TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER™ EL PASO

Texas Tech University Health Sciences Center El Paso
Neoplastic Diseases: Update for Practitioners
June14th, 2019

"Evaluation and Management of Thyroid Nodules by Fine Needle Aspiration Cytology, Endocrine Perspective"

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Disclosures

None

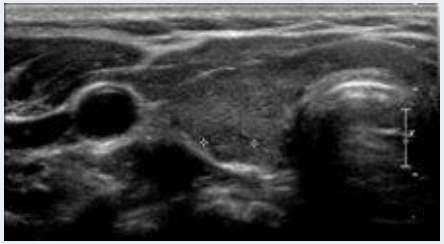
Objectives

- Understand the diagnostic approach and evaluation of thyroid nodules

- Recognize the utility of molecular testing in the management and follow up of thyroid nodules with indeterminate cytology

Background

- Thyroid nodules are common and most of the time benign.
- Prevalence: depends on the population studied and the methods used to detect nodules:

	Prevalence[1]
Palpation 	2-6%
Ultrasound 	19-35%
Autopsy	8-65%

1- Dean DS et all. Best Pract Res Clin Endocrinol Metab. 2008 Dec;22(6):901-11

Background

- Incidence is higher in women and increases with:
  - Age, Iodine deficiency, and after radiation exposure.[1]
- Overall malignancy rate: 5-10%.[2]
- Lifetime risk of being diagnosed with thyroid cancer = 1.1% [3]

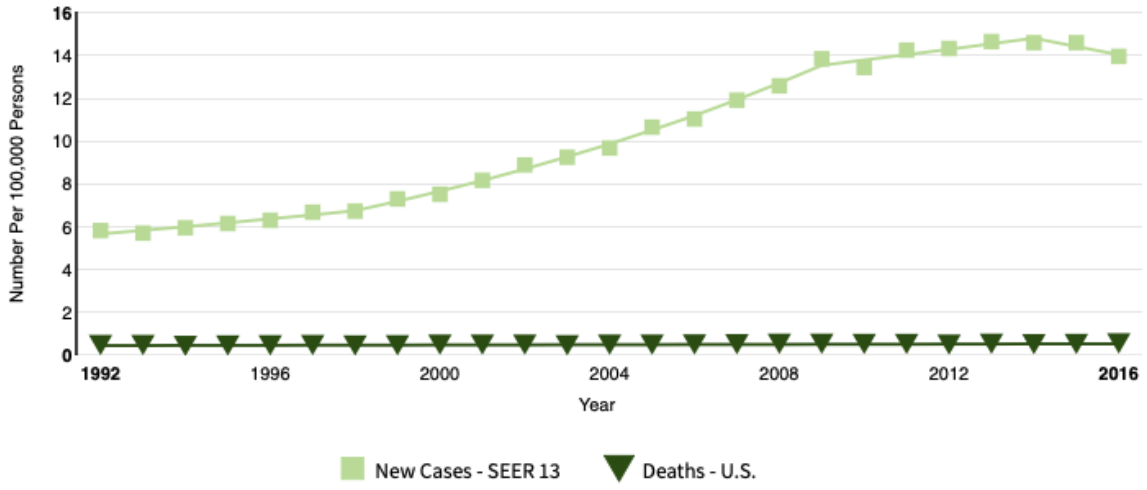
1- Dean DS et all. Best Pract Res Clin Endocrinol Metab. 2008 Dec;22(6):901-11
2- Hegedus, L. N Engl J Med. 2004 Oct 21;351(17):1764-71
3-Howlander et al. SEER Cancer Review 1975-2012. SEER Web Site, 04/2015

Background

NEW!		
	Estimated New Cases in 2019	52,070
	% of All New Cancer Cases	3.0%

Estimated Deaths in 2019	2,170
% of All Cancer Deaths	0.4%

Percent Surviving 5 Years
98.2%
2009-2015



1- National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER)

