The Role of Molecular Markers in Surgical Decision-Making

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University of California, San Francisco

Turkish Association of Endocrine Surgeons
Antalya, Turkey, April 29, 2017

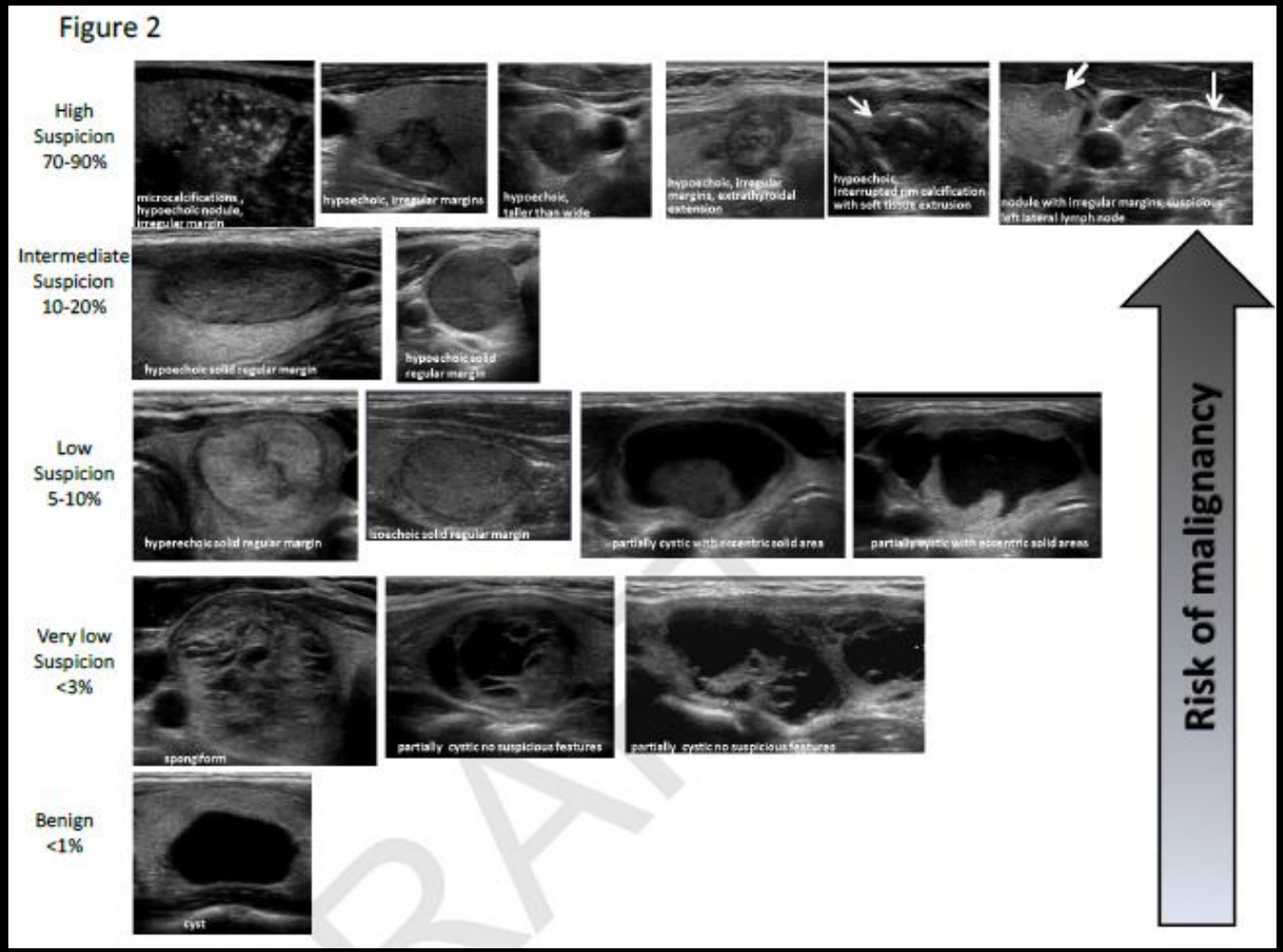
No Conflicts to Declare

How do we know if a thyroid nodule is a cancer? How sure are we?

- BUENOS AIRES, Dec. 28 (UPI) -- Argentine President Cristina Fernandez de Kirchner has been diagnosed with thyroid cancer and is scheduled to have surgery next week, her spokesman said.
- Presidential spokesman Alfredo Scoccimarro said the cancer was detected Dec. 22, stressing it "has not metastasized," the Buenos Aires Herald reported Wednesday.
- Fernandez will undergo surgery Jan. 4 and is on a leave of absence until Jan. 24, 2012. Vice President Amado Boudou will be in charge until her return, government officials said.

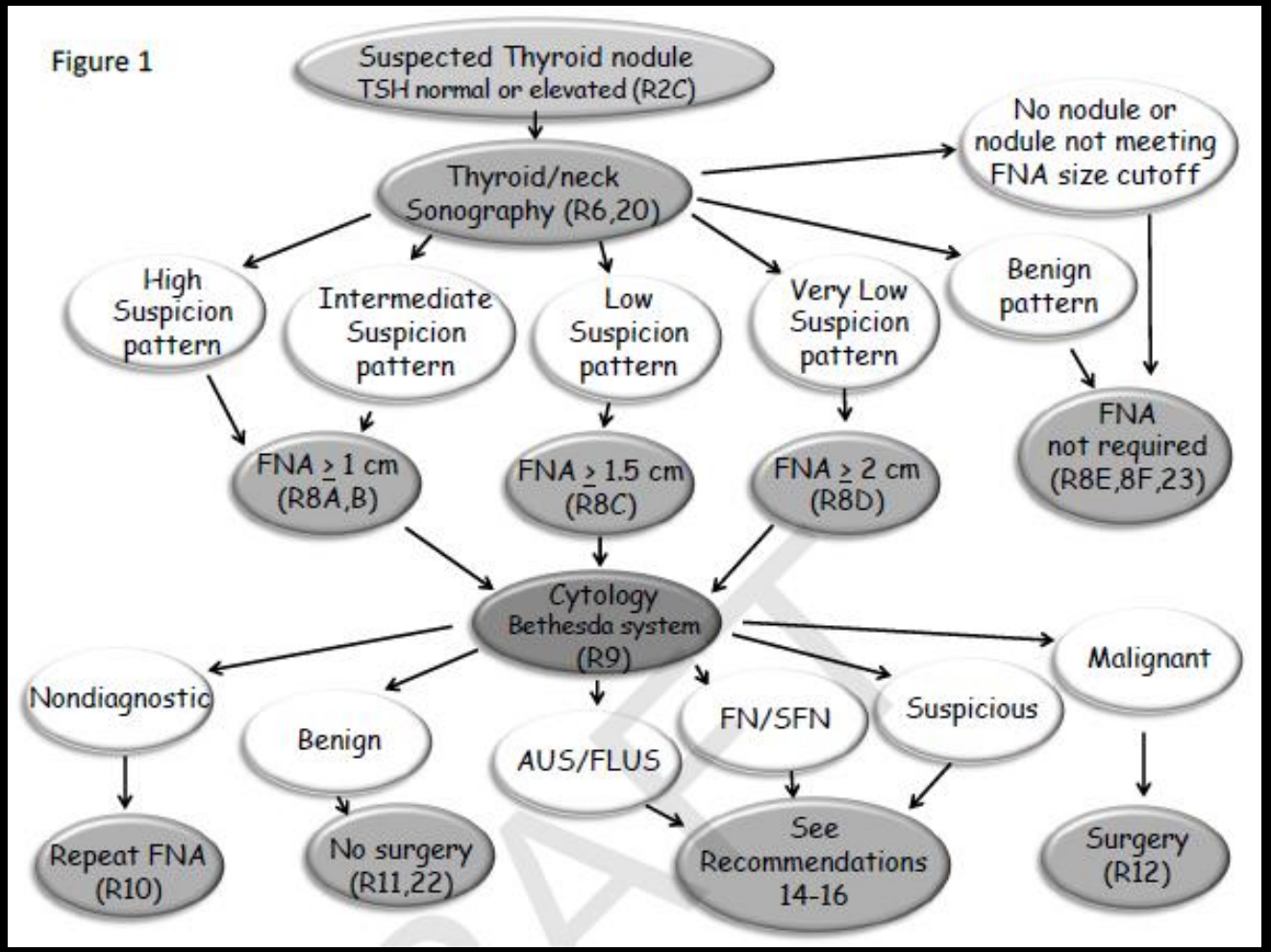
- BUENOS AIRES (Reuters) — President Cristina Fernández de Kirchner of Argentina never had thyroid cancer despite a diagnosis of the disease last month, her spokesman said on Saturday.
- "…an examination of her thyroid gland, which was removed Wednesday, had found no cancerous cells."
- "Eduardo Faure, a thyroid cancer expert in Buenos Aires who is not on the president's medical team, said a small number of such cases turned out to be "false positives." "The cells may originally appear to be cancer, but in 2 percent of cases, after the operation, when a more thorough examination can be performed, it turns out they are not," he said.

