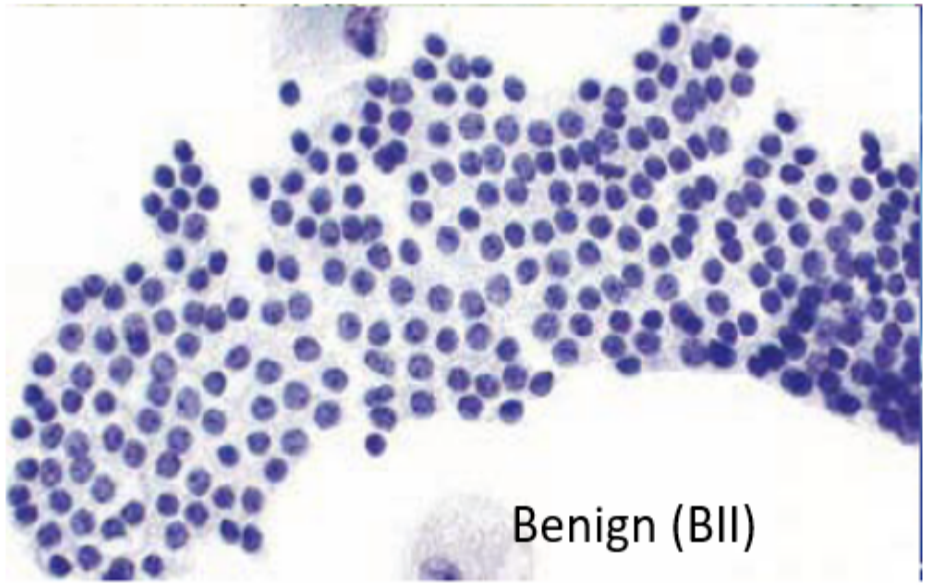
Abbreviations: ACR TI-RADS = American College of Radiology Thyroid Imaging Reporting and Data System; ATA = American Thyroid Association.

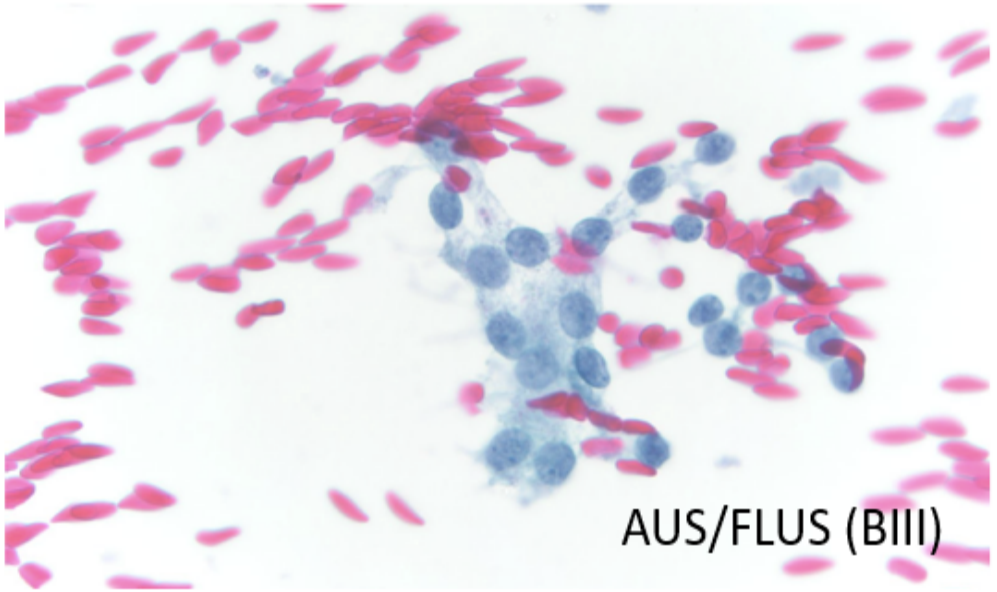
S. Ahmadi, T. Oyekunle, X. Jiang, *et al.***A direct comparison of the ATA and TI-RADS ultrasound scoring systems**. Endocr Pract, 25 (5) (2019), pp. 413-422

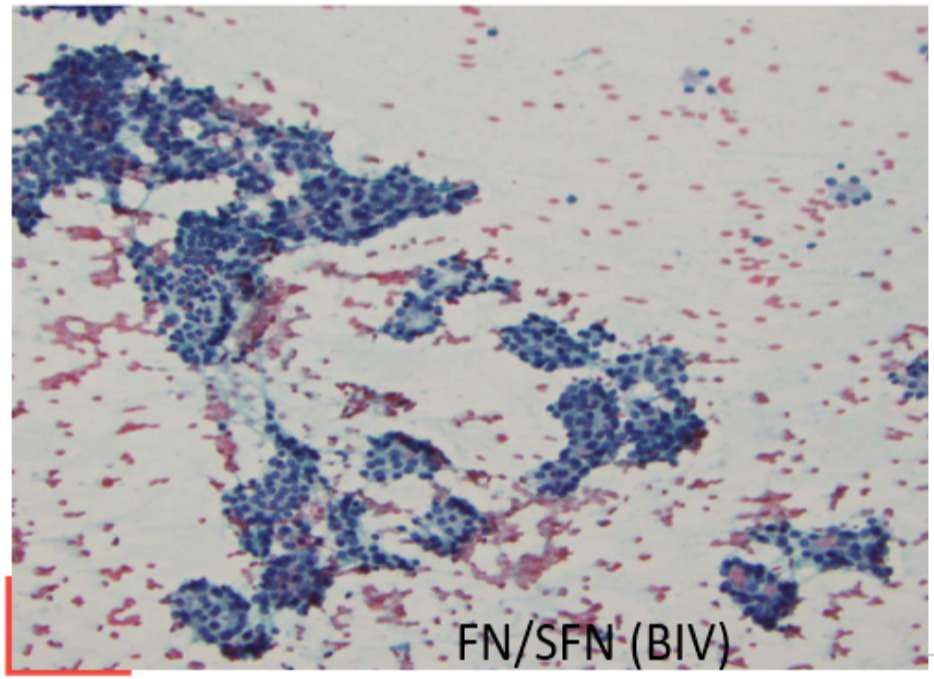
The 2023 Bethesda System for Reporting Thyroid Cytopathology