THYROID
Volume 26, Number 1, 2016

DOI: 10.1089/thy.2015.0020

SPECIAL ARTICLE

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

Bryan R. Haugen,[1,*] Erik K. Alexander,[2] Keith C. Bible,[3] Gerard M. Doherty,[4] Susan J. Mandel,[5] Yuri E. Nikiforov,[6] Furio Pacini,[7] Gregory W. Randolph,[8] Anna M. Sawka,[9] Martin Schlumberger,[10] Kathryn G. Schuff,[11] Steven I. Sherman,[12] Julie Ann Sosa,[13] David L. Steward,[14] R. Michael Tuttle,[15] and Leonard Wartofsky[16]

- Seventy recommendations for Differentiated Thyroid Cancer!

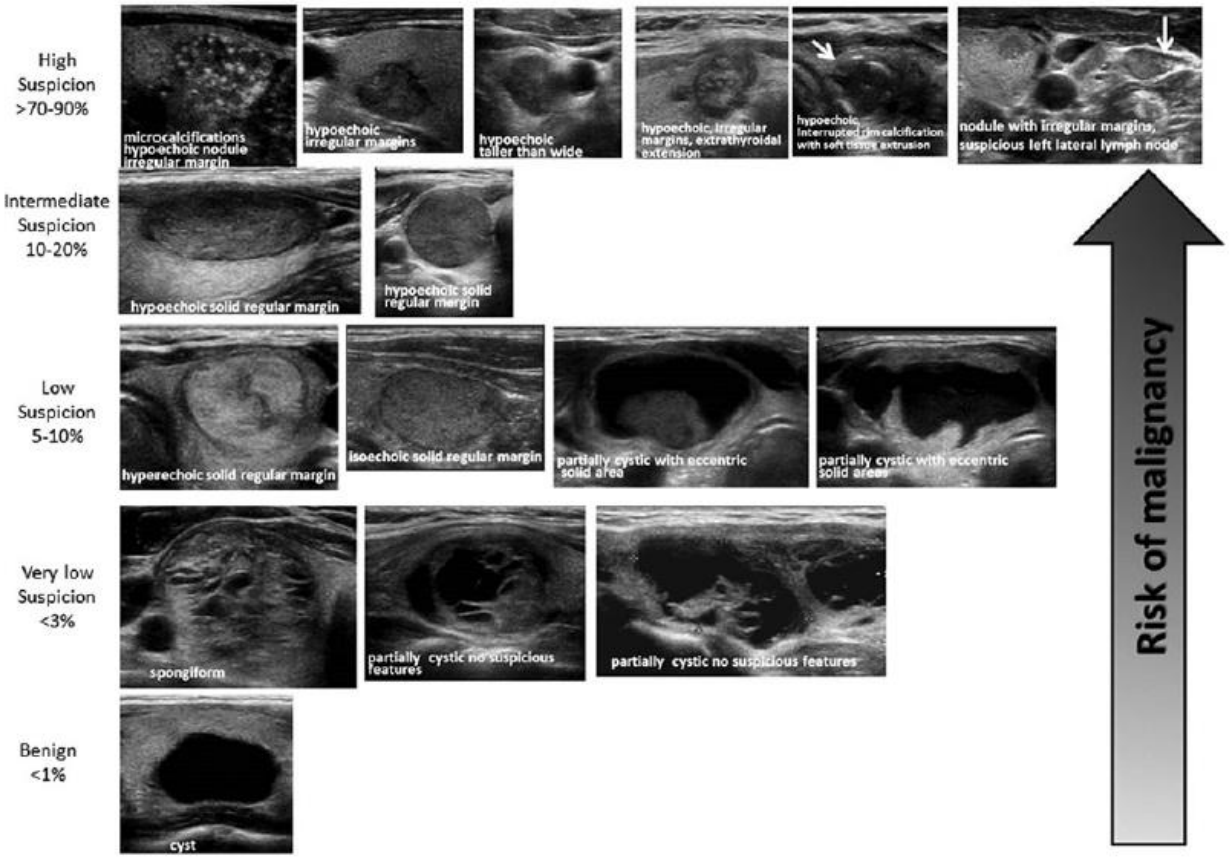
Thyroid Nodules - How to differentiate between benign and suspicious?

