2025 City of Hope Multidisciplinary Thyroid Cancer Symposium

Enhancing Assessment of Thyroid Neoplasm via Next Generation Sequencing

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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:

- *Implicit bias between male vs. female*

Thyroid Neoplasm

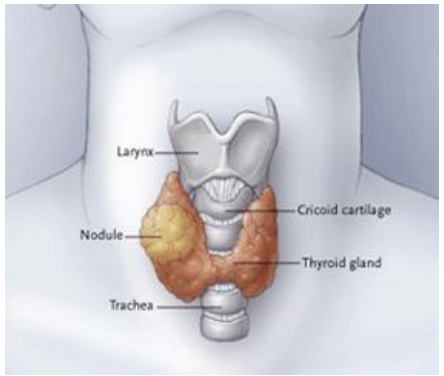
- **The American Cancer Society's most recent estimates for thyroid cancer in the United States for 2025:**
  - **About 44,020 new cases of thyroid cancer (12,670 in men and 31,350 in women)**
  - **About 2,290 deaths from thyroid cancer (1,090 in men and 1,200 in women)**

- **Thyroid cancer is about 3 times more common in women than in men, and it is about 70% more common in White.**

- **Thyroid cancer is often diagnosed at a younger age than most other adult cancers. The average age when a person is diagnosed with thyroid cancer is 51**

- **Palpable thyroid nodules ~4-7% of US population**

- **Cytopathology 15-30% indeterminate, which historically undergo surgery**

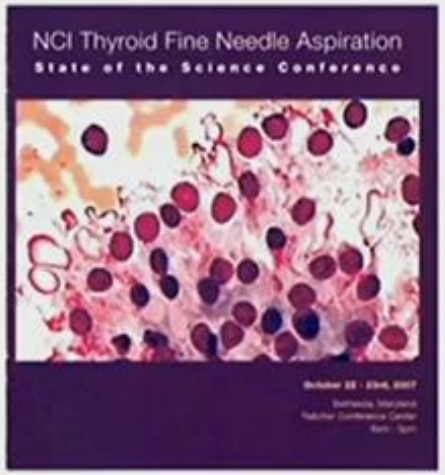


- **70-80% of these cases are benign or have noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP)**

Key Statistics for Thyroid Cancer | American Cancer Society

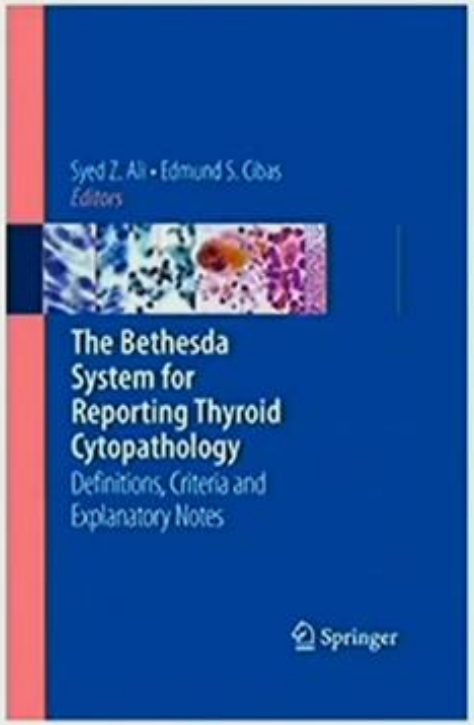
The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) History:

- Bethesda Conference
  October 2007

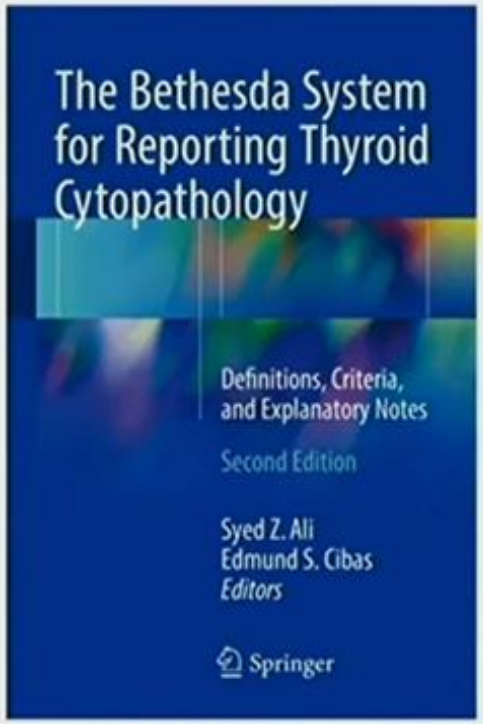


- Proceedings –
  Diagnostic Cytopathology
  June 2008

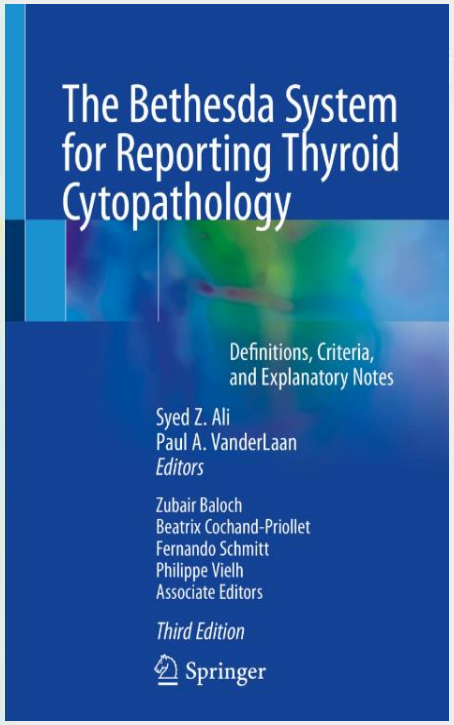
First edition, 2010



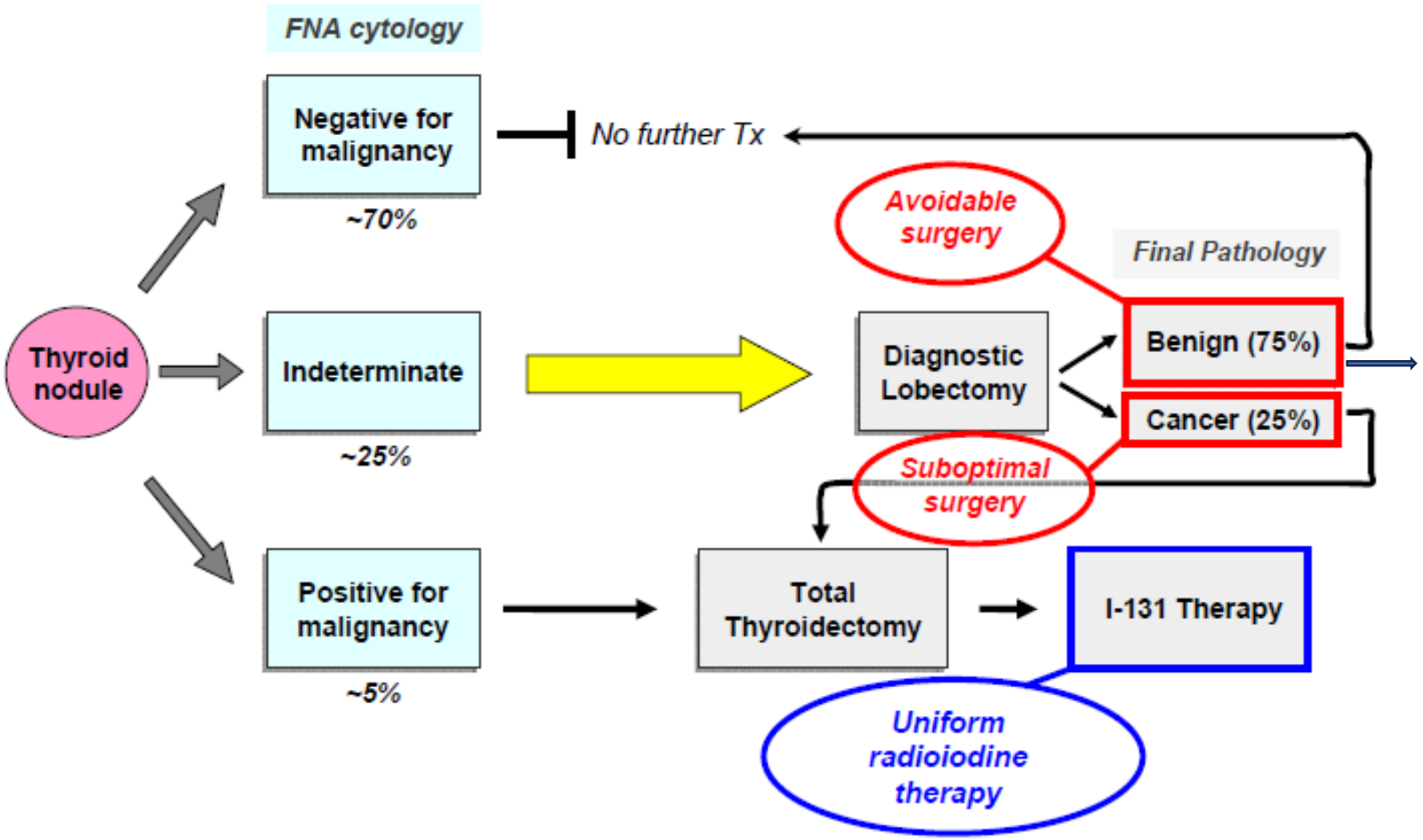
Second edition, 2017



Third edition, 2023



Challenges in Management of Patients with Thyroid Nodules/Cancer

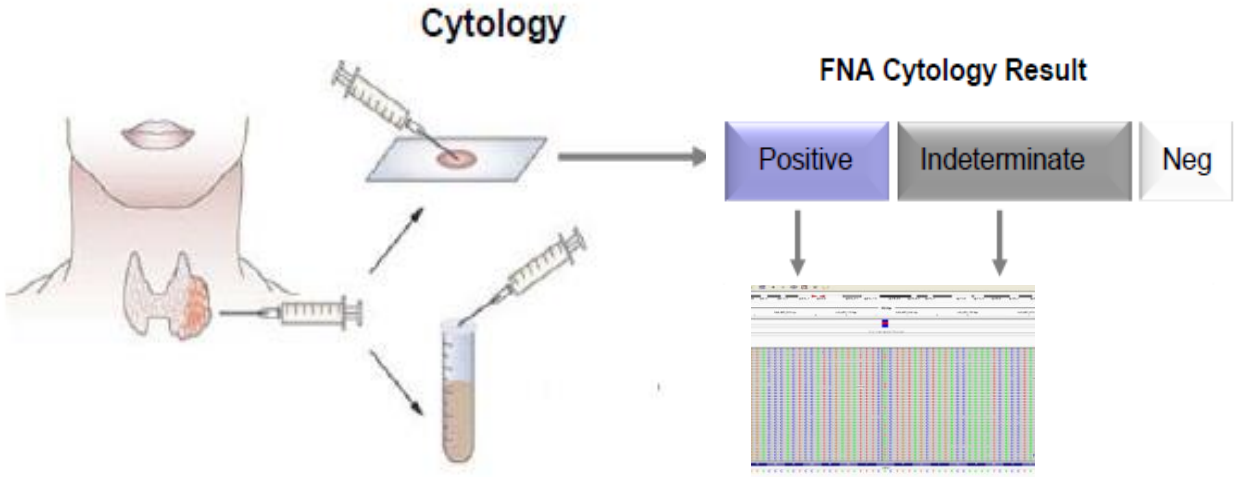


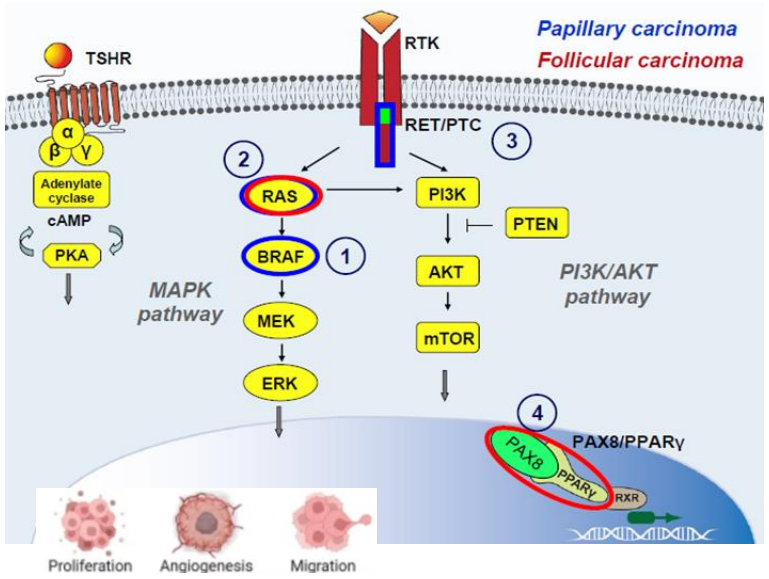
- Important to establish diagnosis preoperatively
- Fine needle aspiration and cytology:
  - About 25% reported as indeterminate of which only 25% malignant.

- **Consequences:**
- Unnecessary and costly surgeries
- Potential of complications
- Lifelong hormone therapy for patients

Nikiforov et al. J Clin Endocrinol Metab. 2009 94(6):2092-8

Methods of diagnosis Pre-Operative:
FNA analysis by cytology + Molecular Genomics Testing





TBSRTC,3rd ed. 2023

I	**Nondiagnostic** Cyst fluid only Virtually acellular specimen Other (obscuring blood, clotting artifact, drying artifact, etc.)
II	**Benign** Consistent with follicular nodular disease (includes adenomatoid nodule, colloid nodule, etc.) Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context Consistent with granulomatous (subacute) thyroiditis Other
III	**Atypia of Undetermined Significance** AUS-nuclear atypia AUS-Other
IV	**Follicular neoplasm** Specify if oncocytic (Hurthle cell) type
V	**Suspicious for Malignancy** Suspicious for papillary thyroid carcinoma Suspicious for medullary thyroid carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma
VI	**Malignant** Papillary thyroid carcinoma High-grade follicular derived carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features Metastatic malignancy Non-Hodgkin lymphoma Other

*Adapted from Ali SZ, VanderLaan P. The Bethesda System for Reporting Thyroid Cytopathology. 3rd ed. New York Springer; 2023 (In Press).

NIFTP

Noninvasive follicular thyroid neoplasm with papillary like nuclear features reclassification of the encapsulated follicular variant of papillary thyroid carcinoma (PTC) in 2017 (Cancer Cytopathol 2017;125(6 suppl):477-85.)

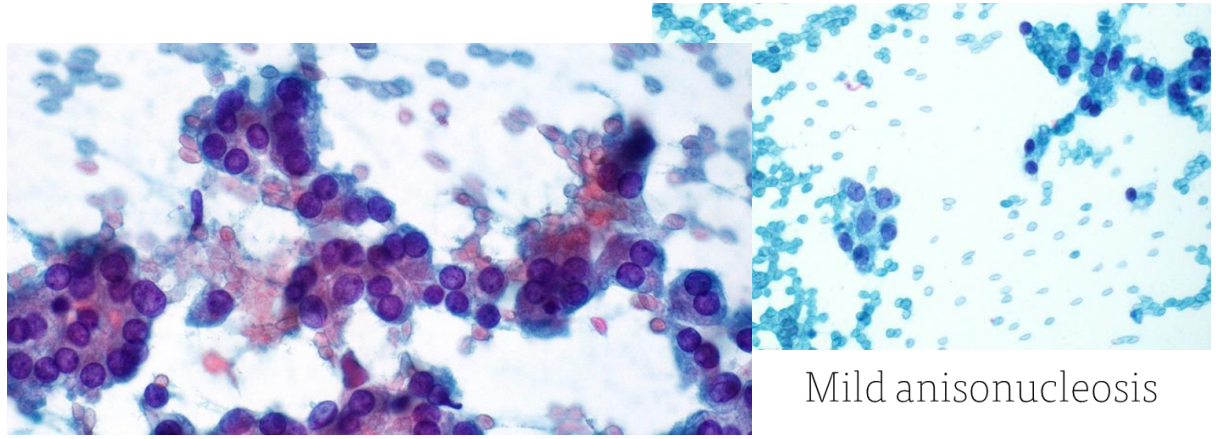
We reported in 2016 that this variant have BRAF (K601E) in contrast to cPTC.