ATA Guidelines 2015
FNA based on US features



Haugen BR, et al. Thyroid 26:1-133, 2016

FNA based on US features
Cytology based on Bethesda System



Haugen BR, et al. Thyroid 26:1-133, 2016

The Bethesda System for Reporting Thyroid Cytopathology

I. Nondiagnostic/unsatisfactory

II. Benign

III. Atypia or follicular lesion of undetermined significance

IV. Follicular neoplasm

V.Suspicious for malignancy

VI. Malignant

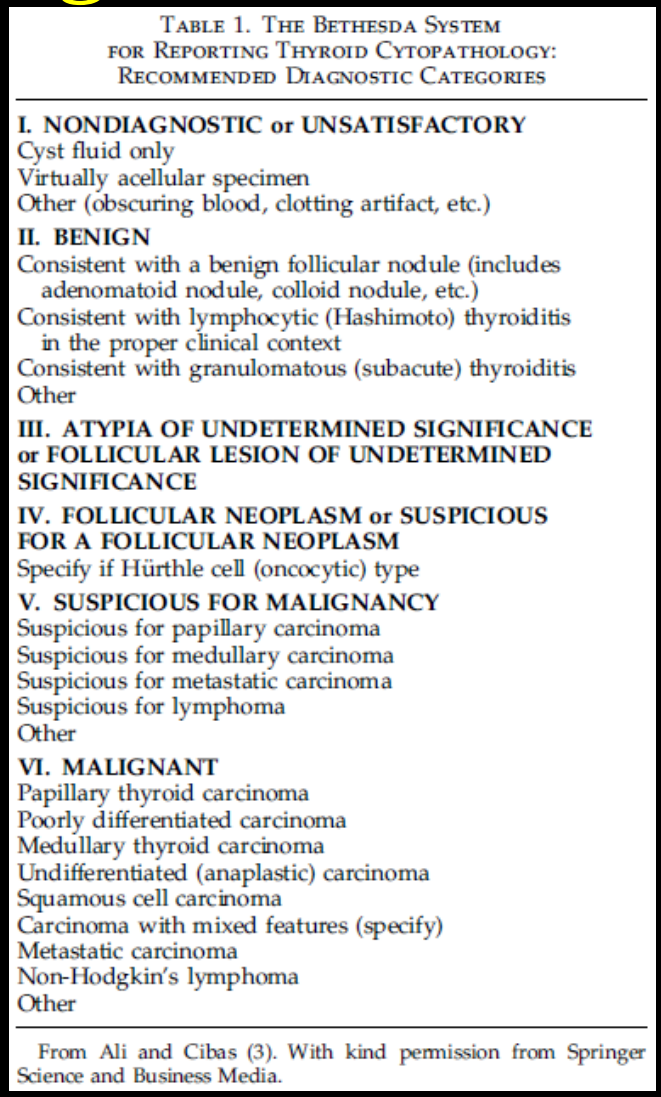


TABLE 1. THE BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY: RECOMMENDED DIAGNOSTIC CATEGORIES

I. NONDIAGNOSTIC or UNSATISFACTORY
Cyst fluid only
Virtually acellular specimen
Other (obscuring blood, clotting artifact, etc.)

II. BENIGN
Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)
Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
Consistent with granulomatous (subacute) thyroiditis
Other

III. ATYPIA OF UNDETERMINED SIGNIFICANCE or FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE

IV. FOLLICULAR NEOPLASM or SUSPICIOUS FOR A FOLLICULAR NEOPLASM
Specify if Hürthle cell (oncocytic) type

V. SUSPICIOUS FOR MALIGNANCY
Suspicious for papillary carcinoma
Suspicious for medullary carcinoma
Suspicious for metastatic carcinoma
Suspicious for lymphoma
Other

VI. MALIGNANT
Papillary thyroid carcinoma
Poorly differentiated carcinoma
Medullary thyroid carcinoma
Undifferentiated (anaplastic) carcinoma
Squamous cell carcinoma
Carcinoma with mixed features (specify)
Metastatic carcinoma
Non-Hodgkin's lymphoma
Other

From Ali and Cibas (3). With kind permission from Springer Science and Business Media.

Cibas ES, Ali SZ. Thyroid. 2009 Nov;19(11):1159-65.
NCI State of the Science Conference Oct 22-23, 2007

The Bethesda System for Reporting Thyroid Cytopathology

TABLE 2. THE BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY: IMPLIED RISK OF MALIGNANCY AND RECOMMENDED CLINICAL MANAGEMENT

Diagnostic category		*Risk of malignancy (%)*		*Usual management*[a]
Nondiagnostic or unsatisfactory		1–4		Repeat FNA with ultrasound guidance
Benign		0–3		Clinical follow-up
Atypia of undetermined significance or follicular lesion of undetermined significance	**Atypia**	~5–15[b]	**10%**	Repeat FNA
Follicular neoplasm or suspicious for a follicular neoplasm	**Follicular**	15–30	**20%**	Surgical lobectomy
Suspicious for malignancy	**Suspicious**	60–75	**70%**	Near-total thyroidectomy or surgical lobectomy[c]
Malignant		97–99		Near-total thyroidectomy[c]

Modified from Ali and Cibas (3). With kind permission from Springer Science and Business Media.

[a]Actual management may depend on other factors (e.g., clinical and sonographic) besides the FNA interpretation.

[b]Estimate extrapolated from histopathologic data from patients with "repeated atypicals."

[c]In the case of "suspicious for metastatic tumor" or a "malignant" interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

Cibas ES, Ali SZ. Thyroid. 2009 Nov;19(11):1159-65.
NCI State of the Science Conference Oct 22-23, 2007

Options for Thyroid Nodules with Indeterminate FNA Cytology

- Bethesda III (AUS/FLUS), 10% risk cancer
  - Diagnostic lobectomy, repeat FNA, observation
- Bethesda IV (follicular neoplasm), 20% risk
  - Diagnostic lobectomy
- Bethesda V (suspicious for cancer), 70%
  - Diagnostic lobectomy with frozen section (PTC)

Molecular Testing

- Mutational analysis (DNA)
  - Oncogenes
    - Point mutations, rearrangements
  - Tumor suppressor genes
- Gene expression classifier (RNA)
  - Profile of RNA expression

Mutational Analysis

Molecular Testing for Cytologically Indeterminate Nodules

Impact of Mutational Testing on the Diagnosis and Management of Patients with Cytologically Indeterminate Thyroid Nodules: A Prospective Analysis of 1056 FNA Samples

Yuri E. Nikiforov, N. Paul Ohori, Steven P. Hodak, Sally E. Carty, Shane O. LeBeau, Robert L. Ferris, Linwah Yip, Raja R. Seethala, Mitchell E. Tublin, Michael T. Stang, Christopher Coyne, Jonas T. Johnson, Andrew F. Stewart, and Marina N. Nikiforova

Departments of Pathology and Laboratory Medicine (Y.E.N., N.P.O., R.R.S., M.N.N.), Surgery (S.E.C., L.Y., M.T.S.), Otolaryngology and Head Neck Surgery (R.L.F., J.T.J.), and Radiology (M.E.T.), and Division of Endocrinology (S.P.H., S.O.L., C.C., A.F.S.), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

Nikiforov YE et al. JCEM 118:3390-7, 2011

Molecular Testing for Cytologically Indeterminate Nodules

- 1056 consecutive FNA cytology indeterminate
- PCR for point mutations & rearrangements
  - *BRAF* V600E, *NRAS* 61, *HRAS* 61, *KRAS* 12/13
  - *RET/PTC1*, *RET/PTC3*, *PAX8/PPAR*.
- 967 yielded 87 mutations
  - 19 *BRAF*, 62 *RAS*, 1 *RET/PTC*, 5 *PAX8/PPAR*.
- 479 pts (513 samples) had surgery