- Complete history
- Identify risk factors:
  - Childhood head and neck radiation therapy
  - Total body radiation for bone marrow transplantation
  - Exposure to ionizing radiation from fallout in childhood or adolescence
  - Familial thyroid carcinoma
  - Excess of thyroid hormone
- Physical examination focusing on the thyroid gland and cervical lymph nodes
- Labs

Thyroid Nodules - Management

1. Physical exam
2. Labs
3. **Thyroid ultrasound**
4. FNA?

ATA Nodule Sonographic Patterns and Risk of Malignancy



Haugen BR et al. Thyroid. 2016 Jan;26(1):1-133.
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

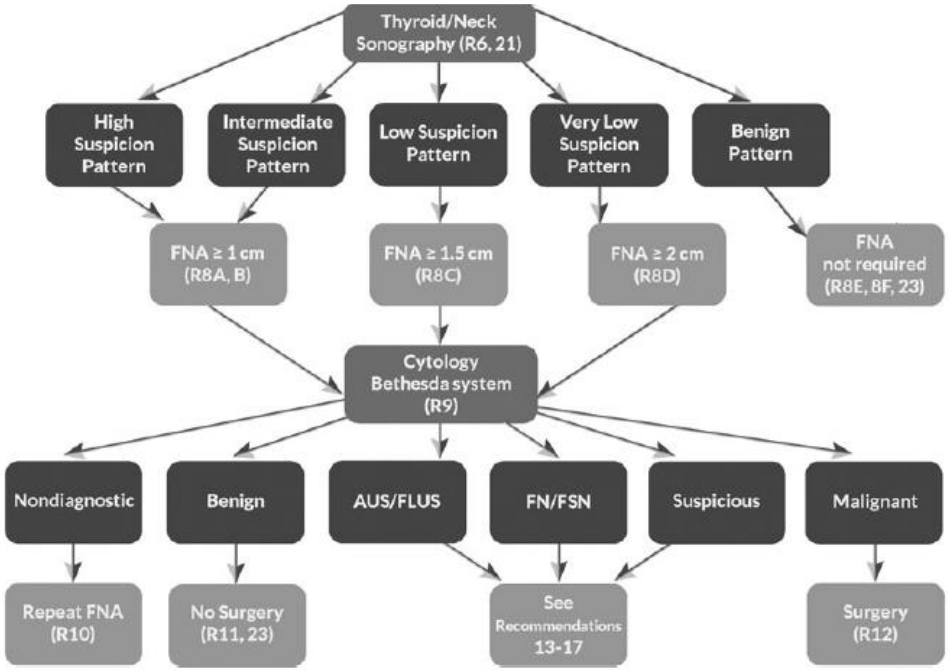
Do all thyroid nodules need a biopsy?

- Depends on US findings, size and suspicion
- NO biopsy
  - Size: <1 cm
  - Purely cystic

- YES biopsy
  - >1 cm with intermediate and high suspicion
  - >1.5 cm with low suspicion

- CONSIDER biopsy
  - >2cm with very low suspicion

Thyroid Nodules - Management



Algorithm for evaluation and management of patients with thyroid nodules based on US pattern and FNA cytology

Haugen BR et al. Thyroid. 2016 Jan;26(1):1-133.
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