Thyroid. 2016 Feb;26(2):242-7. doi: 10.1089/thy.2015.0227. Epub 2015 Dec 17.

Histopathologic and Clinical Characterization of Thyroid Tumors Carrying the BRAF(K601E) Mutation.

Afkhami M[1], Karunamurthy A[1], Chiosea S[1], Nikiforova MN[1], Seethala R[1], Nikiforov YE[1], Coyne C[1].

Studies indicate that the molecular profile of NIFTP is generally distinct from that of cPTC. NIFTP is characterized by alterations in either *RAS*, *PAX8/PPARγ*, or $BRAF^{K601E}$, in contrast to the frequent $BRAF^{V600E}$ and *RET/PTC* alterations observed in cPTC.[8,52]

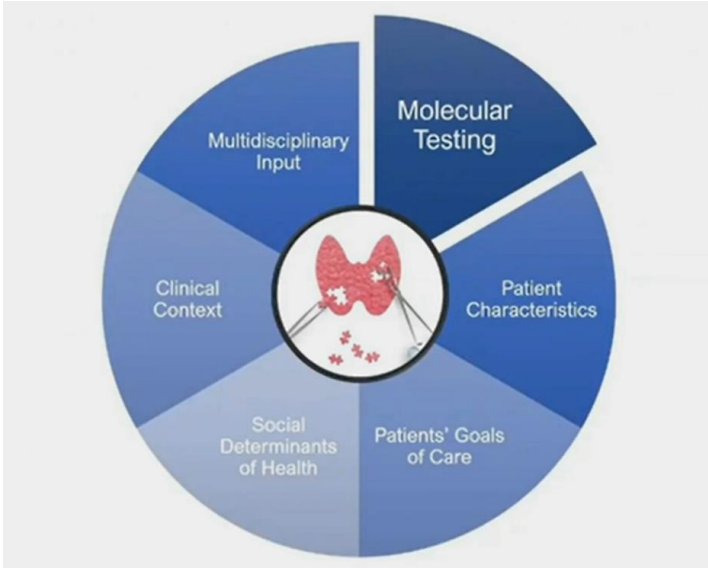


Delicate cytoplasm, round-ish nuclei, pale-ish chromatin

Mild anisonucleosis

When to do molecular testing pre-operative?

- **Thyroid FNA diagnosed as indeterminate by cytology (Bethesda categories III, IV, V): Diagnostics, prognostics, Therapeutics**
- **Thyroid FNA diagnosed as malignant by cytology, when molecular testing is expected to determine the extent of surgery (Bethesda categories VI)**
- **Anaplastic Thyroid Carcinoma**



When to do NGS test post-operative?

- **For advance staged metastatic carcinoma**
- **At time of recurrence or progression**
- **Thyroid malignancy composed of undifferentiated cells with focal features of thyroid follicular differentiation and/or a previous differentiated thyroid carcinoma.**

How to test for Molecular Genomics?

- **Gene expression classifier (GEC)**
- **Gene sequencing classifier (GSC) single mutation testing**
- **NGS DNA and RNA mutation, fusion, copy number variation and gene expression testing**

Mutation-Detection Panels Can Be Used in the AUS/FLUS and SFN/FN Categories to "Rule In" and "Rule Out" Malignancy and Influence the Extent of Thyroid Surgery

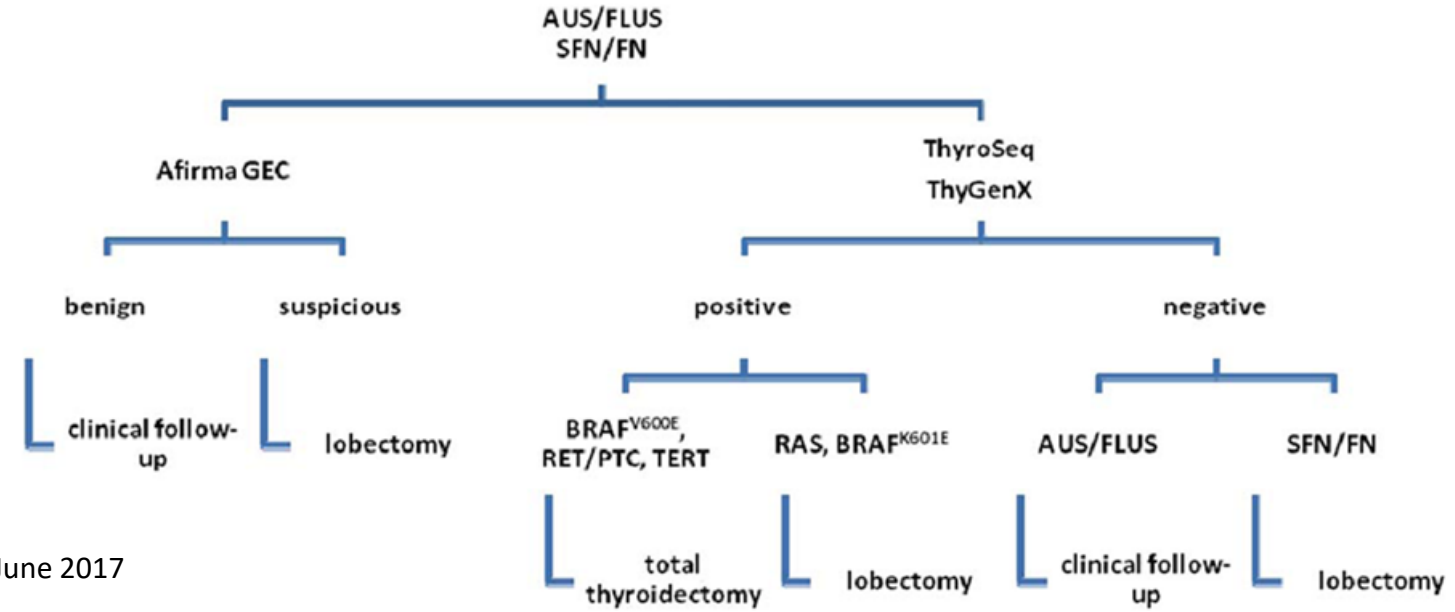
Comparison of Molecular Testing for Screening

TABLE 1. Comparison of Molecular Testing for Thyroid Fine-Needle Aspiration

Measure	Afirma (Sacks 2016,[7] Alexander 2012,[22] McIver 2014,[26] Harell & Bimston 2014,[27] Alexander 2014,[28] Brauner 2015,[29] Lastra 2014[30]	ThyGenX (Labourier 2015[24]	ThyGenX/ThyraMIR (Labourier 2015[24]	ThyroSeq (Nikiforov 2015,[23] 2014[31]
Method	GEC, mRNA expression profile	NGS	NGS/GEC, miRNA expression profile	NGS
Sensitivity, %	83-100	68.6	89	90-91
Specificity, %	7-52	86.5	85	92-93
NPV, %	75-100	85.3	94	96-97.2
PPV, %	14-57	70.6	74	76.9-83
Clinical use	Rule out malignancy	Rule in malignancy/ determine the extent of surgery	Rule out and rule in malignancy/determine the extent of surgery	Rule out and rule in malignancy/determine the extent of surgery
Approximate cost (Nishino 2016[25], $	4875[a] 975[b] 475[c]	1675	3300	3200

[a] This is the cost for Afirma GEC and medullary thyroid carcinoma (MTC).
[b] This is the cost for Afirma MTC alone.
[c] This is the cost for Afirma BRAF alone.

Note: Since 2023 GEC panel specificity increased by adding the mutation panel



Indeterminate Thyroid Aspirate Triage/Onenerk et al. Cancer Cytopathology June 2017

What's the role of liquid biopsy in thyroid cancer?