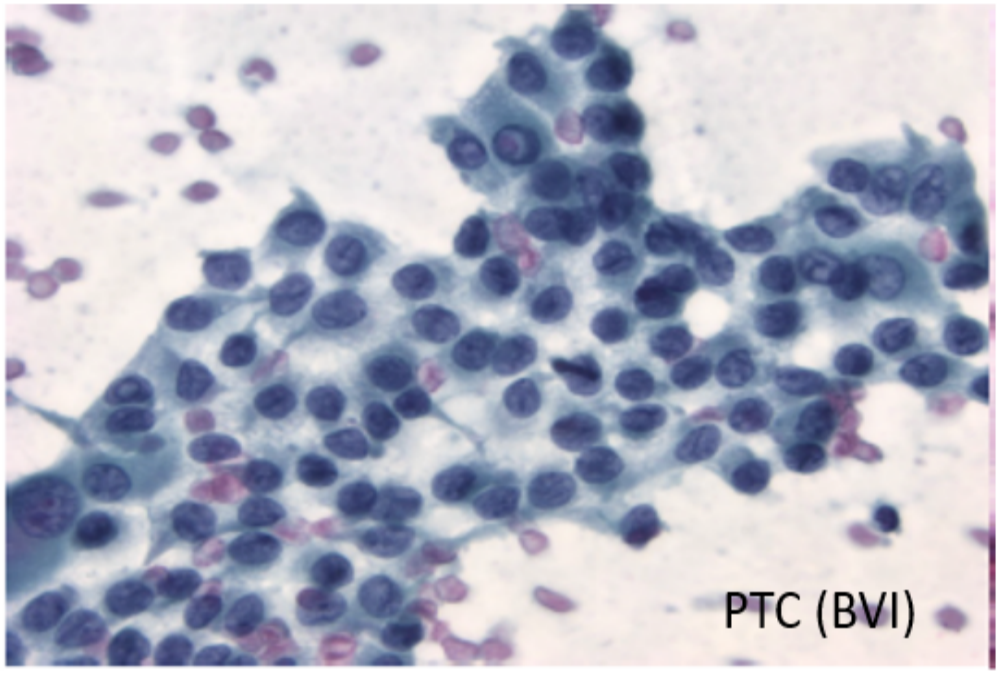
Diagnostic category	ROM[a] Mean % (range)	Usual management[b]
Nondiagnostic	**13** (5–20)[c]	Repeat FNA[d] with ultrasound guidance
Benign	**4** (2–7)[e]	Clinical and ultrasound follow-up
Atypia of undetermined significance[f]	**22** (13–30)	Repeat FNA,[d] molecular testing, diagnostic lobectomy, or surveillance
Follicular neoplasm[g]	**30** (23–34)	Molecular testing,[h] diagnostic lobectomy
Suspicious for malignancy	**74** (67–83)	Molecular testing,[h] lobectomy or near-total thyroidectomy[i]
Malignant	**97** (97–100)	Lobectomy or near-total thyroidectomy[i]

Syed Z. Ali, Zubair W. Baloch et al. The 2023 Bethesda System for Reporting Thyroid Cytopathology. Thyroid® http://doi.org/10.1089/thy.2023.0141


Benign (BII)


AUS/FLUS (BIII)


FN/SFN (BIV)


PTC (BVI)

Fine Needle Aspiration

- FNA biopsy is the recommended as a diagnostic modality of choice for thyroid nodules.
- Introduced in the 1980s, FNAB led to a twofold decrease in diagnostic thyroidectomies with a twofold increase in histologic malignancy
- Cytology reporting is standardized according to the Bethesda System for reporting Thyroid Cytopathology “Bethesda category”
- The benign and malignant categories (Bethesda II and VI) are very accurate and range of malignancy (ROM) is less than 3% and over 99% for these respectively

Gharib H, Goellner JR 1993 Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med 118:282–289
Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017;27(11):1341–6.

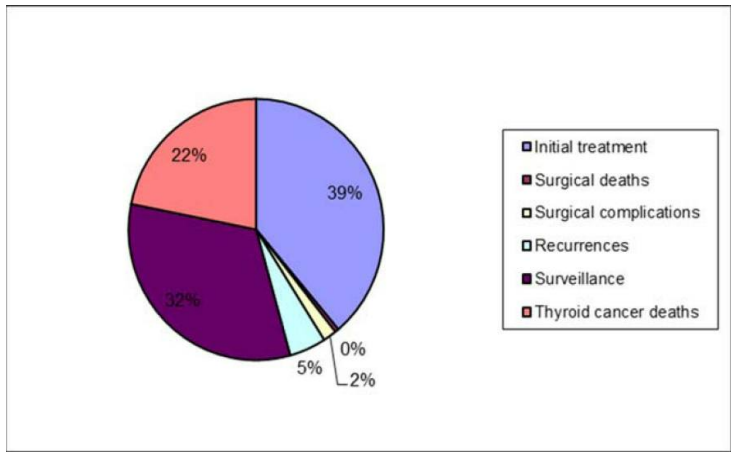
Scope of the problem

- Approximately 20-25% of the cytology results fall in the BIII, IV or V categories
- Associated with a ROM 5-75%
- BV (suspicious for malignancy) is the least commonly reported cytology category (5-7% of all results) and depending on the institution, generally has a high ROM
- As a result, surgery is typically recommended for BV

Bongiovanni M, Spitale A, Faquin WC, et al. The Bethesda system for reporting thyroid cytopathology: a meta-analysis. Acta Cytol 2012;56(4):333–9.