Thyroid Nodules - Management

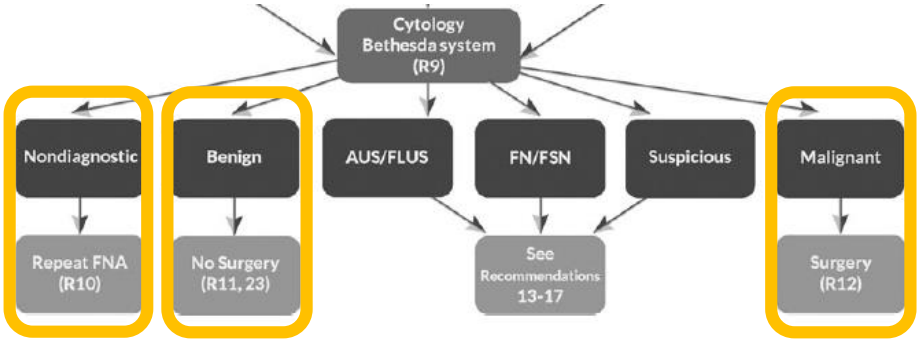
The Bethesda System for Reporting Thyroid Cytopathology with implied risk of malignancy and recommended clinical management

Diagnostic category	*Risk of malignancy (%)* [1]
I. Nondiagnostic or unsatisfactory	1-4
II. Benign	0-3
III. AUS or FLUS	5-15
IV. Follicular neoplasm or suspicious for a follicular neoplasm	15-30
V. Suspicious for malignancy	60-75
VI. Malignant	97-99

AUS: Atypia of undetermined significance, FLUS: Follicular lesion of undetermined significance, FNA: Fine needle aspiration

1- As reported in The Bethesda System by Cibas and Ali (1076).

FNA cytology results



- If initial nondiagnostic cytology result--> Repeat FNA
- Repeatedly nondiagnostic nodules might have indication for surgical excision for histopathologic diagnosis
- If the nodule is benign on cytology, further *immediate* diagnostic studies or treatment are not required
- If a cytology result is diagnostic for primary thyroid malignancy --> surgery

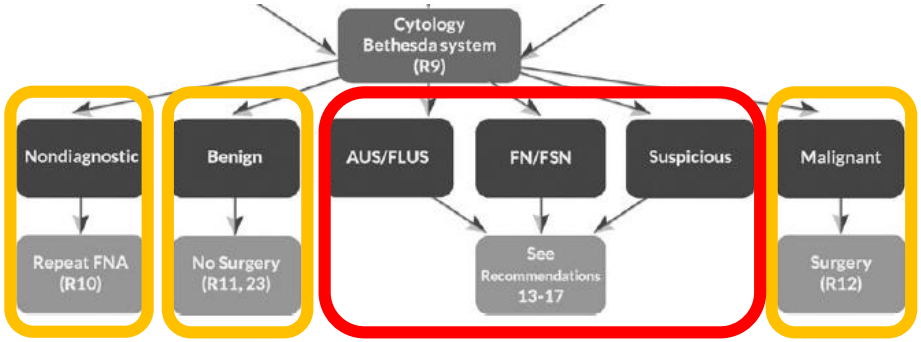
Haugen BR et al. Thyroid. 2016 Jan;26(1):1-133.
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

Malignant FNA cytology results

- Surgery.
  - Active surveillance management approach can be considered:
  - ❑ Patients with very low risk tumors (e.g., papillary microcarcinomas without clinically evident metastases or local invasion, and no convincing cytologic evidence of aggressive disease)
  - ❑ Patients at high surgical risk because of comorbid conditions
  - ❑ Patients expected to have a relatively short remaining life span (e.g., serious cardiopulmonary disease, other malignancies, very advanced age), or
  - ❑ Patients with concurrent medical or surgical issues that need to be addressed prior to thyroid surgery.