Nikiforov YE et al. JCEM 118:3390-7, 2011

Molecular Testing for Cytologically Indeterminate Nodules

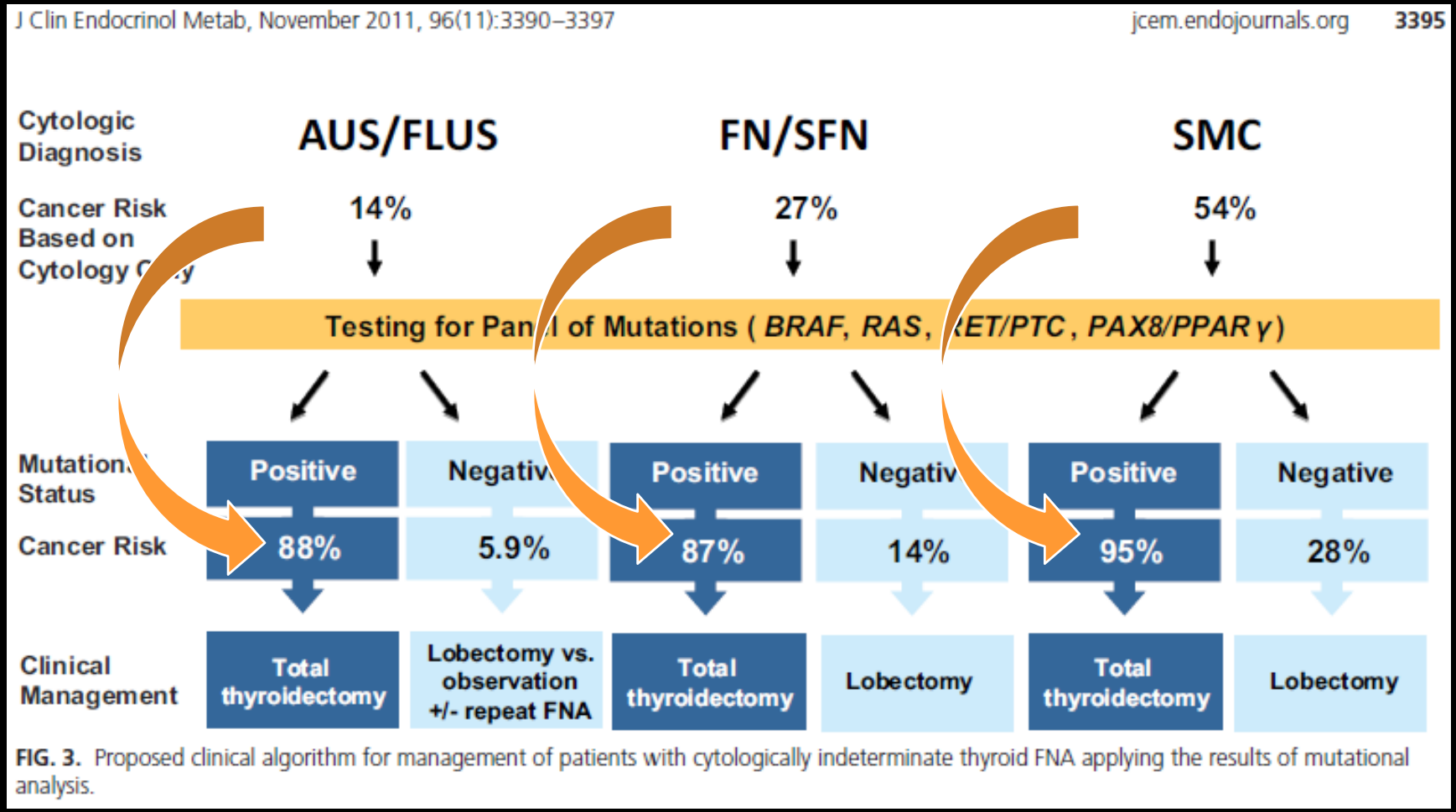


FIG. 3. Proposed clinical algorithm for management of patients with cytologically indeterminate thyroid FNA applying the results of mutational analysis.

Nikiforov YE et al. JCEM 118:3390-7, 2011

Mutational Analysis

- Excellent positive predictive value (PPV)
  - Very specific
  - If the test is positive, it is a cancer
- Low negative predictive value (NPV)
  - Not very sensitive
  - If no mutations are found, can still be a cancer
- A good "rule in test"

Gene Expression Classifier

Gene-Expression Classifier

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology

Erik K. Alexander, M.D., Giulia C. Kennedy, Ph.D., Zubair W. Baloch, M.D., Ph.D., Edmund S. Cibas, M.D., Darya Chudova, Ph.D., James Diggans, Ph.D., Lyssa Friedman, R.N., M.P.A., Richard T. Kloos, M.D., Virginia A. LiVolsi, M.D., Susan J. Mandel, M.D., M.P.H., Stephen S. Raab, M.D., Juan Rosai, M.D., David L. Steward, M.D., P. Sean Walsh, M.P.H., Jonathan I. Wilde, Ph.D., Martha A. Zeiger, M.D., Richard B. Lanman, M.D., and Bryan R. Haugen, M.D.

Alexander EK, et al. NEJM 367:705-715, 2012

Gene-Expression Classifier: Excellent negative predictive value

- 265 indeterminate nodules, 85 malignant.
- Classifier identified 78 of the 85 nodules as suspicious (92% sensitivity, 52% specificity)
- NPV for AUS/FLUS, follicular neoplasm or “suspicious cytologic findings” were 95%, 94%, and 85%.
- 6/7 false negative insufficient sampling.

Alexander EK, et al. NEJM 367:705-715, 2012

Gene Expression Classifier

- Excellent negative predictive value (NPV)
  - Very sensitive
  - If the test is benign, it is not a cancer
- Low positive predictive value (PPV)
  - Not very specific
  - Many GEC “suspicious” tumor are not cancers
- A good “rule out test”

Gene-Expression Classifier: Fewer Operations, Higher Yield

- Multicenter study, 339 patients with FNA indeterminate nodules
  - 165 AUS/FLUS; 161 FN; 13 SUSP for ca
  - GEC 174 (51%) benign, 148 (44%) suspicious
- Surgery recommended for 4 of 175 GEC benign vs 141 of 149 GEC suspicious
- For FNA indeterminate/GEC suspicious and operated, 53/121 (44%) were malignant.

Alexander EK, et al. JCEM 99:119-125, 2014

Gene-Expression Classifier Changes Recommendation for Surgery

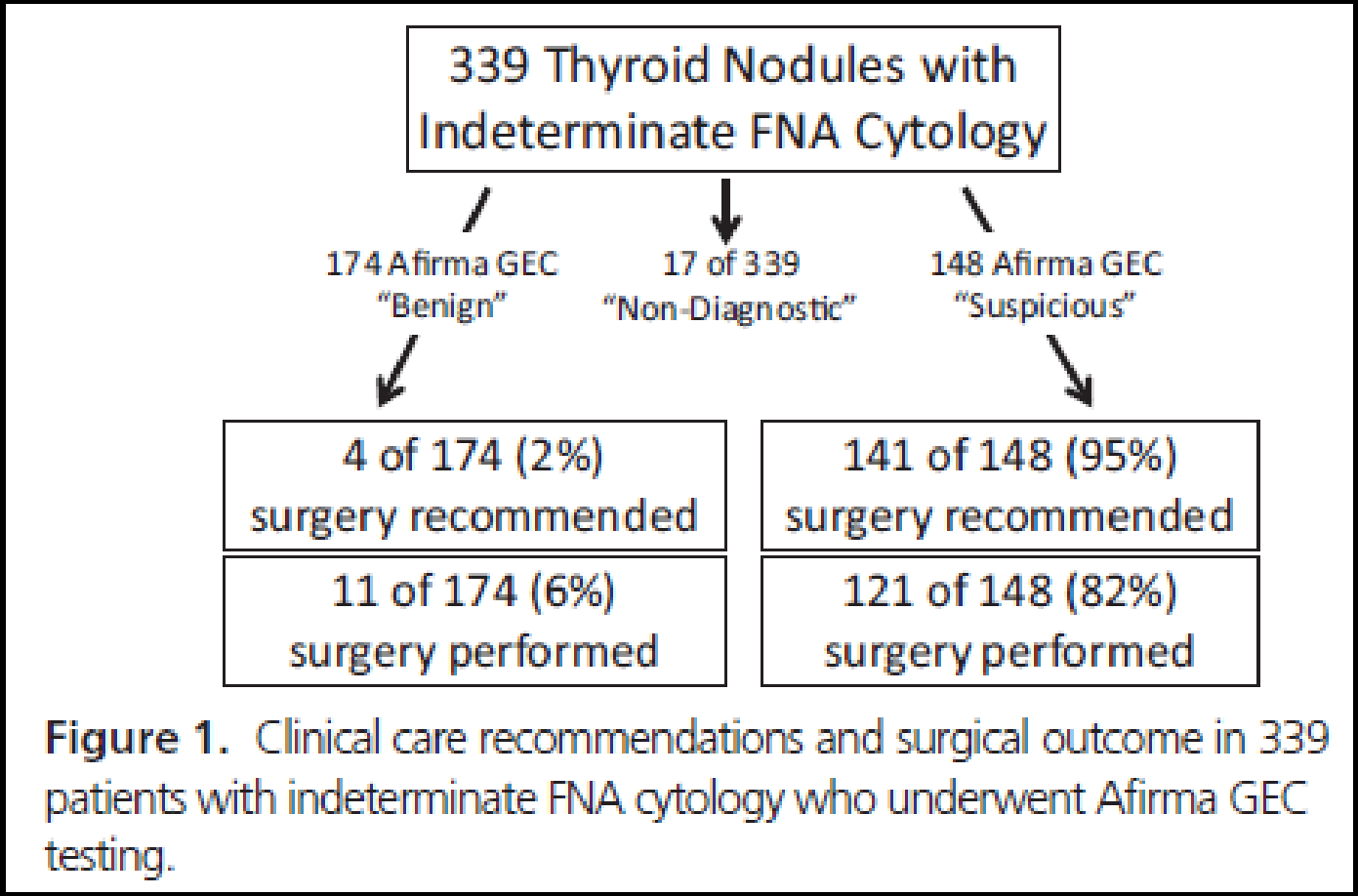


Figure 1. Clinical care recommendations and surgical outcome in 339 patients with indeterminate FNA cytology who underwent Afirma GEC testing.