Numbers & Perspective

- In the US, more than 500,000 FNABs are estimated to be performed each year
- Of these 100,000 are indeterminate (20-25% cases)
- These nodules represent a target for improving diagnostic accuracy
- Cost of treating and monitoring patients with thyroid cancer reached $1.6 billion in the U.S. in 2013



Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74(11):2913–21.
Lubitz CC, Kong CY, McMahon PM, et al. Annual financial impact of well-differentiated thyroid cancer care in the United States. Cancer. 2014;120:1345-1352

What is the gold standard? Pathology?

- 653 patients with 776 surgically resected thyroid nodules >=1 cm
- 14 academic and 35 community clinical sites, between June 2009 and December 2010.
- FNA cytology inter-observer concordance: 64.0%
- FNA cytology intra-observer concordance: 74.7%
- Histology (Surgical Pathology) inter-observer concordance: 90%
- The variability was higher for Bethesda III and IV nodules

Cibas ES, Baloch ZW, Fellegara G, et al. A Prospective Assessment Defining the Limitations of Thyroid Nodule Pathologic Evaluation. Ann Intern Med. 2013;159:325–332

Role of Molecular testing in evaluation of Cytologically indeterminate thyroid nodules

City of Hope®

ATA 2015 Guidelines recommendations

RECOMMENDATION 15

(A) For nodules with AUS/FLUS cytology, after consideration of worrisome clinical and sonographic features, investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. Informed patient preference and feasibility should be considered in clinical decision-making.

(Weak recommendation, Moderate-quality evidence)

(B) If repeat FNA cytology, molecular testing, or both are not performed or inconclusive, either surveillance or diagnostic surgical excision may be performed for an AUS/FLUS thyroid nodule, depending on clinical risk factors, sonographic pattern, and patient preference.

(Strong recommendation, Low-quality evidence)

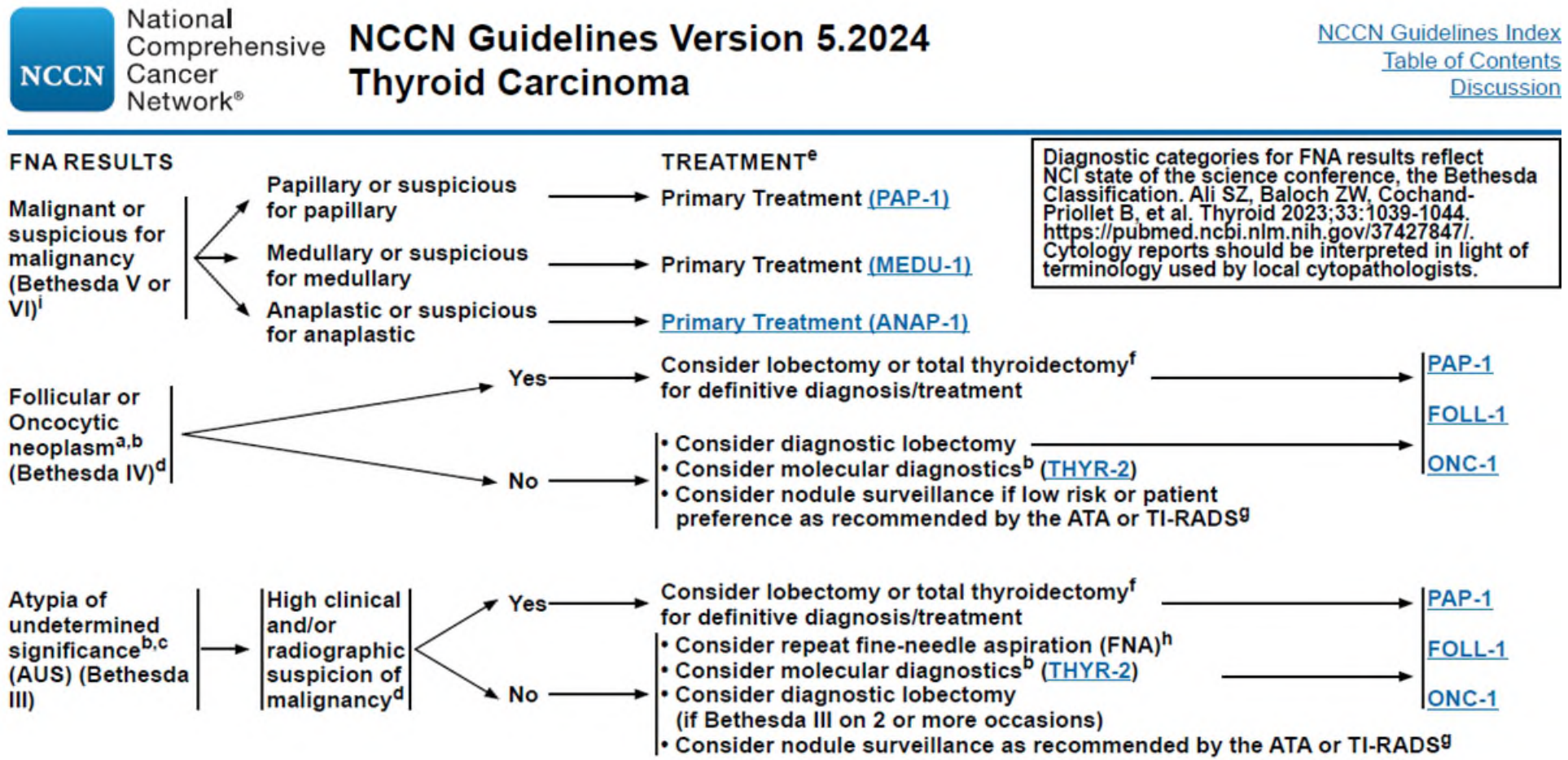
RECOMMENDATION 16

(A) Diagnostic surgical excision is the long-established standard of care for the management of FN/SFN cytology nodules. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery. Informed patient preference and feasibility should be considered in clinical decision-making.