The highest level of concordance between ctDNA and tumor tissue was demonstrated in the context of ATC. Iyer *et al.* (2018) demonstrated that the level of BRAFV600E ctDNA correlated with tumor response, where no definitive biomarker exists. Target therapy with dabrafenib and trametinib has shown promising results in BRAFV600E patients with ATC (Subbiah *et al.* 2018), and shows it's possible to monitor treatment response by measuring BRAFV600E ctDNA (Schreuer *et al.* 2016). Hence, this data might imply that monitoring BRAFV600E ctDNA in ATC could be a valuable tool to determine treatment efficacy and resistance to therapy.

Serum DNA methylation assessment as a novel diagnostic tool for thyroid cancer was introduced in 2006[1]. In that research, the evaluation of methylation status of five genes (CALCA, CDH1, TIMP3, DAPK, and RARβ2) been done by real-time quantitative methylation-specific PCR. Finally, they have confirmed the potential efficacy of serum DNA methylation markers as an innovative diagnostic marker for both patients with thyroid nodules and thyroid cancer recurrence in earlier treated patients[1]. Afterwards, the detectable free circulating BRAF in patients with PTC was mentioned as a possible determinant of tumor clinical implication[2].

	Tissue-based NGS	ctDNA-based NGS (liquid biopsy)
Nature of procedure	Invasive, requires a biopsy	✓ Minimally invasive
Turnaround time	Longer	✓ Shorter (7 – 14 days)
Source of molecular alterations	Biopsied tissue	✓ Better captures intratumoral heterogeneity and clonal evolution
Sensitivity	✓ Higher sensitivity	Limited sensitivity, dependent on amount pf DNA shedded into bloodstream Negative results require confirmation by tissue-based testing
Concurrent PD-L1 testing	✓ Concurrent PD-L1 testing possible	Concurrent PD-L1 testing not possible
Testing for acquired resistance mechanism	May document histologic transformation	May detect various resistance mechanisms from multiple clones

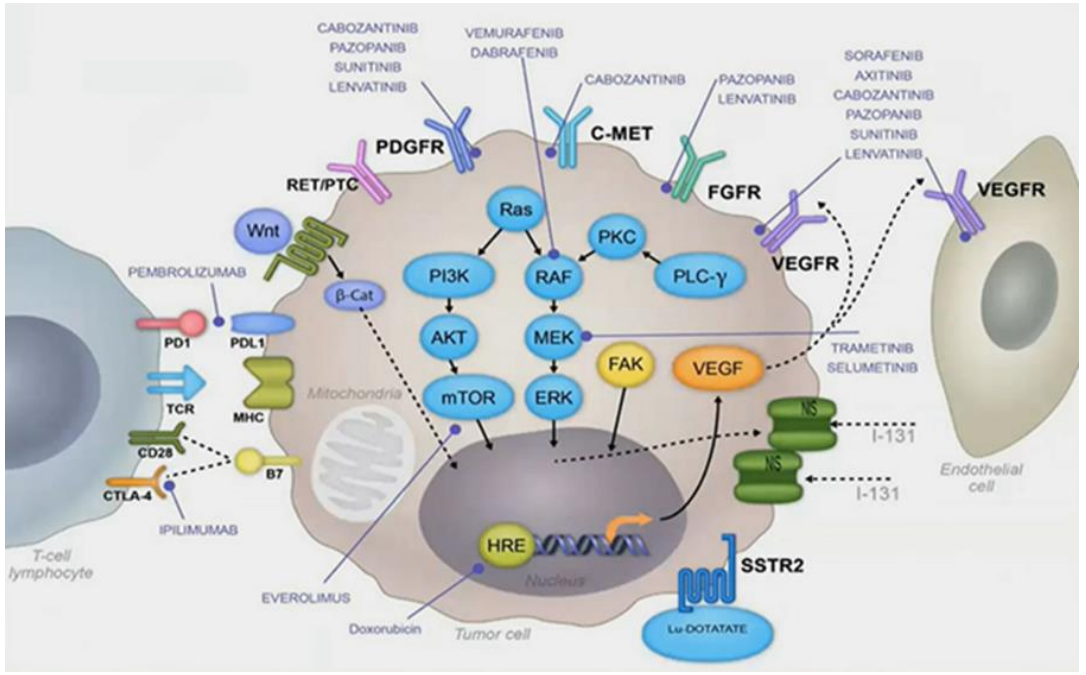
•1.Hu S, Ewertz M, Tufano RP, et al. Detection of serum deoxyribonucleic acid methylation markers: a novel diagnostic tool for thyroid cancer. J Clin Endocrinol Metab. 2006;91(1):98–104. doi: 10.1210/jc.2005-1810.

•2..Sandulache VC, Williams MD, Lai SY, et al. Real-time genomic characterization utilizing circulating cell-free DNA in patients with anaplastic thyroid carcinoma. Thyroid. 2017;27(1):81–87. doi: 10.1089/thy.2016.0076.

•Zeyghami, W., Hansen, M. U., Jakobsen, K. K., Groenhøj, C., Feldt-Rasmussen, U., von Buchwald, C., & Hahn, C. H. (2023). Liquid biopsies in thyroid cancers: a systematic review and meta-analysis. *Endocrine-Related Cancer*, *30*(12), e230002.

Other Biomarker testing for Personalization of treatment

- Immunohistochemistry studies:
  - BRAF V600E
  - Calcitonin
  - PD-L1 immune markers for prediction
  - of response to immunotherapy
  - HER2 IHC to direct therapy



- Cytogenetics and FISH analysis
  - Example RET fusions or HER2 (ERBB2) amplification to guide therapy

Molecular testing, such as Sanger Sequencing, polymerase chain reaction (PCR), Real-Time PCR, multiplex ligation-dependent probe amplification (MLPA), etc. for single gene testing

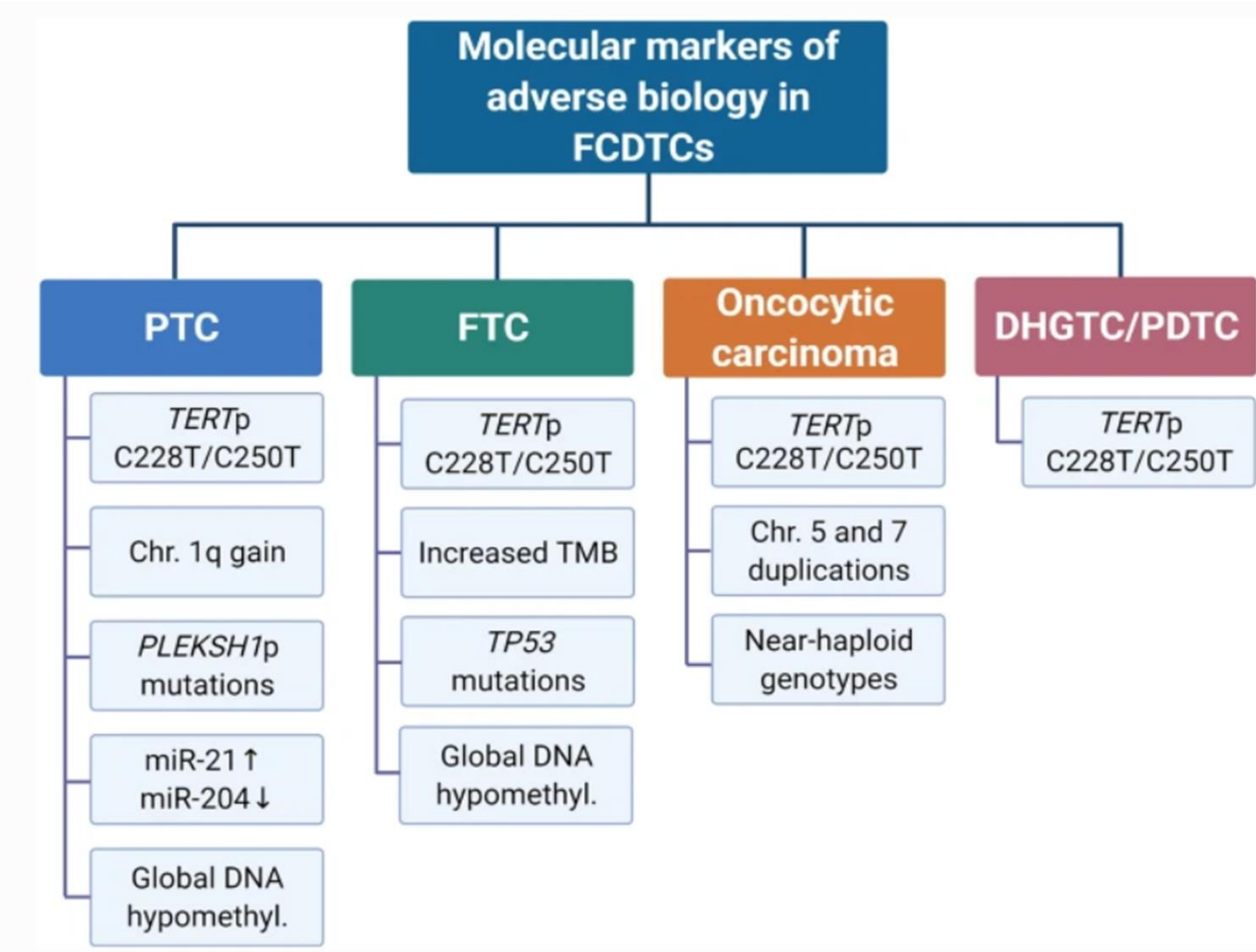
- Gene alteration such as BRAF, RAS pathway, PICK3CA, TERT promoter mutations, BRCA1/2