Alexander EK, et al. JCEM 99:119-125, 2014

Gene Expression Classifier: Prevents unnecessary thyroidectomy

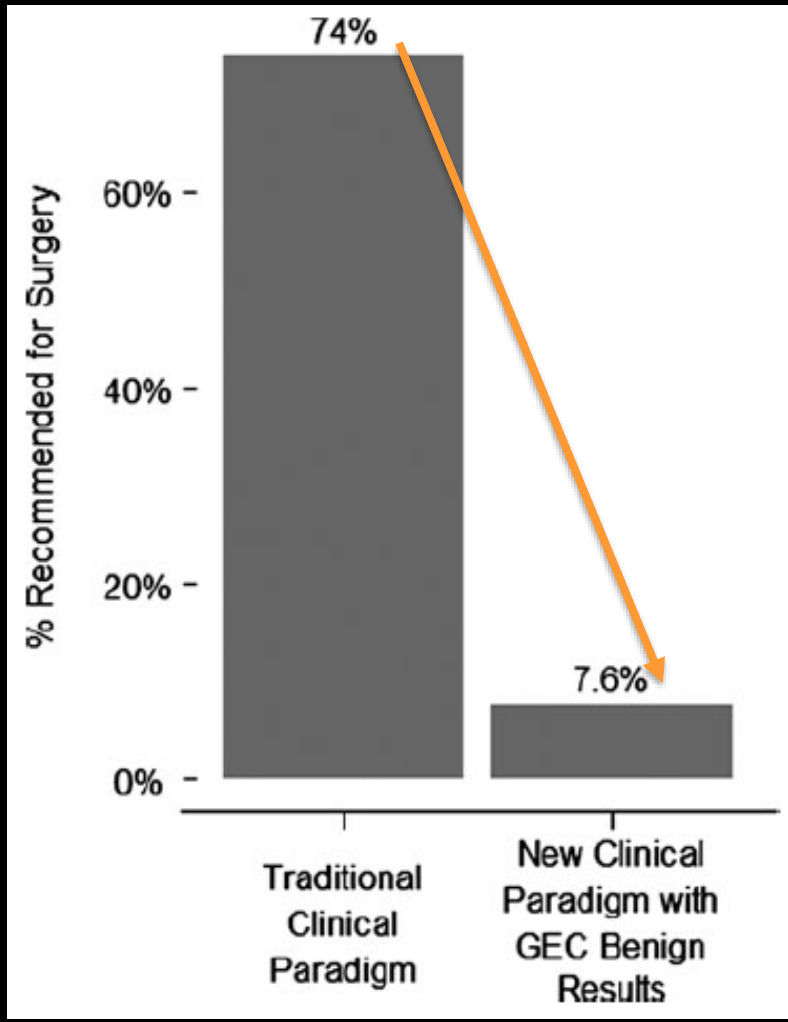


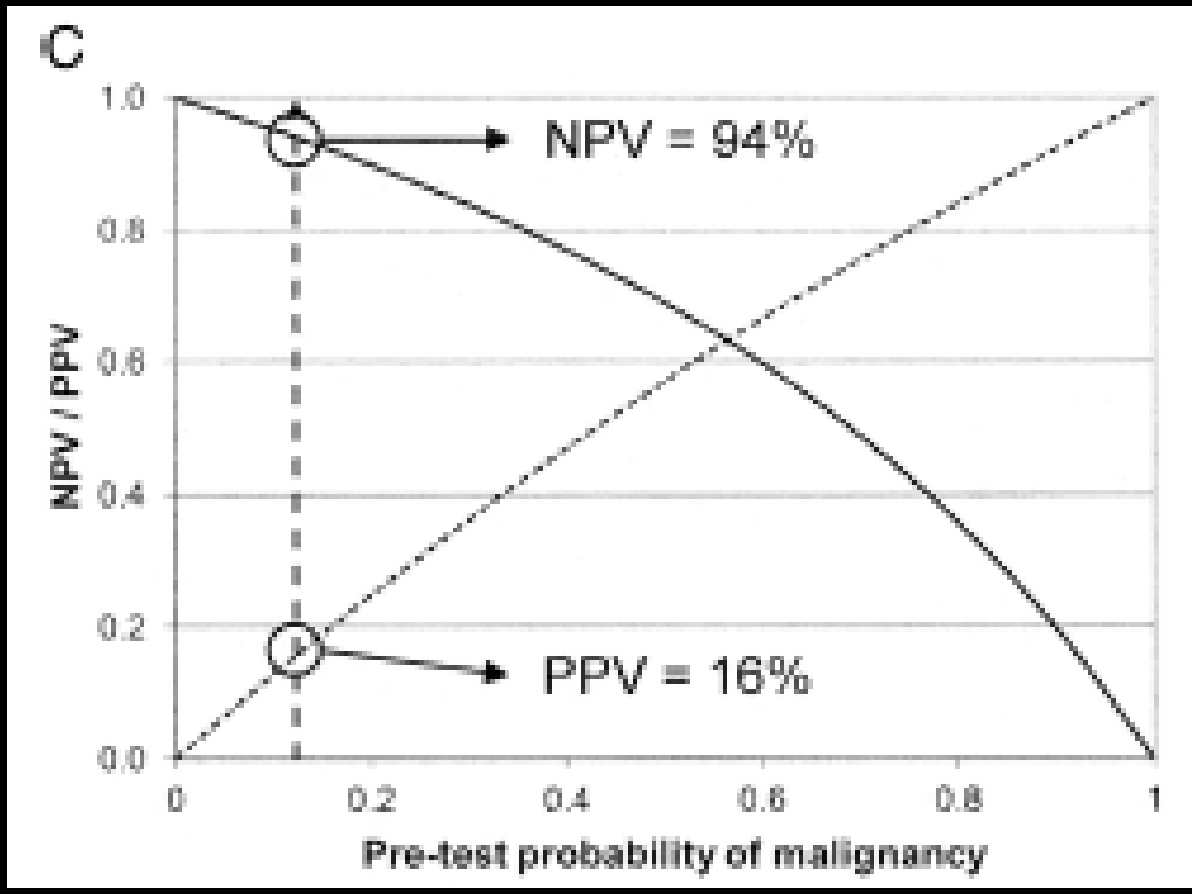
TABLE 3. NONSURGERY MANAGEMENT VERSUS SURGERY RECOMMENDED WHEN CYTOLOGY IS INDETERMINATE, BUT GENE EXPRESSION CLASSIFIER RESULT IS BENIGN

	n (%)	[95% CI]
Nonsurgery management	340 (92.4%)	[89.2%–94.9%]
Surgery performed	28 (7.6%)	[5.12%–10.8%]
Reason surgery recommended		
Large nodule	13 (46.4%)	[27.5%–66.1%]
Local pressure symptoms	7 (25.0%)	[10.7%–44.9%]
Rapid nodule growth	3 (10.7%)	[2.27%–28.2%]
Other suspicious nodule	3 (10.7%)	[2.27%–28.2%]
Suspicious by cytology	2 (7.1%)	[0.9%–23.5%]
Suspicious by ultrasound	2 (7.1%)	[0.9%–23.5%]
Other	12 (42.9%)	[24.5%–62.8%]
Type of surgery recommended		
Hemithyroidectomy	19 (67.9%)	[47.6%–84.1%]
Total thyroidectomy	8 (28.6%)	[13.2%–48.7%]
Unknown	1 (3.6%)	[0.1%–18.3%]

Duick DS, et al. Thyroid 22:996-1001, 2012

Poor PPV in GEC "suspicious": Cytology reading? Low prevalence?

- Mayo Clinic
- 72 samples, 12 insufficient, 60 evaluated (III & IV)
- 16 (27%) "benign".
- 44 (73%) "suspicious"
- 32/44 had operation, only 5/32 (17%) ca



McIver B, et al. JCEM 99:4069-77, 2014

Molecular Testing

- Mutational analysis (DNA)
  - Good Positive Predictive Value, RULE-IN test
- Gene expression classifier (RNA)
  - Good Negative Predictive Value, RULE-OUT test

Mutation Analysis: When to use it

- When a more certain diagnosis of cancer will change:
  - decision to operate (III: AUS/FLUS)
  - extent of operation (IV: FOL)
  - need for frozen section (V: SUSP)