(Weak recommendation, Moderate-quality evidence)

(B) If molecular testing is either not performed or inconclusive, surgical excision may be considered for removal and definitive diagnosis of an FN/SFN thyroid nodule.

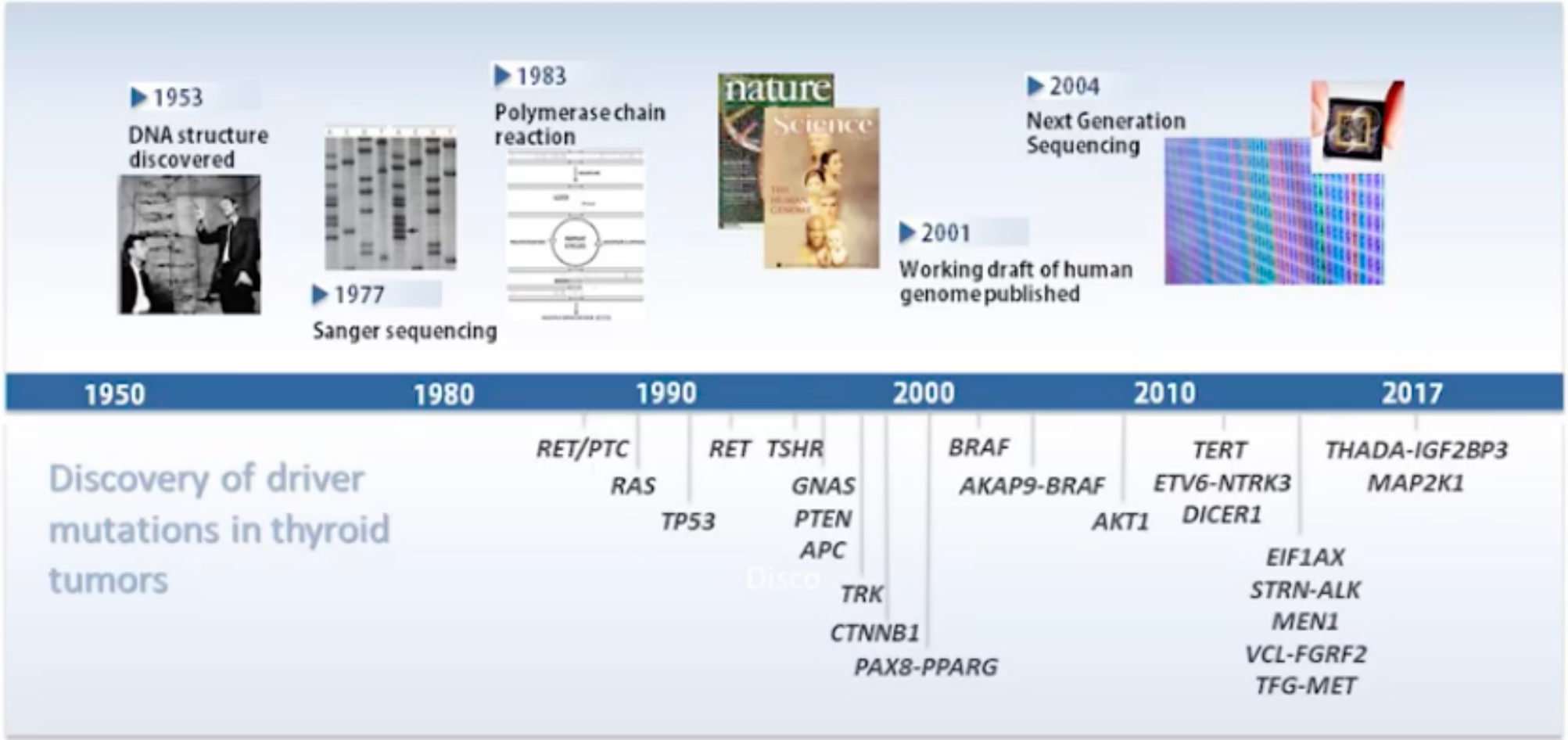
(Strong recommendation, Low-quality evidence)



Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw 16, 12; 10.6004/jnccn

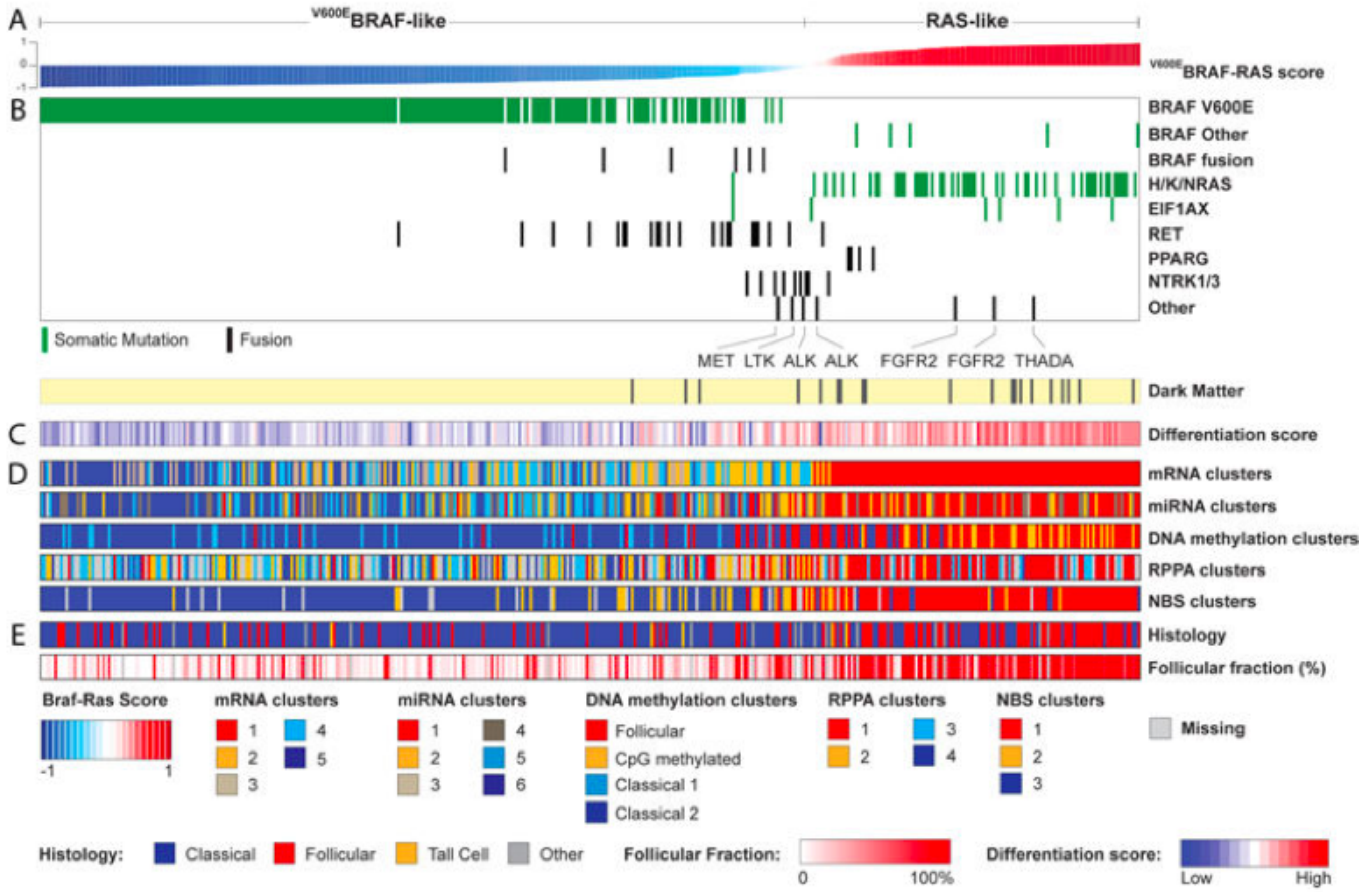
Basis of Molecular testing in thyroid nodules

Genetic Landscape of Thyroid Cancer



Slide courtesy of Dr. Y. Nikiforov

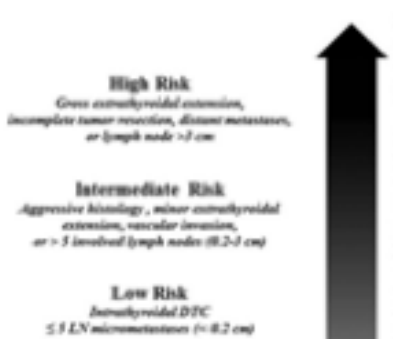
Thyroid Cancer Genome Atlas, 2014



- 496 PTC
- well differentiated, intra-thyroidal
- Sample from the central part of the tumor (homogenous)
- No poorly differentiated and no FTC
- Identified BRAF-like and RAS-like profiles

Agrawal N. et al, Integrated Genomic Characterization of Papillary Thyroid Carcinoma, Cell, Volume 159, Issue 3, 2014, Pages 676-690, https://doi.org/10.1016/j.cell.2014.09.050

2015 ATA Guidelines: Risk of Cancer Recurrence



AMERICAN THYROID ASSOCIATION
FOUNDED 1923

Molecular Signature

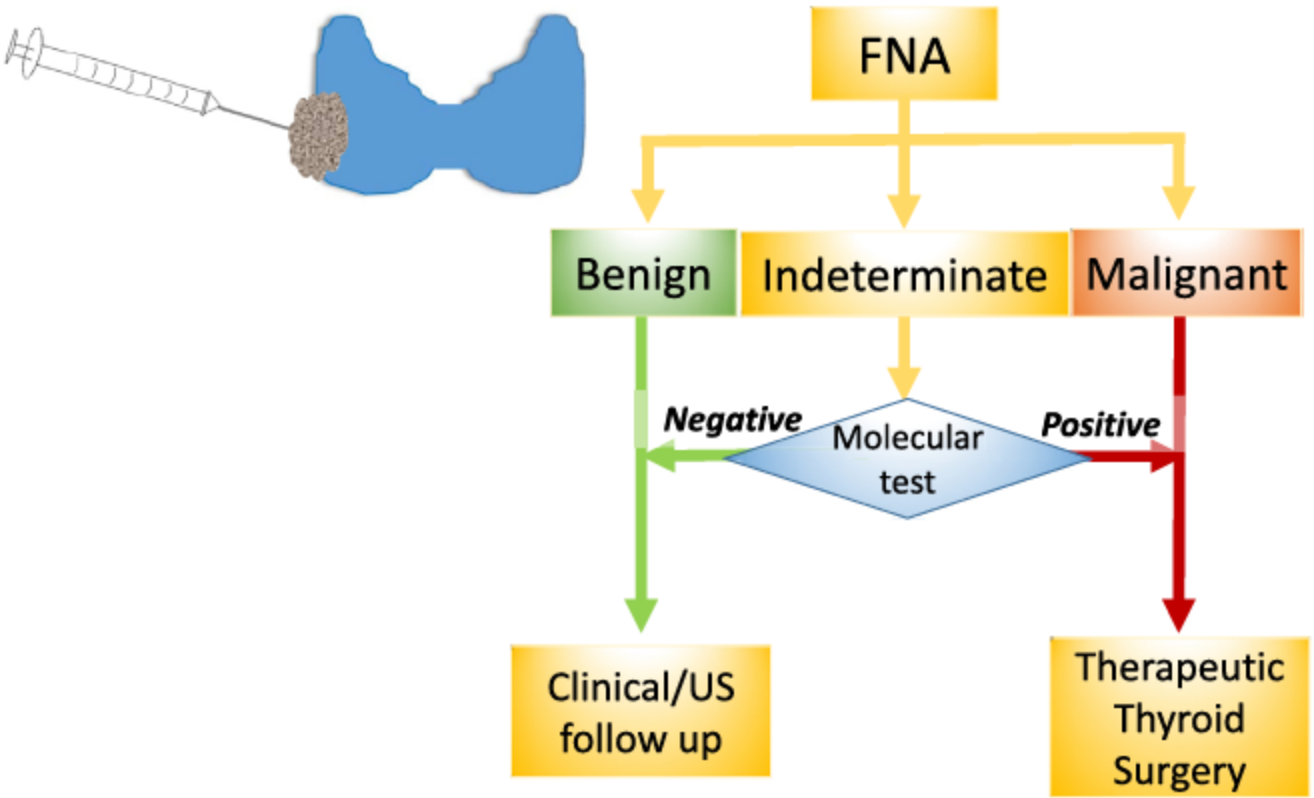
- **BRAF + TERT**
- **Multiple driver mutations (eg. NRAS and PIK3CA or TP53)**
- **TERT**