Follicular Cell-Derived Neoplasm of thyroid

Benign tumours
- Thyroid follicular nodular disease
- Follicular thyroid adenoma
- Follicular thyroid adenoma with papillary architecture
- Oncocytic adenoma of the thyroid

Low-risk neoplasms
- Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
- Thyroid tumours of uncertain malignant potential
- Hyalinizing trabecular tumour

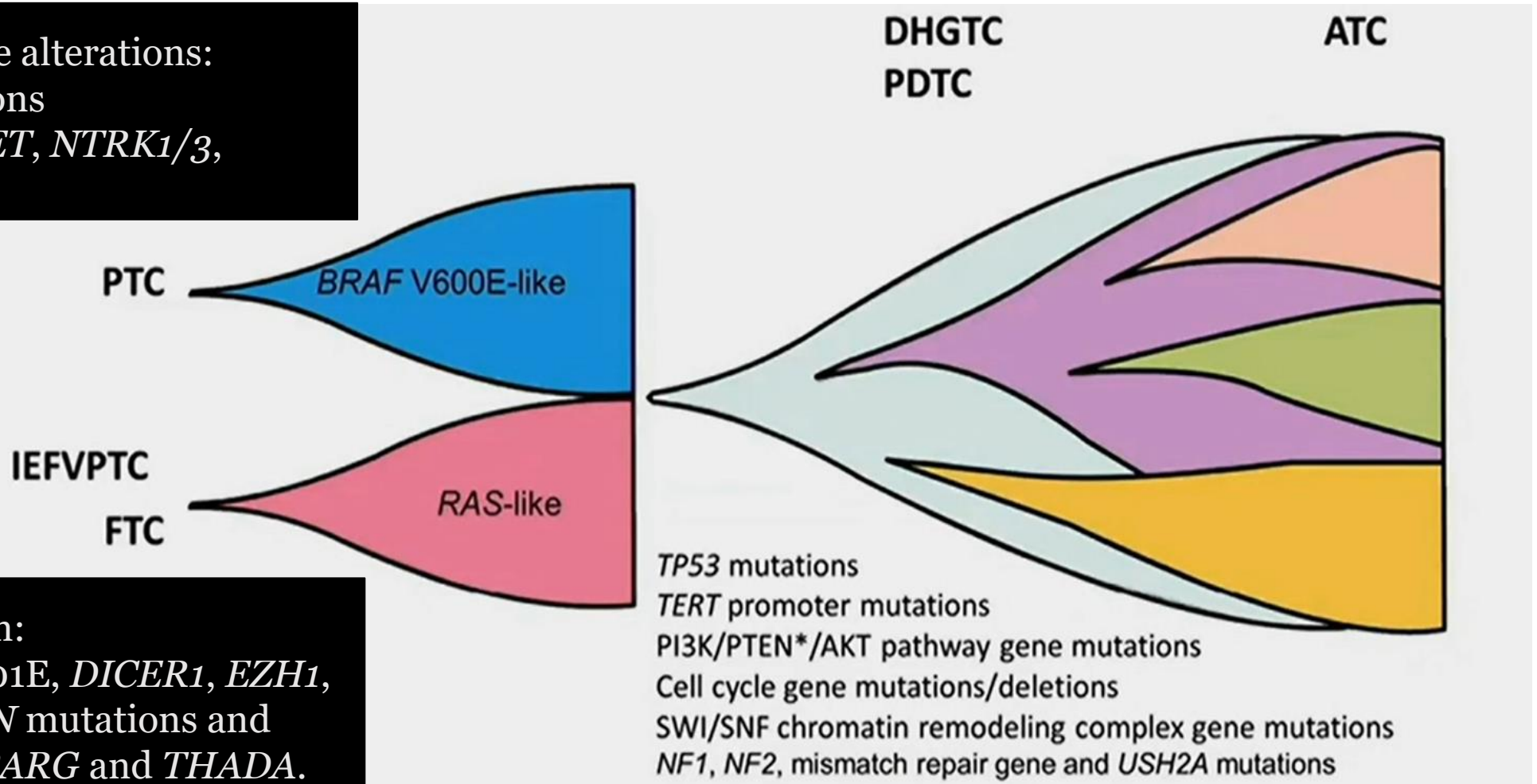
Malignant neoplasms
- Follicular thyroid carcinoma
- Invasive encapsulated follicular variant of papillary thyroid carcinoma
- Papillary thyroid carcinoma
- Oncocytic carcinoma of the thyroid
- High-grade follicular cell-derived non-anaplastic thyroid carcinoma
- Anaplastic thyroid carcinoma



WHO Classification of Tumours of Endocrine Organs. Vol 10. 5th ed. Lyon, France: WHO/IARC Press 2022

BRAF V600E–like alterations:
Include gene fusions
in *ALK*, *BRAF*, *RET*, *NTRK1/3*,
and *MET*

RAS-like alteration:
Include *BRAF* K601E, *DICER1*, *EZH1*,
EIF1AX, and *PTEN* mutations and
gene fusions in *PPARG* and *THADA*.



Baloch ZW, et al.
Endocr Pathol. 2022;

WHO Classification of Tumours of Endocrine Organs. Vol 10. 5th ed. Lyon, France: WHO/IARC Press 2022

Candidate “driver” gene fusions in PTC

PMC full text: Cell. Author manuscript; available in PMC 2015 Oct 23.
Published in final edited form as:
Cell. 2014 Oct 23; 159(3): 676–690.
doi: 10.1016/j.cell.2014.09.050