Haugen BR et al. Thyroid. 2016 Jan;26(1):1-133.
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

FNA cytology results



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FNA cytology results

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- Traditionally, patients with AUS or FLUS would undergo repeat FNA.
- Cytology results with Follicular neoplasms or suspicious for follicular neoplasms would be referred for diagnostic surgery.
- 70% to 80% of these nodules ultimately prove to be benign by surgical histopathology.
- Patients with confirmed thyroid cancer may not receive the surgery they need. [1]

1- Baloch ZW, et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. *Diagn Cytopathol*. 2008;36:425-437

Indeterminate FNA cytology results

- Diagnostic uncertainty
- Often resulting in repeat FNA and/or unnecessary diagnostic surgery
- These limitations have led to the emergence of molecular testing to improve diagnostic accuracy of FNA cytology

Role of molecular studies in Indeterminate FNA cytology results

- To identify patients who can avoid unnecessary surgery – while minimizing the risk of missing cancer.[1]
- Many markers are in development

1- Shanik, M. How Might Molecular Testing Advances the Care of Patients with Thyroid Nodules?

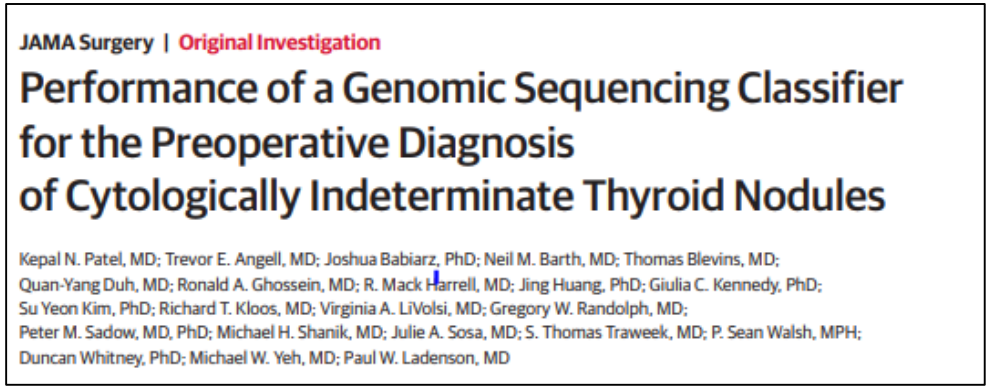
Role of molecular studies in Indeterminate FNA cytology results

- Two principal tests are currently in the market to improve the malignancy risk assessment of "indeterminate" cytology:
  - "Rule In" → attempt to confirm the presence of cancer in a thyroid nodule.
    - Assess for the presence of single gene point mutations (BRAF or RAS) or gene rearrangements (RET/PTC, PAX8/PPARγ) known to increase the ability to predict cancer
  - "Rule Out" → attempt to exclude the presence of cancer in a thyroid nodule.
    - Proprietary gene expression classifier (RNA expression) designed to maximize the ability to define a process as benign[1]

1- Woeber KA . Writing Group for the AACE Thyroid Scientific Committee

Role of molecular studies in Indeterminate FNA cytology results

- Rule out test: Afirma®



JAMA Surgery | Original Investigation

Performance of a Genomic Sequencing Classifier for the Preoperative Diagnosis of Cytologically Indeterminate Thyroid Nodules

Kepal N. Patel, MD; Trevor E. Angell, MD; Joshua Babiarz, PhD; Neil M. Barth, MD; Thomas Blevins, MD; Quan-Yang Duh, MD; Ronald A. Ghossein, MD; R. Mack Harrell, MD; Jing Huang, PhD; Giulia C. Kennedy, PhD; Su Yeon Kim, PhD; Richard T. Kloos, MD; Virginia A. LiVolsi, MD; Gregory W. Randolph, MD; Peter M. Sadow, MD, PhD; Michael H. Shanik, MD; Julie A. Sosa, MD; S. Thomas Traweek, MD; P. Sean Walsh, MPH; Duncan Whitney, PhD; Michael W. Yeh, MD; Paul W. Ladenson, MD