- **ALK fusions**
- **NTRK1 fusions**
- **NTRK3 fusions**
- **BRAF V600E**
- **RET/PTC**

- **RAS**
- **BRAF K601E**
- **PAX8/PPARγ**
- **PTEN**

Thyroid. 2016 Jan;26(1):1-133. doi: 10.1089/thy.2015.0020.
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer.

Ideal molecular test



Mayson SE & Haugen BR. Endocrinol Metab Clin North A.2019

Commercially available Molecular tests for indeterminate thyroid nodules

City of Hope®

Commercially available Molecular Tests

Afirma GSC

- RNA sequencing
- Expression profile of > 10000 genes, genetic alterations of 593 genes, 905 variants and 235 fusions
- Results: Benign or suspicious
- BRAF V600E, RET/PTC1, and RET/PTC3 mutations are described when present
- Xpression Atlas (XA) is a supplemental component which can be requested additionally in Afirma GSC “suspicious” cases
- It is described as additional DNA and fusion data, 593 genes informing on 905 variants and 235 fusions
- TERT DNA analysis is available on request

Thyroseq v3

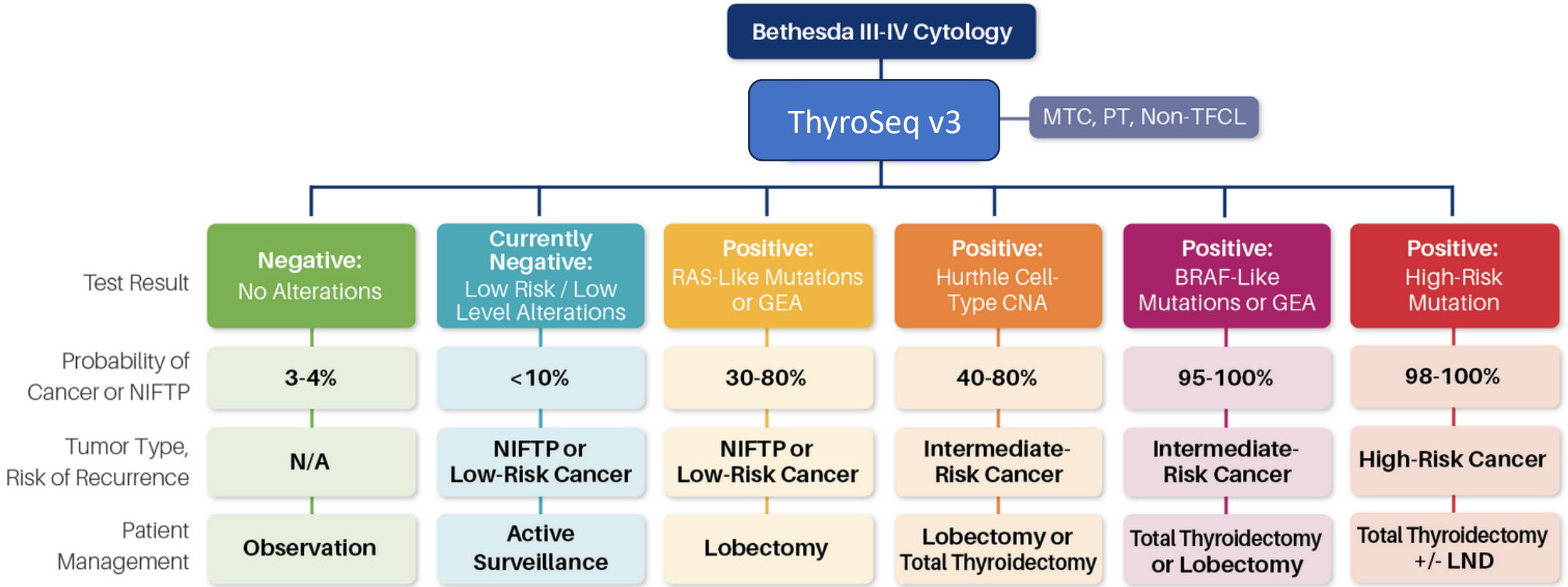
- DNA and RNA based sequencing
- analyzes 112 genes, providing information on >12,000 mutation hotspots and >150 gene fusion types
- Detects 4 classes of genetic alterations-mutations (indels),gene fusions,gene expression alterations and copy number variations (CNVs).
- Results: Negative, Currently negative and Positive
- Detailed information on types of genetic alterations detected, their association with a specific type of thyroid cancer, and with the risk of cancer recurrence

ThyGeNEXT/ThyraMIR v2

- DNA and RNA based sequencing+ miRNA evaluation
- 11 genes, 37 fusions and 11 miRNA
- Results: Negative, Moderate and Positive
- low-risk results lack detectable mutations/fusions AND miRNA results are not strongly positive
- moderate-risk results either lack detectable mutations/fusions BUT miRNA results are strongly positive or those that have weak driver mutations/fusions but miRNA results are not strongly positive
- high-risk results have strong driver mutations/fusions and those that have weak driver mutations or fusions in which microRNA results were strongly positive