Figure 3

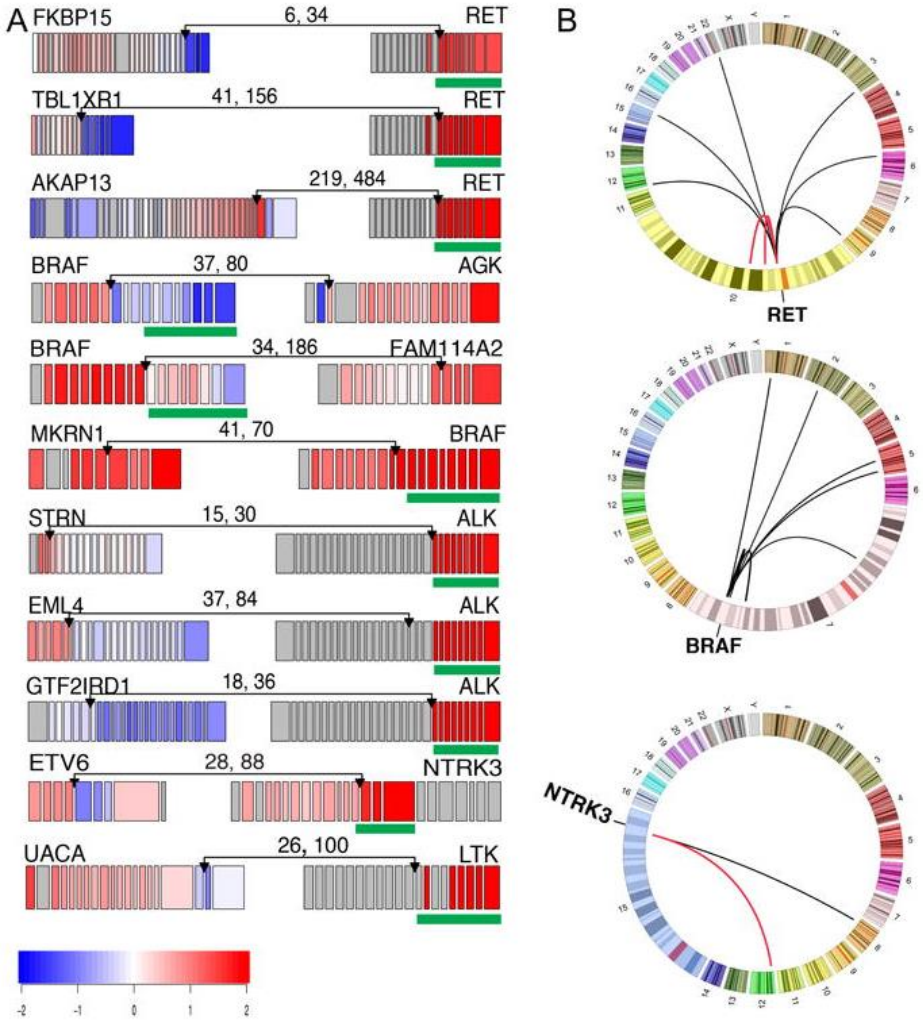


Table 7 Top 20 pathways for the four thyroid cancer subtypes as extracted from the literature.

Top	PTC		ATC		FTC		MTC	
	Pathway	Evidence	Pathway	Evidence	Pathway	Evidence	Pathway	Evidence
#1	Apoptosis	22120515	Apoptosis	20067110	Apoptosis	24213562	Apoptosis	10614665
#2	Cell cycle	23231932	Cell cycle	22688732	Angiogenesis	14605010	Cell cycle	21973234
#3	MAPK pathway	23544999	Angiogenesis	17575107	Cell cycle	19190121	Angiogenesis	20133461
#4	Angiogenesis	23528368	PI3K/Akt pathway	22918703	PI3K/Akt pathway	18492751	RET pathway	15316058
#5	DNA Repair	21860547	MAPK pathway	17989125	DNA Repair	22331172	mTOR pathway	22136849
#6	S Phase	22329804	S Phase	18813835	S Phase	2874658	S Phase	18791128
#7	PI3K/Akt pathway	22744707	M Phase	22399519	MAPK pathway	18492751	Focal Adhesion	12850460
#8	Glucose transport	21606885	NF-kB pathway	19158360	PI3K pathway	23128507	MAPK pathway	15746253
#9	PI3K pathway	20804548	Glucose transport	12667615	Focal Adhesion	20225271	Hedgehog (Hh) pathway	23410206
#10	Wnt/beta-catenin pathway	23261982	Focal Adhesion	19293266	Oxidative Stress	22331172	Notch1 pathway	18520232
#11	TGF-beta pathway	21874046	Wnt pathway	15650354	TGF-beta pathway	10942134	bone remodeling	6611007
#12	mTOR pathway	21822208	Glycolysis	3155492	Glucose transport	16273245	mRNA Processing	2582437
#13	Oxidative Stress	9774495	Notch1 pathway	23594881	thyroid hormone production	N/A	Raf-1 pathway	17363508
#14	MAPK/ERK pathway	22426956	G1 Phase	9038381	Glucose metabolism	19433487	PI3K pathway	17188151
#15	MEK/ERK pathway	20629553	mTOR pathway	20689131	cAMP pathway	N/A	Notch pathway	20182588
#16	cAMP pathway	21479404	Hedgehog (Hh) pathway	23860623	thyroid hormone biosynthesis	N/A	ERK activation	21470995
#17	Focal Adhesion	22513979	STAT3 pathway	22328572	Cytokinesis	15886755	PI3K/Akt pathway	23934677
#18	Notch pathway	23544172	Wnt/beta-catenin pathway	17218945	Hedgehog (Hh) pathway	N/A	Glucose transport	9426419
#19	Glycolysis	23846818	p21 pathway	22918703	Glycolysis	N/A	EGFR pathway	22025146
#20	Glucose metabolism	20473281	Rb/E2F pathway	15118916	VEGF pathway	18509004	Glycolysis	3155492

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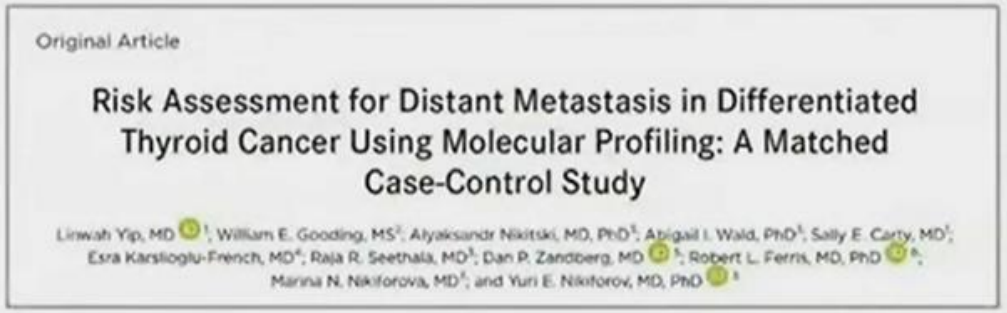
City of Hope

Use of Genetic Markers for Cancer Risk Assessment



Original Article

Risk Assessment for Distant Metastasis in Differentiated Thyroid Cancer Using Molecular Profiling: A Matched Case-Control Study

Linwah Yip, MD [1], William E. Gooding, MS [2], Alyaksandr Nikitski, MD, PhD [3], Abigail I. Wald, PhD [3], Sally E. Carty, MD [1], Esra Karslioglu-French, MD [4], Raja R. Seethala, MD [3], Dan P. Zandberg, MD [5], Robert L. Ferris, MD, PhD [6], Marina N. Nikiforova, MD [3], and Yuri E. Nikiforov, MD, PhD [3]

- Case-control study
  - 64 patients with DTC with distant mets
  - Propensity matched cohort to DTC without distant mets (age, gender, tumor size)
- ≥5 years follow-up

Proposed Clinical Impact

MRG-Low	MRG-Intermediate	MRG-High
• Lobectomy • Active surveillance • RFA • No RAI	• Total thyroidectomy • Neck US with lymph node mapping • RAI	• Total thyroidectomy • Prophylactic CND • Chest CT • Laryngoscopy • RAI
3-yr recurrence 97.1%	3-yr recurrence 79.2%	3-year recurrence 54.3%

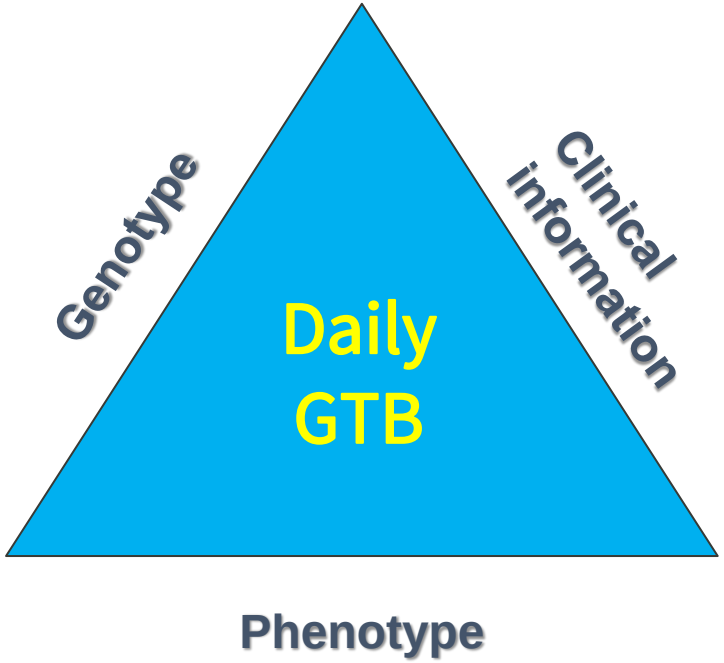
ThyroSeq Molecular Risk Groups (MRGs)