FNA Molecular Testing Guides Extent of Initial Thyroidectomy

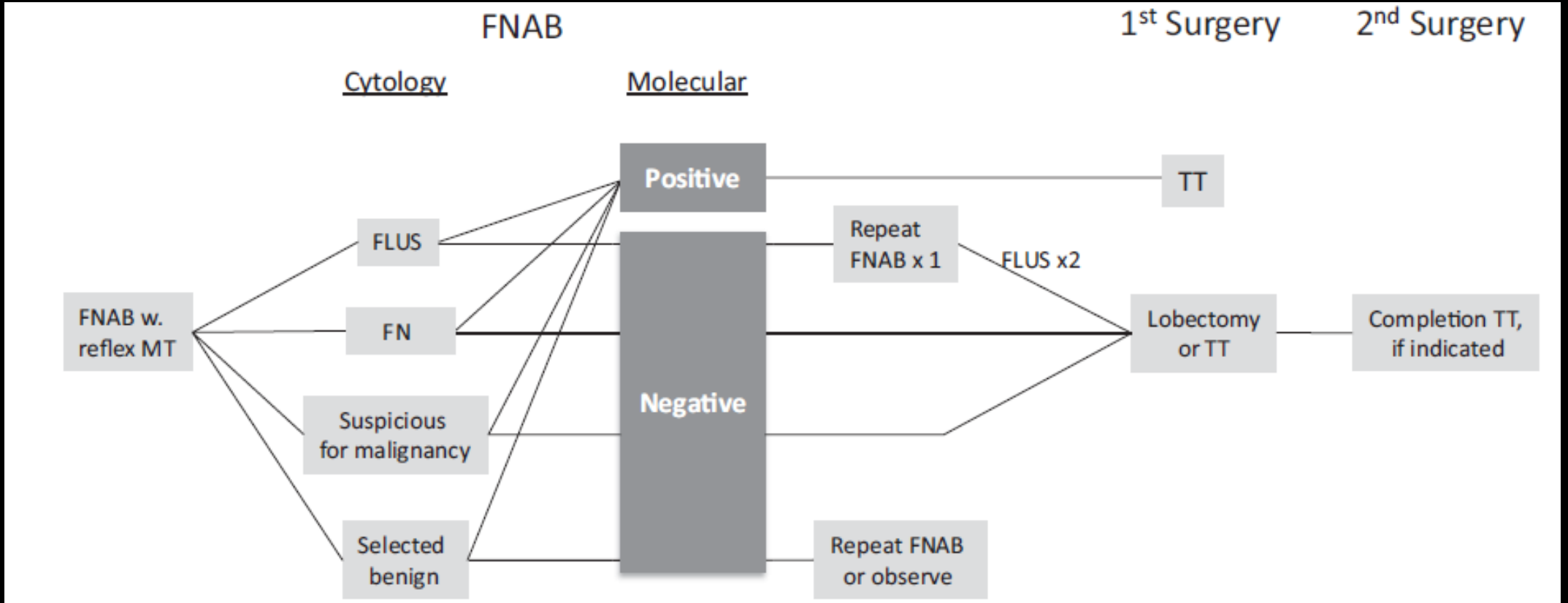


FIGURE 1 . Surgical algorithm for routine prospective MT.

Yip L, et al. Ann Surg 260:163-8, 2014

Gene Expression Classifier: When to use it

- PPV and NPV depends on Pretest probability
  - Pretest rate of malignancy (ROM) affect posttest ROM

- Use it for FNA cytology follicular (20-30%) or AUS/FLUS (10%) lesions.
  - If GEC suspicious then 40-45% will be cancer
  - If GEC benign then 5% only will have cancer

Alexander EK, et al. JCEM 99:119-125, 2014

Gene-Expression Classifier: When NOT to use it

- At extreme pretest probability
  - Cytology benign (3%, →false positive)
  - Cytology malignant (99%, →false negative)
  - Cytology suspicious for cancer (→false negative)

- If there are other indications for surgery
  - Local symptoms
  - High risk (family hx, radiation hx, difficult follow up)

Alexander EK, et al. JCEM 99:119-125, 2014

Molecular Testing for Thyroid Nodules

- Use it only if it will change management
- Don’t use it for Bethesda II (benign) or VI (CA)
- Probably not useful for Bethesda V (SUSP)
  - High chance for false negative
- For Bethesda III (AUS/FLUS) and IV (FN)
  - GEC, if low risk, 5% chance cancer, can observe
  - Mutation analysis, if positive may avoid reoperation

Other Molecular Testing?

Mutations + miRNA GEC

Multicentre validation of a microRNA-based assay for diagnosing indeterminate thyroid nodules utilising fine needle aspirate smears

- 189 FNA samples
- microRNA expression
- No need for fresh tissue
- Sensitivity 85%
- Specificity 72%

Lithwick-Yanai G, et al. J Clin Patholo 0:1-8, 2016

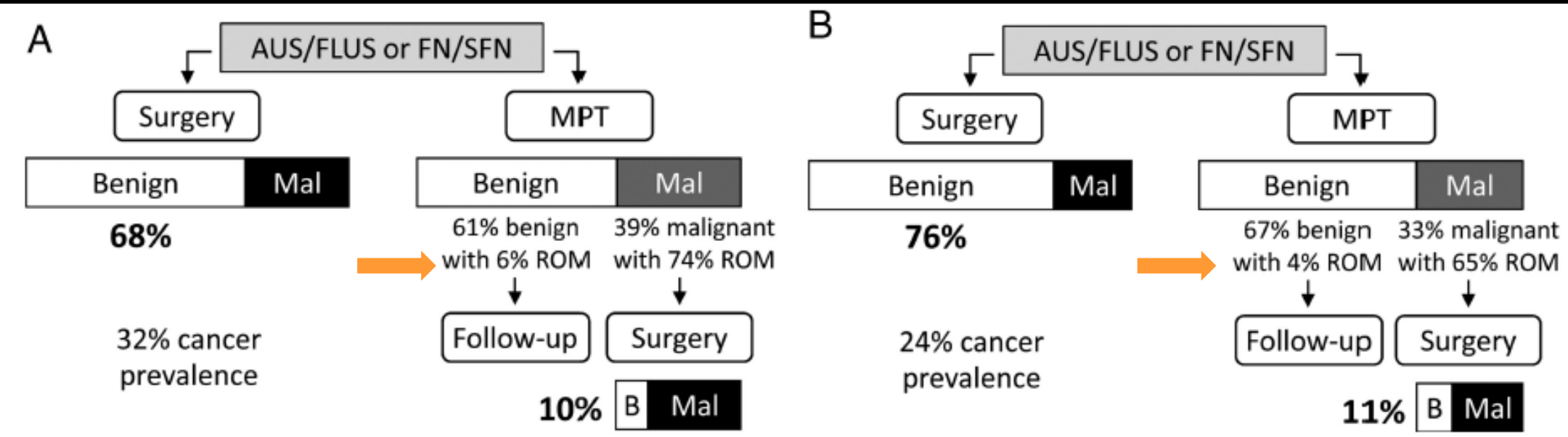
Multiplatform Mutation and miRNA Test (MPT)

- Mutational analysis (7-gene MT)
  - BRAF, N/K/H RAS, RET-PTC, PAX8/PARg
  - found 69% of cancer
- 10 miRNA gene expression classifier (mirGEC)
  - found another 64% in mutation negative group
- sens 89% (CI: 73–97%) spec 85% (75–92%)
  - found 65% more benign than mRNA GEC
  - 69% fewer diagnostic lobectomy.

Labourier E, et al J Clin Endocrinol Metab. 100:2743, 2015

Multiplatform Mutation and miRNA Test (MPT)

- NPV 94-96% for AUS/FLUS and FN/SFN
- Fewer diagnostic lobectomy than GEC?



Labourier E, et al J Clin Endocrinol Metab. 100:2743, 2015

Cost Effectiveness

Cost-Effectiveness of Molecular Testing for AUS/FLUS Thyroid Nodules

Diagnostic test characteristics, %	
GEC sensitivity[c]	90.3 (74.2–98.0)
GEC specificity[c]	53.1 (42.7–63.2)
GMP sensitivity[c]	62.9 (44.9–78.5)
GMP specificity[c]	98.6 (95.9–99.7)

	Estimate[a] (range[b])[c]
GEC	3500 (1750–7000)
GMP	850 (425–1700)
Thyroid lobectomy	9042 (2521–18 084)
Total thyroidectomy	10 155 (5078–20 310)
Completion thyroidectomy	10 364 (5182–20 728)
Neck dissection	16 729 (8365–33 458)
Radioactive iodine ablation (whole body I^{131} scan, I^{131} ablation, 1 inpatient day)	451 (226–902)