Comparative Overview of Molecular Tests

Characteristics	ThyroSeq v3	Afirma GSC	ThyGeNEXT+ThyraMIR
Methodology	DNA+RNA seq	RNA seq	DNA+RNA Seq+ miRNA
Performance (BIII & BIV nodules)	NPV 97% PPV 66% Sens 94% Spec 82%	NPV 96% PPV 47% Sens 91% Spec 68%	NPV 95% PPV 74% Sens 93% Spec 90%
Prevalence of cancer	28%	24%	30%
Sample Accepted	1 dedicated pass+ Slides	1 dedicated pass	1 dedicated pass+ Slides
Detects BRAF V600E	YES	YES	YES
Detects ALK fusion	YES	NO	YES
Detects TERT promoter mutation	YES	NO	YES


Bethesda III-IV Cytology
ThyroSeq v3
MTC, PT, Non-TFCL
Test Result
Probability of Cancer or NIFTP
Tumor Type, Risk of Recurrence
Patient Management
Negative: No Alterations
3-4%
N/A
Observation
Currently Negative: Low Risk / Low Level Alterations
<10%
NIFTP or Low-Risk Cancer
Active Surveillance
Positive: RAS-Like Mutations or GEA
30-80%
NIFTP or Low-Risk Cancer
Lobectomy
Positive: Hurthle Cell-Type CNA
40-80%
Intermediate-Risk Cancer
Lobectomy or Total Thyroidectomy
Positive: BRAF-Like Mutations or GEA
95-100%
Intermediate-Risk Cancer
Total Thyroidectomy or Lobectomy
Positive: High-Risk Mutation
98-100%
High-Risk Cancer
Total Thyroidectomy +/- LND

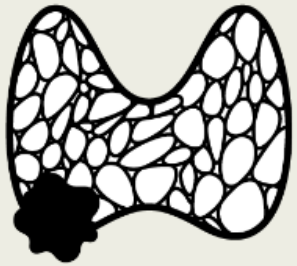
Comparison of the commercially available molecular tests

JAMA Oncology

RCT: Effectiveness of Molecular Testing Techniques for Diagnosis of Indeterminate Thyroid Nodules

POPULATION

80 Men, 266 Women



Thyroid nodule with indeterminate cytology results sent for molecular testing

Median (IQR) age, 55 (44-67) y

SETTINGS / LOCATIONS

9 Clinical sites in the UCLA Health system

INTERVENTION

346 Patients randomized and analyzed

189 Afirma genomic sequencing classifier
RNA expression–based testing

Artificial intelligence–based binary result (yes/no)

149 Thyroseq v3 multigene genomic classifer
DNA-RNA–based testing

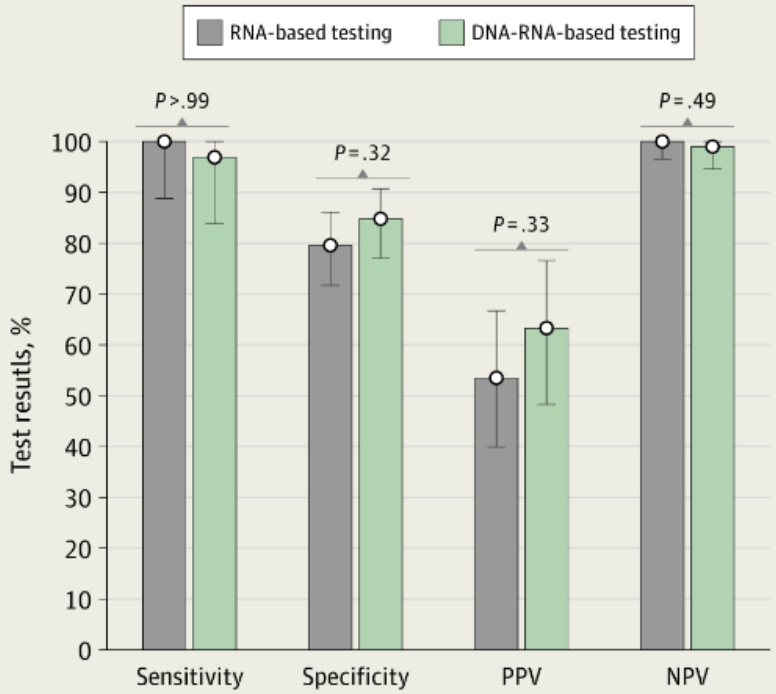
Numeric malignancy risk estimate

PRIMARY OUTCOME

Diagnostic test performance of RNA expression–based testing vs DNA-RNA–based testing as measured by sensitivity, specificity, and predictive values

FINDINGS

Differences in test performance were not statistically significant



Abbreviations: NPV, negative predictive value; PPV, positive predictive value

Livhits MJ, Zhu CY, Kuo EJ, et al. Effectiveness of molecular testing techniques for diagnosis of indeterminate thyroid nodules: a randomized clinical trial. *JAMA Oncol*. Published online November 19, 2020. doi:10.1001/jamaoncol.2020.5935

Table 2. Summary of the current commercially available molecular tests for indeterminate thyroid nodules and their validation studies

	ThyroSeq v.3		Afirma GSC			ThyGeNEXT/ThyraMIR
	Steward et al (107)	Lee et al (108)	Patel et al (109)	Vuong et al (110)	Lee et al (108)	Lupo et al (111)
Study type	Prospective	Meta-analysis	Prospective	Meta-analysis	Meta-analysis	Retrospective
Bethesda class	III and IV	III and IV	III and IV	III and IV	III and IV	III and IV
No. of nodules	247	530 (6 studies)	190	804	472 (7 studies)	178
Cancer prevalence	28%		24%			30%
Sensitivity	94%	95%	91%	94.3%	96%	93%
NPV	97%	92%	96%	90%	96%	95%
Specificity	82%	50%	68%	43%	53%	90%
PPV	66%	70%	47%	63.1%	63%	74%
Used as	Mainly a rule-out but also rule-in test		A rule-out test			Mainly a rule-out but also rule-in test
Methodology	NGS of DNA and RNA		NGS of mRNA and gene expression			NGS and mRNA sequencing, PCR miRNA expression

Abbreviations: NGS, next-generation sequencing; NPV, negative predictive value; PPV, positive predictive value.