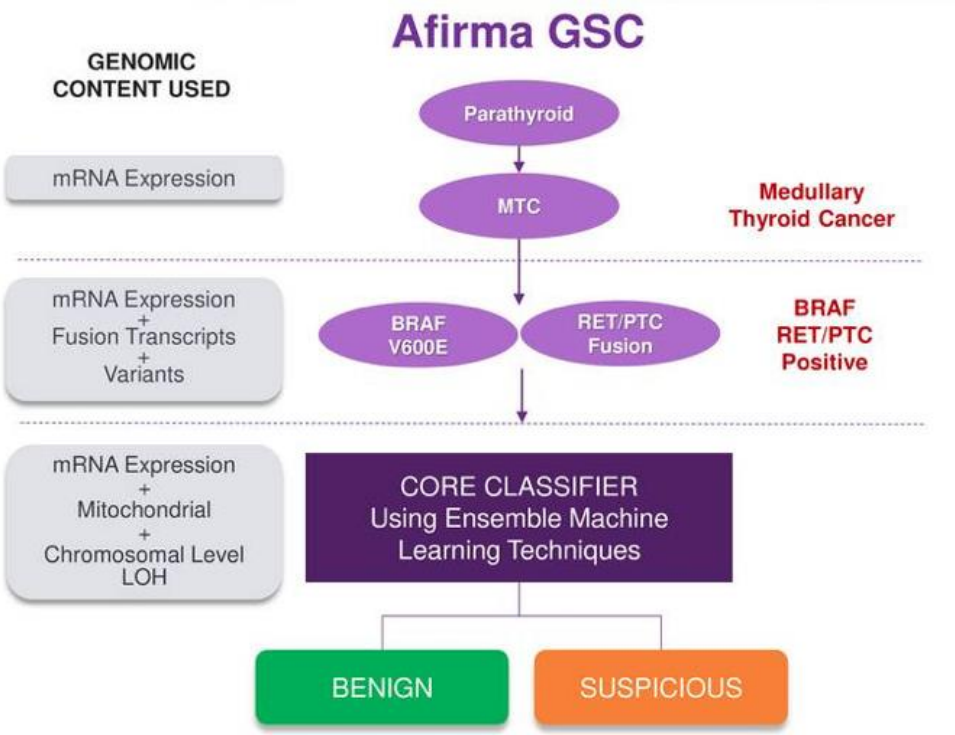
1- Patel, KN et al. JAMA Surg. 2018;153(9):817-824.

Role of molecular studies in Indeterminate FNA cytology results

- Retrospective, blinded study conducted on 49 academic and community centers in the United States. FNA samples from June 2009 and December 2010.
- All patients underwent surgery without genomic information and were assigned a histopathology diagnosis by an expert panel blinded to all genomic information.
- 210 potentially eligible thyroid biopsy samples with Bethesda III or IV indeterminate cytopathology.
- The genomic sequencing classifier had a sensitivity of 91% (95% CI, 79-98) and a specificity of 68% (95% CI, 60-76).
- At 24% cancer prevalence, the negative predictive value was 96% (95% CI, 90-99) and the positive predictive value was 47% (95% CI, 36-58).

1- Patel, KN et al. JAMA Surg. 2018;153(9):817-824.

Role of molecular studies in Indeterminate FNA cytology results



1-Image courtesy of Veracyte

Role of molecular studies in Indeterminate FNA cytology results

- Rule in test: ThyroSeq v3®

JAMA Oncology | Original Investigation

Performance of a Multigene Genomic Classifier in Thyroid Nodules With Indeterminate Cytology
A Prospective Blinded Multicenter Study