Lee L, et al. JCEM 99:2674-2682, 2014

Cost-Effectiveness of Molecular Testing for AUS/FLUS Thyroid Nodules

- Low probability of being cost-effective

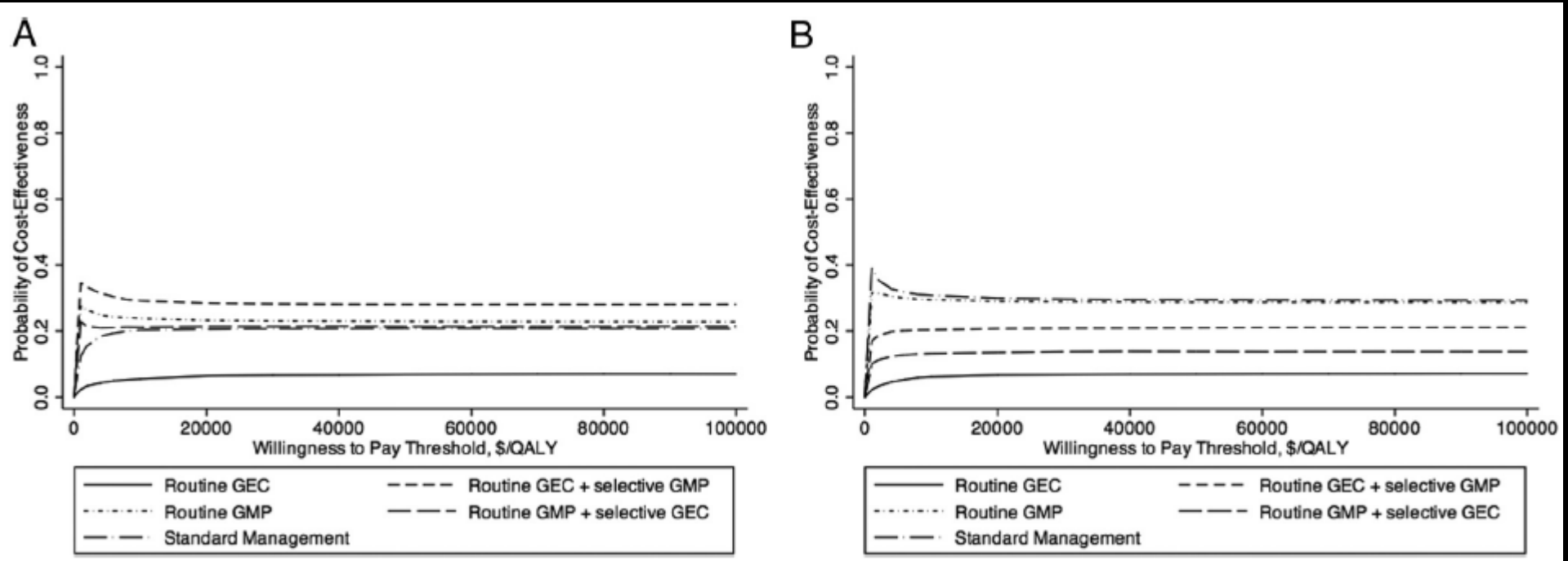


Figure 3. Cost-effectiveness acceptability curves from the US third-party payer (A) and Canadian healthcare system (B) perspectives.

Lee L, et al. JCEM 99:2674-2682, 2014

Cost-Effectiveness of Molecular Testing for AUS/FLUS Thyroid Nodules

- Routine GEC then selective GMP (gene mutation panel) is best strategy but not cost-effective

Lee L, et al. JCEM 99:2674-2682, 2014

Guidelines?

American Thyroid Association Statement on Surgical Application of Molecular Profiling for Thyroid Nodules: Current Impact on Perioperative Decision Making

Robert L. Ferris,[1] Zubair Baloch,[2] Victor Bernet,[3] Amy Chen,[4] Thomas J. Fahey III,[5] Ian Ganly,[6] Steven P. Hodak,[7] Electron Kebebew,[8] Kepal N. Patel,[9] Ashok Shaha,[6] David L. Steward,[10] Ralph P. Tufano,[11] Sam M. Wiseman,[12] and Sally E. Carty[13]

for the American Thyroid Association Surgical Affairs Committee

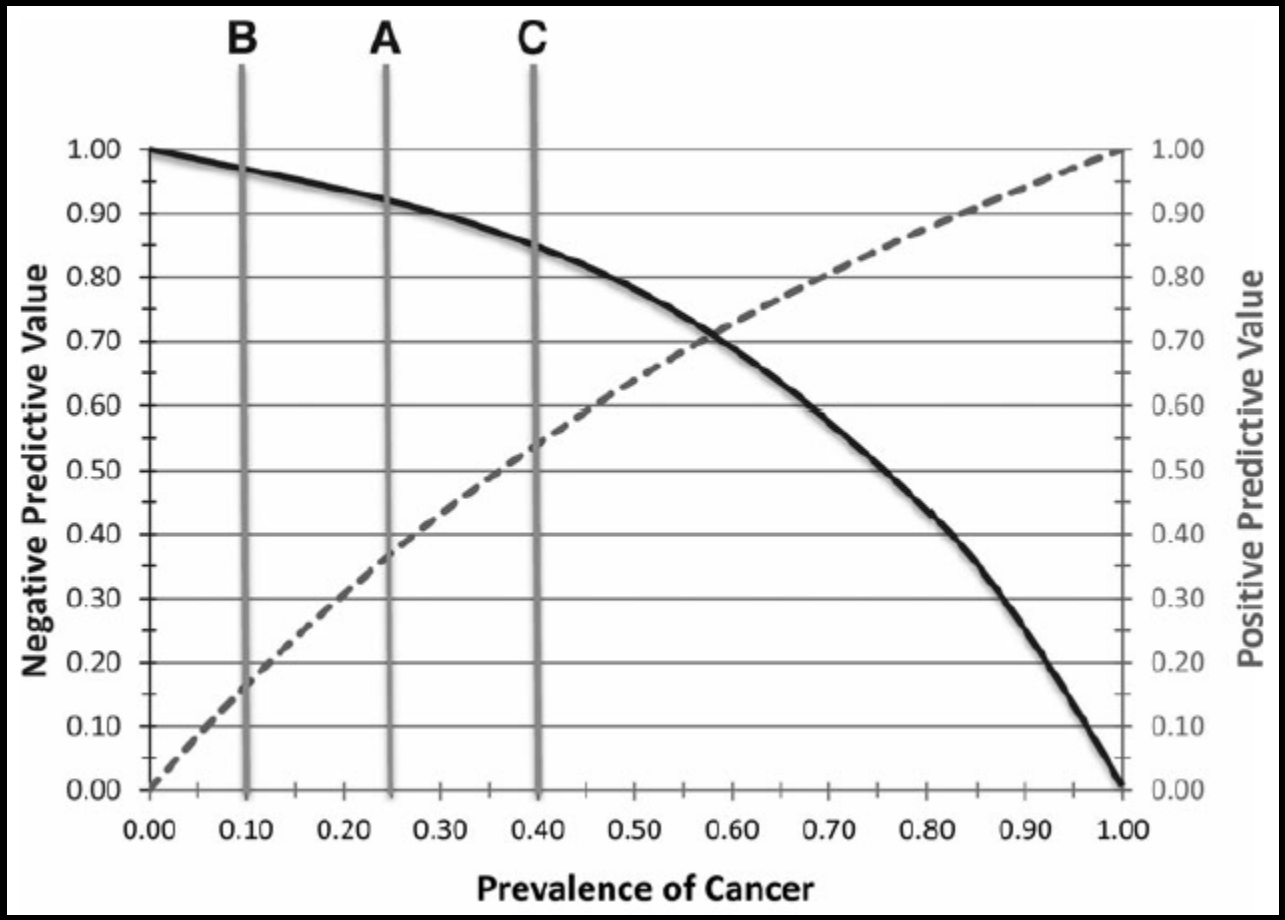
- ATA “Statement” not “Guidelines”
- No strong recommendations

Ferris RL, et al. Thyroid. 25:760, 2015

III (AUS/FLUS)	None			6–48% (14%)
	GEC[b] (reported prevalence 24%)	Suspicious		38%
		Benign	GEC -	5%
	7-gene MT[c] (reported prevalence 14%)	Positive	MT +	88%
		Negative		6%
IV (FN/FL)	None			14–34% (25%)
	GEC[b] (reported prevalence 25%)	Suspicious		37%
		Benign	GEC -	6%
	7-gene MT[c] (reported prevalence 27%)	Positive	MT +	87%
		Negative		14%
	ThyroSeq2.0 panel[d] (reported prevalence 27%)	Positive		87%
		Negative		5%
V (SMC)	None			53–87% (70%)
	GEC[b] (reported prevalence 62%)	Suspicious		76%
		Benign	GEC -	15%
	7-gene MT[c] (reported prevalence 54%)	Positive	MT +	95%
		Negative		28%

Ferris RL, et al. Thyroid. 25:760, 2015

PPV & NPV depend on Prevalence/ Pretest Probability



Ferris RL, et al. Thyroid. 25:760, 2015

2x2 Table Calculation of Test Performance

	Malignant	Benign	Total
Test Negative	FN	TN	FN+TN
Test Positive	TP	FP	TP+FP
Total	FN+TP	TN+FP	FN+TP+TN+FP

Sensitivity = TP/(TP+FN)

Specificity = TN/(TN+FP)

PPV = TP/(TP+FP)

NPV = TN/(TN+FN)

Can We Improve Molecular Testing?