Ali S Alzahrani, Clinical use of Molecular Data in Thyroid Nodules and Cancer, JCEM 2023 https://doi.org/10.1210

Cost Consideration

Cost consideration

- The study modeled a decision tree from the payor perspective
- Compares the cost-effectiveness of diagnostic lobectomy, ThyroSeq v3, and Afirma GSC for indeterminate (Bethesda III/IV) thyroid nodules
- Based on the model, the cost per correct diagnosis was $14,277 for ThyroSeq v3, $17,873 for Afirma GSC, and $38,408 for diagnostic lobectomy
- The study stated that in no range of tested cost variations was diagnostic lobectomy the preferred strategy over molecular testing.
- Costs were obtained from the Centers for Medicare & Medicaid Services (CMS) 2018 reimbursement schedule

Nicholson, K.J, Roberts, M.S., Mccoy, K.L., Carty, S.E., & Yip, L. (2019). Molecular Testing Versus Diagnostic Lobectomy in Bethesda III/IV Thyroid Nodules: A Cost-Effectiveness Analysis. *Thyroid 2019 Sep;29(9):1237-1243.*

COST-EFFECTIVENESS ANALYSIS OF MOLECULAR TESTING FOR CYTOLOGICALLY INDETERMINATE THYROID NODULES

Dharampal N, Smith K, Harvey A, Paschke R, Rudmik L, Chandarana S

OBJECTIVE

To evaluate the cost-effectiveness of Afirma, a commercially available molecular test, in indeterminate thyroid nodules

METHODS

Decision tree analysis from a single payer perspective with 1-year time horizon & micro-costing. Assessed cost per surgery avoided

RESULTS

Current management: diagnostic lobectomy after indeterminate thyroid cytology

Mean cost estimates

$8176.28 *0.58 effectiveness*
Molecular testing strategy

VS.

$6016.83 *0.07 effectiveness*
Current standard management

At willingness-to-pay threshold of $5000 per surgery avoided, molecular testing is cost-effective with 63% certainty

With a $5000 willingness-to-pay threshold, molecular testing has a 63% chance of being the more cost effective strategy for avoiding unneccessary surgery for indeterminate thyroid nodules

JOURNAL OF OTOLARYNGOLOGY - HEAD & NECK SURGERY
THE OFFICIAL JOURNAL OF THE CANADIAN SOCIETY OF OTO-HNS

UNIVERSITY OF CALGARY

Dharampal N et al. Cost-effectiveness analysis of molecular testing for cytologically indeterminate thyroid nodules. J Otolaryngol Head Neck Surg. 2022 Dec 21;51(1):46. doi: 10.1186/s40463-022-00604-7.

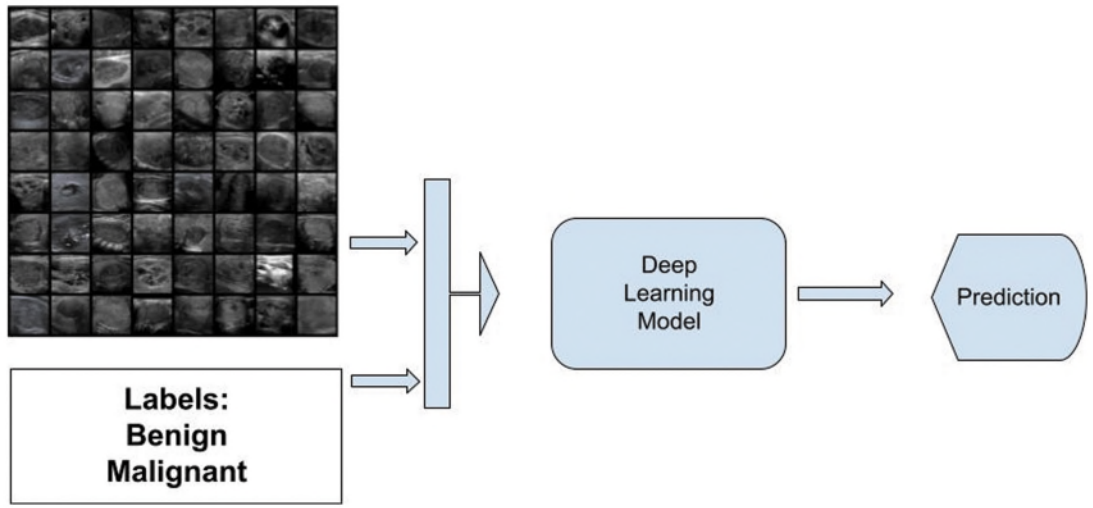
Limitations of Molecular testing

- The natural history of mutation-negative cytologically indeterminate nodules has not yet been characterized and require ongoing surveillance
- The NPV and PPV of diagnostic testing vary with prevalence of malignancy which is geographically and institutionally variable
- Histologic classification of follicular patterned lesions is associated with an approximately 70% inter-observer and intra-observer variability
- For tests providing prognostic information, it is not yet known if the preoperative detection of such markers should alter the initial extent of surgery

Marti JL, Avadhani V, Donatelli LA, et al. Wide inter-institutional variation in performance of a molecular classifier for indeterminate thyroid nodules. Ann Surg Oncol 2015;22(12):3996–4001.

Future Directions

- Role of AI in thyroid nodule evaluation and management in various stages- Interpretation of Thyroid US images and thyroid nodule risk classification, interpretation of cytology slides and cytological diagnosis, interpretation of molecular tests and risk stratification



Tessler FN, Thomas J. Artificial Intelligence for Evaluation of Thyroid Nodules: A Primer. Thyroid. 2023 Feb;33(2):150-158. doi: 10.1089/thy.2022.0560. Epub 2023 Jan 25. PMID: 36424829.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