David L. Steward, MD; Sally E. Carty, MD; Rebecca S. Sippel, MD; Samantha Peiling Yang, MBBS, MRCP, MMed; Julie A. Sosa, MD, MA; Jennifer A. Sipos, MD; James J. Figge, MD, MBA; Susan Mandel, MD, MPH; Bryan R. Haugen, MD; Kenneth D. Burman, MD; Zubair W. Baloch, MD, PhD; Ricardo V. Lloyd, MD, PhD; Raja R. Seethala, MD; William E. Gooding, MS; Simion I. Chiosea, MD; Cristiane Gomes-Lima, MD; Robert L. Ferris, MD, PhD; Jessica M. Folek, MD; Raheela A. Khawaja, MD; Priya Kundra, MD; Kwok Seng Loh, MBBS; Carrie B. Marshall, MD; Sarah Mayson, MD; Kelly L. McCoy, MD; Min En Nga, MBBS; Kee Yuan Ngiam, MBBS, MRCS, MMed; Marina N. Nikiforova, MD; Jennifer L. Poehls, MD; Matthew D. Ringel, MD; Huaitao Yang, Md, PhD; Linwah Yip, MD; Yuri E. Nikiforov, MD, PhD

1- Steward, DL et al. JAMA Oncol. Nov, 2018;5(2):204-212.

Role of molecular studies in Indeterminate FNA cytology results

- Prospective, blinded cohort study conducted at 10 medical centers, with 782 patients with 1013 nodules enrolled.
- Total of 286 FNA samples from thyroid nodules underwent molecular analysis using the multigene GC (ThyroSeq v3).
- In Bethesda III and IV nodules combined, the test demonstrated a 94% sensitivity and 82% specificity.
- With a cancer/NIFTP prevalence of 28%, the negative predictive value (NPV) was 97% (95% CI, 93%-99%) and the positive predictive value (PPV) was 66% (95% CI, 56%-75%).

1- Steward, DL er al. JAMA Oncol. 2019;5(2):204-212.

Role of molecular studies in Indeterminate FNA cytology results

- Highest NPV and PPV among well validated tests
- Highest reduction in diagnostic surgery – allowing avoidance of surgery for up to 61% of all Bethesda III/IV nodules and 82% of indeterminate nodules with benign pathology
- Reliable detection of all types of thyroid tumors including Hurthle cell cancer
- Reports probability of cancer and predicted risk of cancer recurrence, empowering individualized patient management

1- Steward, DL er al. JAMA Oncol. 2019;5(2):204-212.

	ThyroSeq GC[1]	*Afirma GSC*[2]
Study type	Multicenter, prospective, double-blind	Multicenter, retrospective, double-blind
Total number, samples	247	191
Nodule size by ultrasound, median (range), cm	2.1 (0.5-7)	2.6 (1.0-9.1)
Disease prevalence	27.5%	23.7%
Sensitivity, (95%CI)	94.1% (86-98%)	91.1% (79-98%)
Specificity, (95%CI)	81.6% (75-87%)	68.3% (60-76%)
NPV	97.3% (93-99%)	96.1% (90-99%)
PPV	65.9% (56-75%)	47.1% (36-58%)
Benign call rate	61%	54%
Avoidable surgeries for histologically benign nodules with indeterminate cytology	82%	68%

Initial follow-up of nodules with benign FNA cytology

- Follow-up should be determined by risk stratification based upon US pattern.
  - Nodules with high suspicion US pattern: repeat US and US-guided FNA within 12 months.
  - Nodules with low to intermediate suspicion US pattern: repeat US at 12–24 months. If sonographic evidence of growth (20% increase in at least two nodule dimensions) or new suspicious sonographic features, the FNA could be repeated or observation continued with repeat US, with repeat FNA in case of continued growth.
  - Nodules with very low suspicion US pattern: If US is repeated, it should be done at ≥24 months.

Follow-up of nodules with two benign FNA cytology results

- If a nodule has undergone repeat US-guided FNA with a second benign cytology result, US surveillance for this nodule for continued risk of malignancy is no longer indicated.

Take home points

- Thyroid nodules are common but just a very small percentage are malignant
- Not all thyroid nodules have indication for biopsy
- Molecular markers are promising to decrease rate of unnecessary thyroid surgeries
- More advances in the molecular testing field will provide additional valuable diagnostic information to guide appropriate treatment for patients with thyroid nodules and will likely aim to guide surgical management in a considerable number of cases.