Improve Molecular Testing

- Mutational Analysis
  - Find more thyroid cancer specific mutations to improve sensitivity (and NPV)
- Gene Expression Classifier
  - Find more expression patterns that are from benign nodules to improve specificity (and PPV)

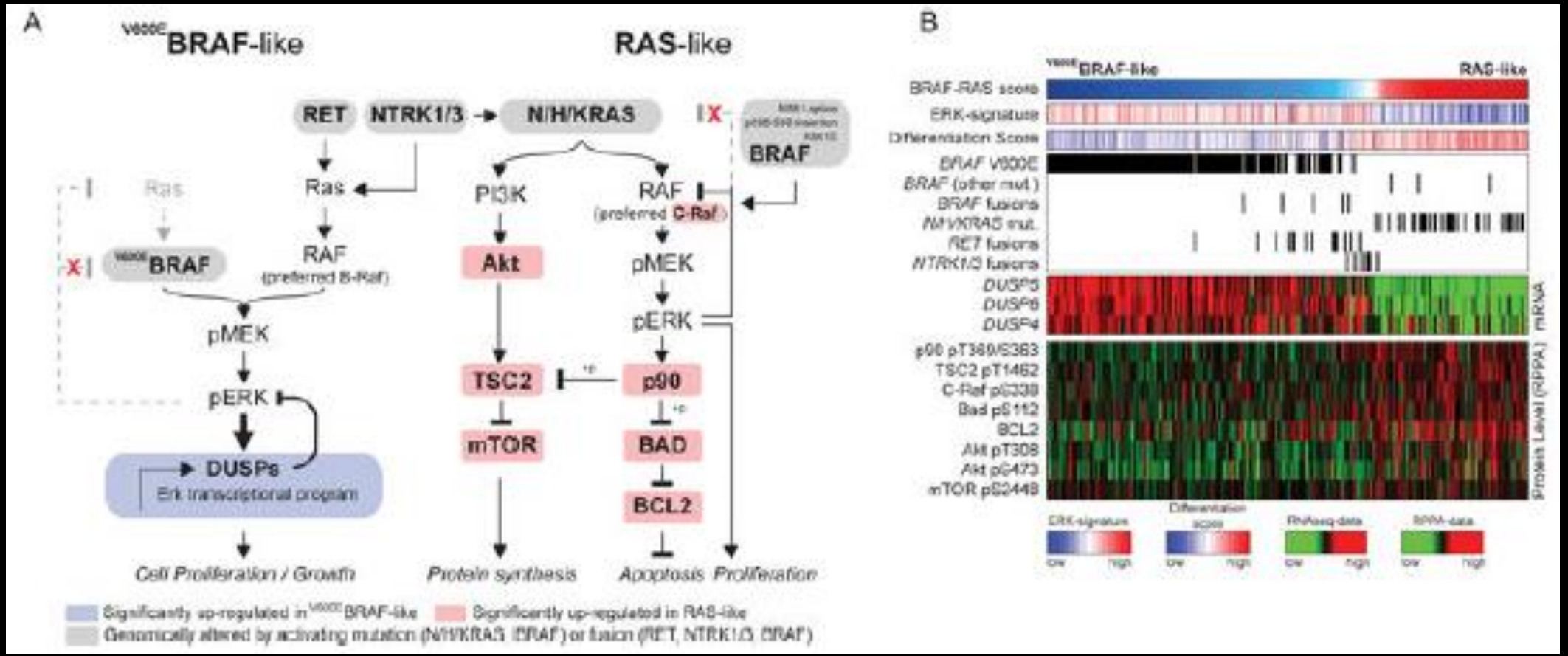
Thyroid Cancer Genome Atlas (TCGA)

Thyroid Cancer Genome Atlas

- 496 PTC
- Low frequency of somatic alterations compared with other cancers
- Most have a single oncogenic driver
- Unknown oncogenic driver decreased from 25% to 3.5%
- Subtypes: BRAF vs. RAS molecular subtype

Giodano TJ, Cancer Genome Atlas Research Network. Cell 159:676, 2014

Thyroid Cancer Genome Atlas
BRAF-like vs RAS-like



Giodano TJ, Cancer Genome Atlas Research Network. Cell 159:676, 2014

Thyroid Cancer Genome Atlas: Implications

- We can add more cancer-specific mutated genes to the molecular testing panels to lower false negative rate to below 5%
- Mutational analysis may be also useful for prognosis (in addition to diagnosis)
- Most thyroid cancer is associated with only one mutation. Those with more than one have worse prognosis.

Mutational Analysis:
More Genes = Better?

Mutational Analysis Improving: Faster, Cheaper, Miss Fewer Cancers

- 2007 7 gene panel, 70% of thyroid ca has BRAF, RTE-PTC1/3, N.K.RAS, PAX8/PPARg
- 2013 15 gene panel using NextGen Sequencing ThyroSeq v.1, ↑ to 81% sensitive
- 60 gene panel ThyrSeq v.2, ↑ to > 90%
  - Need only 300 cells
  - 14 point mutations, 46 rearrangements
  - 95.6% NPP (4.4% cancer if test benign)

Nikiforov YE, Boston, AAES Apr 28, 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

Yuri E. Nikiforov, MD, PhD[1]; Sally E. Carty, MD[2]; Simon I. Chiosea, MD[1]; Christopher Coyne, MD[3]; Umamaheswar Duvvuri, MD[4]; Robert L. Ferris, MD, PhD[4]; William E. Gooding, MS[5]; Steven P. Hodak, MD[3]; Shane O. LeBeau, MD[3]; N. Paul Ohori, MD[1]; Raja R. Seethala, MD[1]; Mitchell E. Tublin, MD[6]; Linwah Yip, MD[2]; and Marina N. Nikiforova, MD[1]

- Mutational analysis
- ThyroSeq v2 (60-gene, 13 genes + 42 fusions)
- 100% cancer for TERT, HRAS, BRAF V600E, TP53, PIK3CA and any gene fusion.
- 81% to 83% for NRAS or KRAS.
- 1 of 3 TSHR

Nikiforov YE, et al. Cancer. 120:3627, 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

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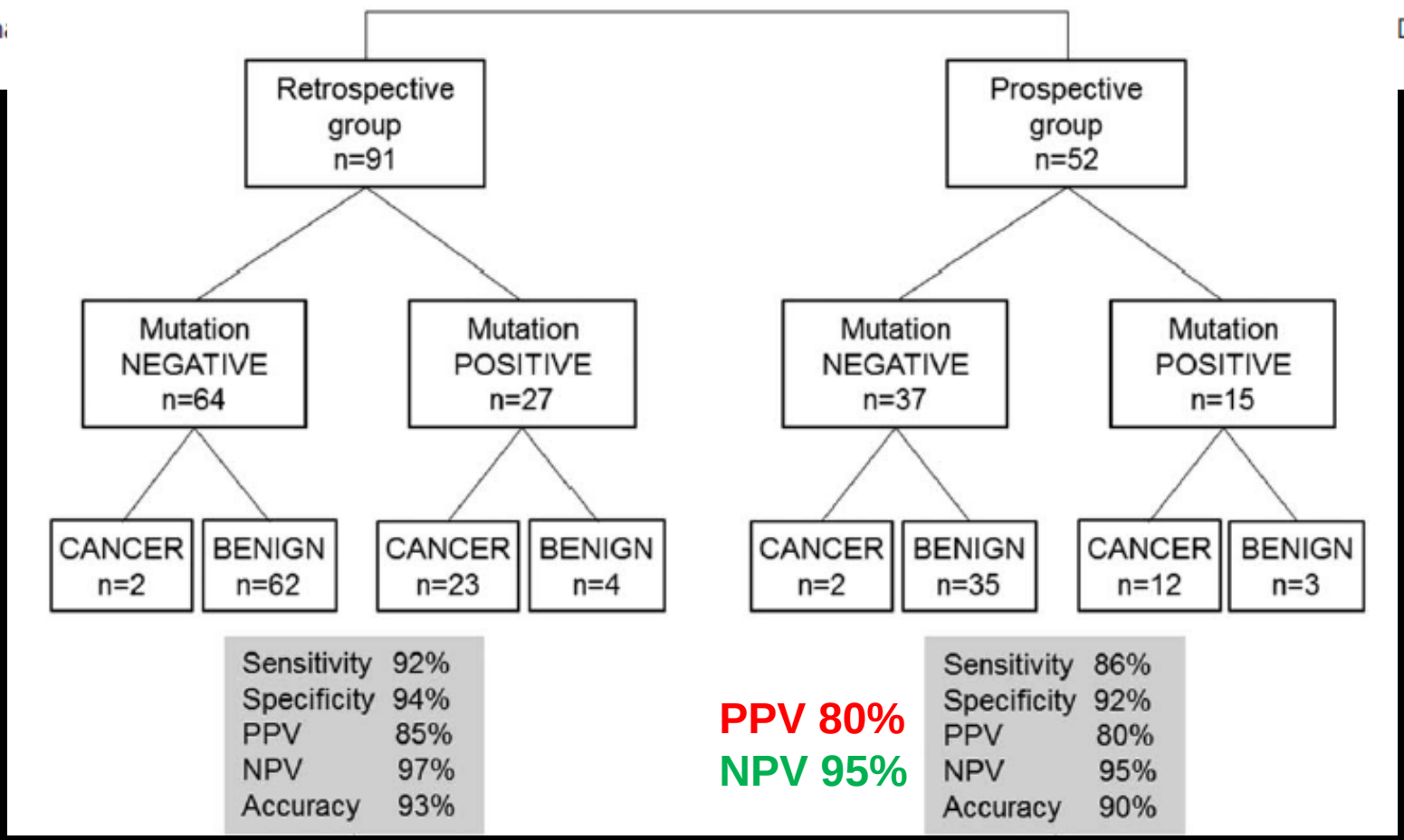