Low risk	Intermediate Risk	High Risk
RAS	BRAF V600E	TERT, TP53, AKT1, or PIK3CA co-occurring with BRAF, RAS or other alterations
RAS-like mutations, fusions, gene expression alterations (eg. PTEN mutation, PPARG fusion)	BRAF-like mutations and gene fusions (eg. RET fusion)	*TERT* mutations alone at high AF
Copy number alterations of focal chromosomal type	Copy number alterations of genome haploidization (GH) type	DICER1 mutation + CNA characteristic of PDTC of children and young adults
		GH-type CNA + MET CNA
		RET mutation in MTC

Yip L. et al. *Cancer* 2021

Personalized Genomic at COH

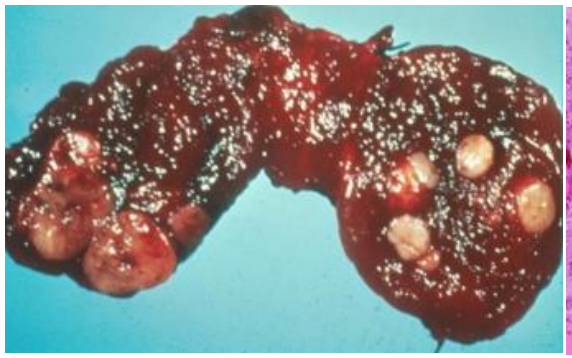
- Daily Genomic Tumor Board (GTB)
- Accessibility to pathologists and CMDL team by Text, EPIC, and Email
- Communication of plan for treatment or next testing plan during disease team and GTB
- Low tumor cellularity requirements for both DNA and RNA sequencing
- Rapid Solid tumor panel with same DNA/RNA extraction
- Fusion detection of genes included with any known and novel partner >5000 rearrangements
- Immunostain addition to the test, PD-L1, CLND18, HER2, FOLR1,…
- High depth of coverage: MMRD detection
- Fast Turn Around Time
- Ease of ordering

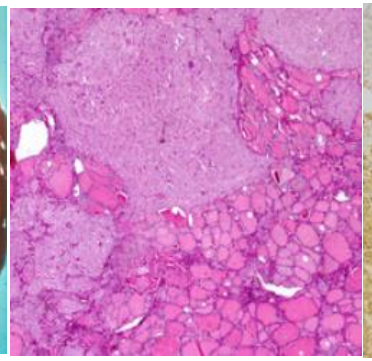


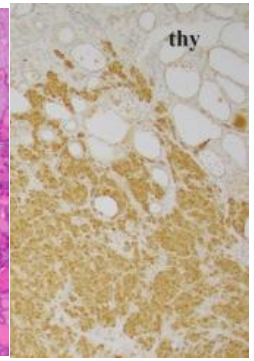
Personalized Genomic and Cytogenomics Pathology

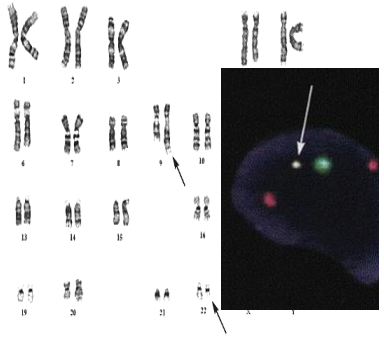
Tissue pathology → **Molecular Genomics & Cytogenomics Pathology**

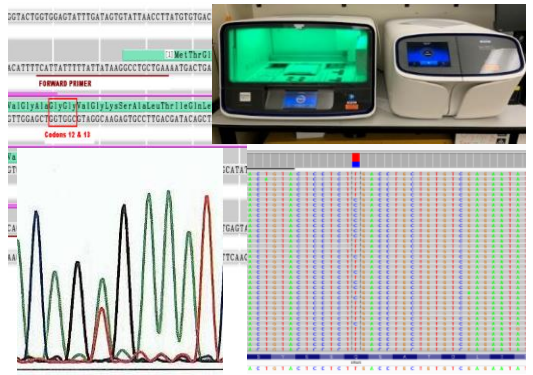
Microscopy → Immunophenotyping → Karyotyping & FISH → PCR & Sequencing









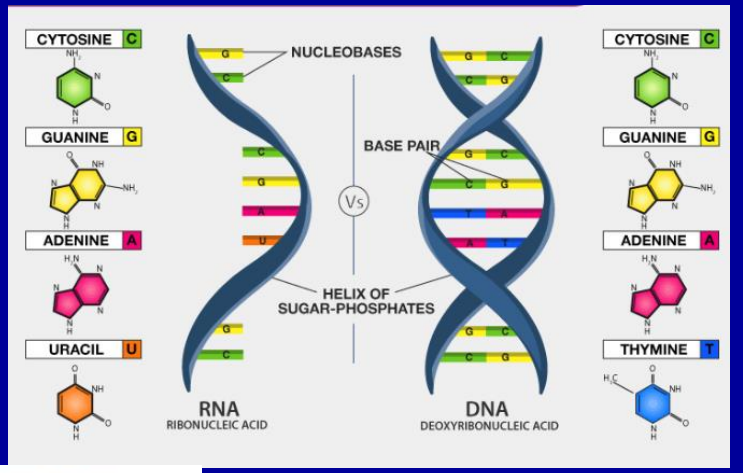


Phenotype + Genotype = Personalized Genomics

What assays are available in house at COH?

1. Multigene HopeSeq Solid Tumor Comprehensive NGS assay (DNA+RNA)
2. Rapid Solid tumor assay (EGFR, BRAF, NRAS,KRAS, HRAS, PIK3CA)*
3. Single gene panel for **TERT promoter mutations**, BRAF, TP53, etc.

Needs FFPE of the cytology cell block or core biopsies or resection
Very small amount of DNA or RNA



Specimen	Extract nucleic acids	Library prep and enrichment	Sequence	Data processing and variant calling	Interpretation and reporting
FFPE 40ng DNA / 40 ng RNA	DNA/RNA extraction kits	TruSight™ Oncology 500 Kit + TruSight™ Oncology 500 HRD Kit	NextSeq™ 550 and NextSeq 550Dx System (RUO mode) Up to 8 samples NovaSeq™ 6000 System SP Up to 16 samples	DRAGEN TruSight™ Oncology 500 (on-premise and on cloud)	Commercially available software solutions. (Not included)

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Thyroid, Vol. 31, No. 6 | Thyroid Cancer and Nodules

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Papillary Thyroid Carcinoma with High-Grade Features Versus Poorly Differentiated Thyroid Carcinoma: An Analysis of Clinicopathologic and Molecular Features and Outcome

Kristine S. Wong, Fei Dong, Milhan Telatar, Jochen H. Lorch, Erik K. Alexander, Ellen Marqusee, Nancy L. Cho, Matthew A. Nehs, Gerard M. Doherty, Michelle Afkhami, and Justine A. Barletta