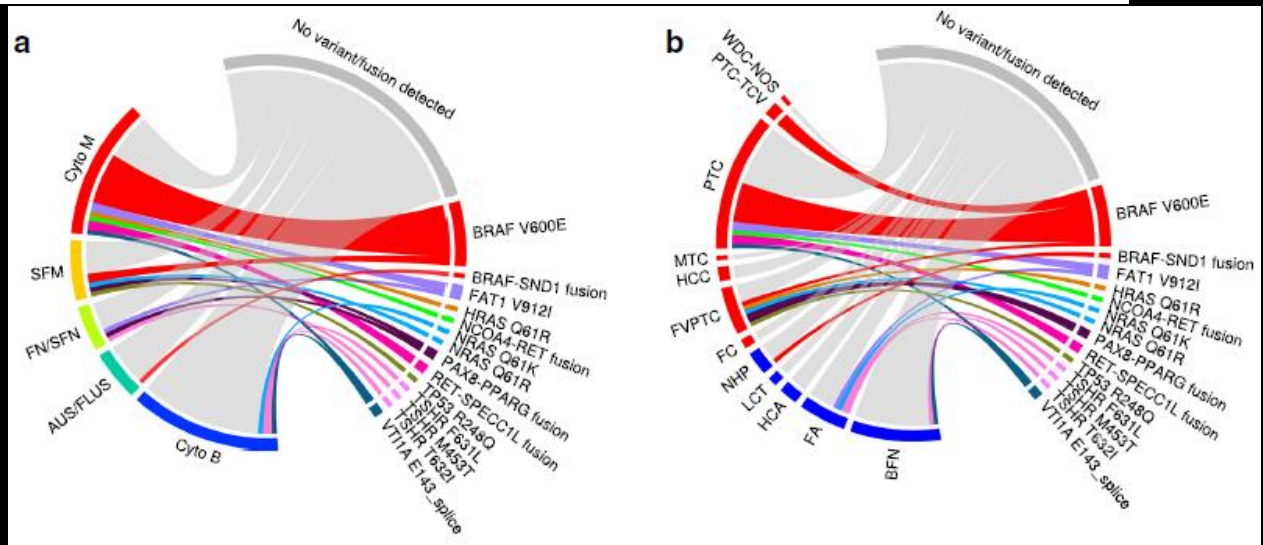
Nikiforov YE, et al. Cancer. 120:3627, 2014

Mutational Analysis: The Future

- Will specificity decreases when more gene mutations are added to the panel? i.e. lower PPV?
- Is it subject to the effect of pretest probability (prevalence of disease) just like GEC?
- Need to study mutational profile of BENIGN thyroid tissue.
  - Is Ras mutation specific for diagnosis of cancer?

The diagnostic application of RNA sequencing in patients with thyroid cancer: an analysis of 851 variants and 133 fusions in 524 genes

- 38/76 (50%) of cancer had genetic alterations
- 15/75 (20%) of benign had genetic alterations



Genetic Alteration	Histology Malignant (n=44)	Histology Benign (n=44)
Positive	19	7
Negative	25	37

Sensitivity, 43% (28-59); Specificity, 84% (70-93); PPV, 73% (56-85); NPV, 60% (53-66)
Prevalence of malignant lesions, 50%. Estimated performance when prevalence equals 24%: PPV, 46% (29-65%); NPV, 82% (78-86).

Pagan M, et al (Kloos, Veracyte) BMC Bioinformatics 2016, 17 (Supp1):6

FNA Aspirate Molecular Testing
N-Ras ↑ sensitivity↓ specificity

- 417 pts, 455 nodules (300 surgical pathology)
- 50 mutations found
  - 23 BRAF, 4 RET/PTC1, 2 RET/PTC3, 21 NRAS
- Sens 38%, Spec 65%, PPV 42%, NPV 65%.
- Sens 12%, Spec 98% if NRAS excluded
- 137 FNA cytology indeterminate/suspicious
  17 positive for BRAF, RET/PTC1-3
  - Excellent PPV, but cannot catch all cancers

Moses W (Kebebew E), et al: World J Surg 34:2589-94, 2010

Mutational Analysis (7 Gene Panel): Positive Predictive Value

- Routine use 2 years, Germany.
- 564 FNA
- BRAF 98% (PPV)
- RET/PTC 100%
- RAS 31%
- PAX8/PPARG 0%

TABLE 2. COMPARISON OF THE ROM BEFORE MOLECULAR PANEL TESTING (PRE-ROM) AND AFTER MOLECULAR TESTING (POST-ROM) FOR MUTATION-POSITIVE AND MUTATION-NEGATIVE SAMPLES

	AUS/FLUS	*FN/SFN*	*SFM*	*MAL*
Cytology alone (pre-ROM)	15%	17%	86%	100%
Mutation positive (post-ROM)	41%	36%	90%	100%
BRAF positive	100%	100%	94%	100%
NRAS positive	57%	31%	50%	—
HRAS positive	0%	20%	—	—
KRAS positive	—	0%	—	—
PAX8/PPARG positive	0%	—	—	—
RET/PTC 1 positive	—	—	100%	100%
RET/PTC 3 positive	100%	100%	—	—
Mutation negative (post-ROM)	10%	13%	79%	100%

ROM, risk of malignancy.

Eszlinger M, et al. Thyroid 27:402-478, 2017

NIFTP
Noninvasive Follicular Neoplasm with Papillary-Like Nuclear Features

Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features Accounts for More Than Half of "Carcinomas" Harboring *RAS* Mutations

Vera A. Paulson,[1] Priyanka Shivdasani,[1] Trevor E. Angell,[2] Edmund S. Cibas,[1] Jeffrey F. Krane,[1] Neal I. Lindeman,[1] Erik K. Alexander,[2] and Justine A. Barletta[1]

- 27 RAS-mutant thyroid tumors
  - 15 (56%) NRAS 9 (33%) HRAS 3 (11%) KRAS
  - 24 (89%) had FNA, 19 (79%) indeterminate FNA
- FVPTC in 20 (74%)
  - classical PTC 2 (7%), solid variant 1 (4%), follicular carcinoma 4 (15%).
  - Of the 20 FVPTCs, 16 (80%) NIFTP.

Paulson VA, et al. Thyroid 27:506-511, 2017

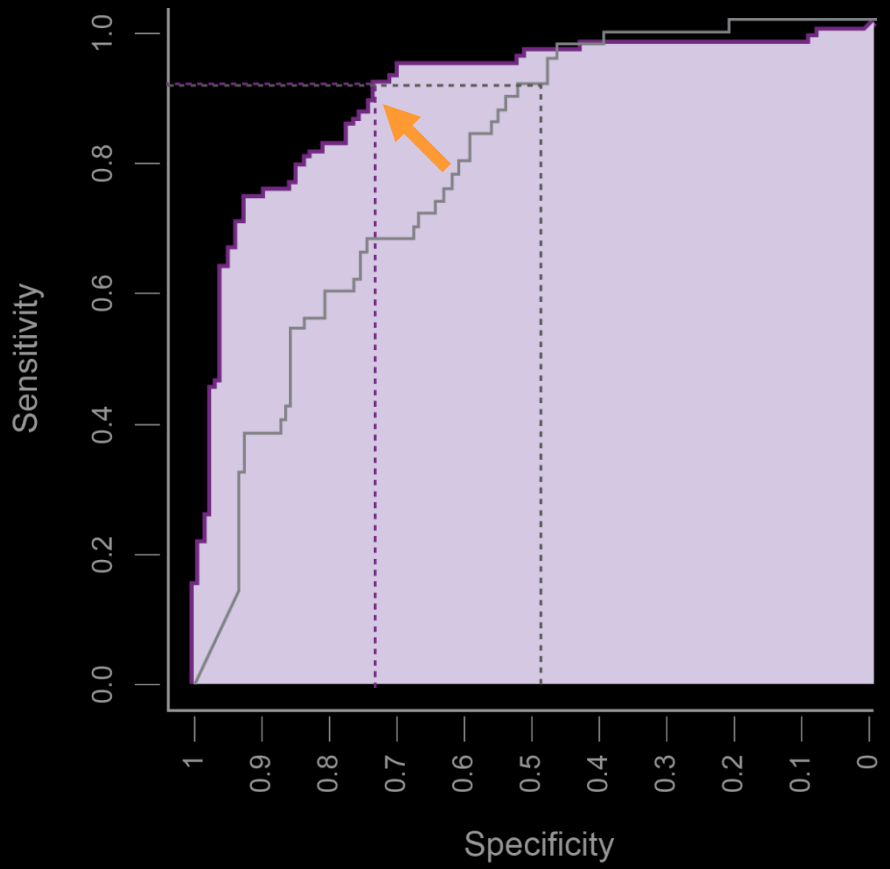
Gene Expression Classifier: The Future

- Continue to be a rule out test
  - Need to have good sensitivity
- Improve PPV without changing sensitivity
  - Better separation of Hurthle cell adenoma vs. Hurthle cell cancer

GEC → Genome Sequencing Classifier: Improve PPV, Fewer Operations?

- 268 nodules (106 ca) cross-validated
- GEC → GSC
- Sensitivity 0.90 → 0.91
- Specificity 0.52 → 0.74
- Benign Call Rate

42% → 58%



Landerson PW, et al: AACE, 2017
Alexander EK, et al. NEJM 367:705-715, 2012

Molecular Testing for Thyroid Nodule FNA: Summary

- Mutational analysis (DNA)
  - Good Positive Predictive Value, RULE-IN test
  - But increasing # of genes to improve sensitivity may also decrease the specificity.
  - Problem with RAS mutation, NIFTP
- Gene expression classifier (RNA)
  - Good Negative Predictive Value, RULE-OUT test
  - Need to know pretest rate of malignancy (ROM) to interpret appropriately
- Use only for AUS/FLUS and FOL cytology


Thank You