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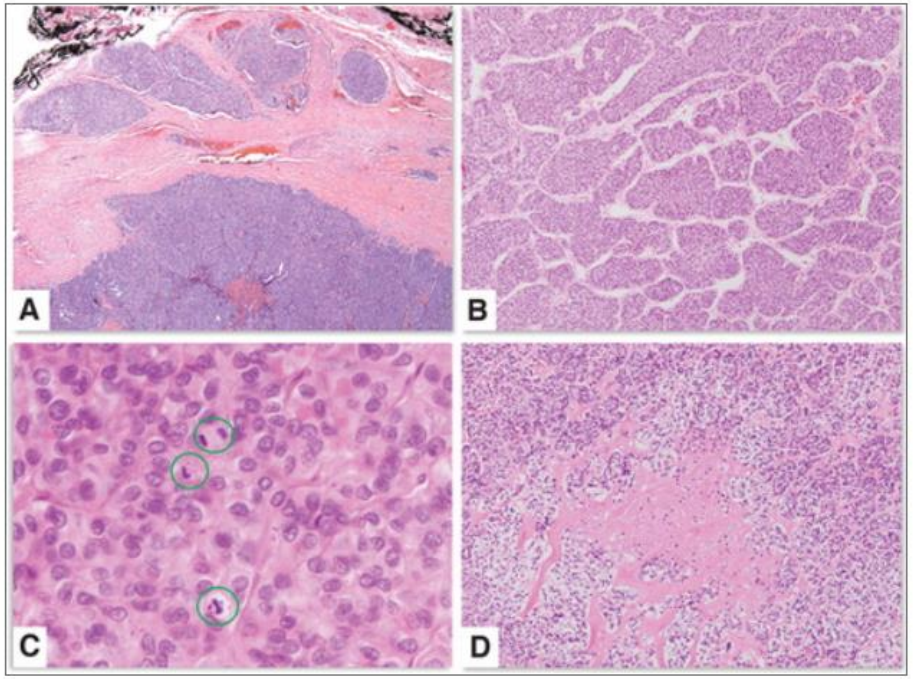

FIG. 2. Examples of WHO-defined PDTC. All tumors demonstrated invasive growth (**A**), solid/trabecular/insular growth (**B**), and increased mitotic activity (**C**) (mitoses circled), and/or tumor necrosis (with true tumor-type coagulative necrosis with ghosts of tumor cells required as shown) (**D**), along with a loss of nuclear features of papillary thyroid carcinoma. PDTC, poorly differentiated thyroid carcinoma; WHO, World Health Organization. Color images are available online.

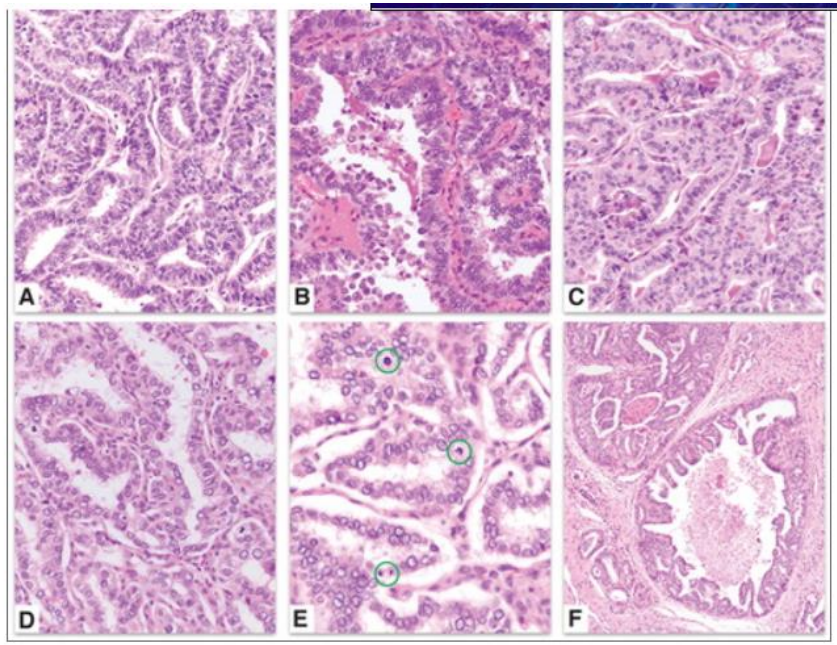

FIG. 1. Examples PTC HGF. Most tumors had the morphology of an aggressive PTC subtype such as columnar cell variant (**A**), hobnail variant (**B**), or tall cell variant (**C**), although one case was a classic PTC (**D**). All cases of PTC HGF had maintained nuclear features of PTC along with either increased mitotic activity (**E**) (mitoses circled) and/or tumor necrosis (with tumor associated with comedo necrosis shown) (**F**). PTC HGF, papillary thyroid carcinoma with high-grade features.

Comparative Study > Thyroid. 2021 Jun;31(6):933-940. doi: 10.1089/thy.2020.0668.
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Kristine S Wong [1], Fei Dong [1], Milhan Telatar [2], Jochen H Lorch [3], Erik K Alexander [4], Ellen Marqusee [4], Nancy L Cho [4], Matthew A Nehs [5], Gerard M Doherty [5], Michelle Afkhami [2], Justine A Barletta [1]

We believe it is important to distinguish PTC HGF from WHO-defined PDTC based on molecular differences between these tumors. PTC HGF had a higher *BRAF*^{V600E} mutation rate (42% of cases) as a driver event compared with PDTC (3% of cases). Conversely, PDTC had a higher rate of *RAS* mutations (30% of cases), although the difference with PTC HGF (17% of cases) did not reach significance. These findings are not surprising given that the *BRAF*^{V600E} mutation has been associated with pronounced nuclear features of PTC, and that the tall cell and hobnail variants of PTC have been shown to frequently harbor the *BRAF*^{V600E} mutation (21–24). In contrast, *RAS* mutations are more commonly seen in follicular-patterned tumors without or with only subtle nuclear features of PTC (25–27). Our findings are consistent with those of an MSKCC study by Landa and

Characteristic	PTC HGF (*n* = 12)	PDTC (*n* = 33)	p-Value
Driver alteration			
BRAF mutation [*n* (%)]			
BRAF^{V600E}	5 (42)	1 (3)	0.0033
BRAF N486_P490del	1 (8)	1 (3)	ns
RAS mutation [*n* (%)][a]	2 (17)	10 (30)	ns
Gene fusion [*n* (%)]	3 (25)	1 (3)	0.052
ETV6-NTRK3	1 (8)		
AGK-BRAF	1 (8)		
CCDC30-ROS1	1 (8)		
PAX8-PPARG		1 (3)	
Secondary alteration			
TERT	4 (33)	10 (30)	ns
TP53	4 (33)	5 (15)	ns
Copy number alterations			
1q gain	8 (67)	5 (15)	0.0017
22q loss	5 (33)	8 (24)	ns

[a]*RAS* mutations included: *NRAS*^{Q61R}, *NRAS*^{Q61K}, *HRAS*^{G13R}, *HRAS*^{Q61R}, and *KRAS*^{Q61R}.

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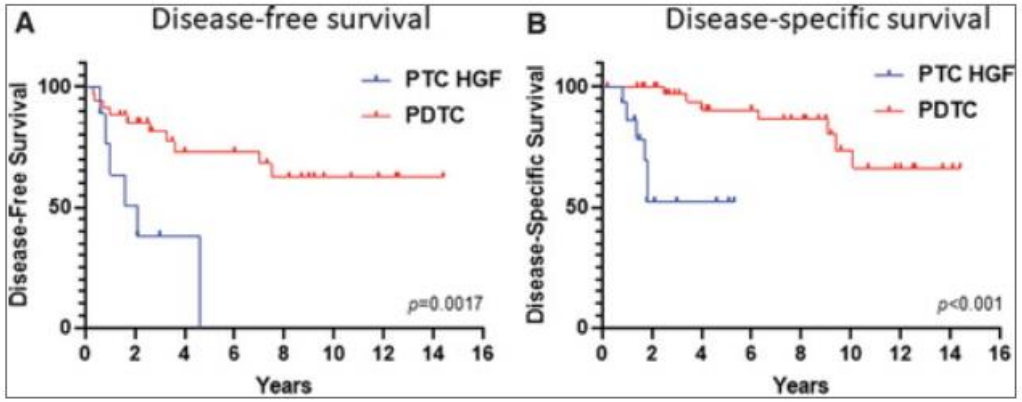


FIG. 3. DFS for patients with M0 disease with PTC HGF and PDTC (**A**). DSS for patients with PTC HGF and PDTC (**B**). DFS, disease-free survival; DSS, disease-specific survival. Color images are available online.

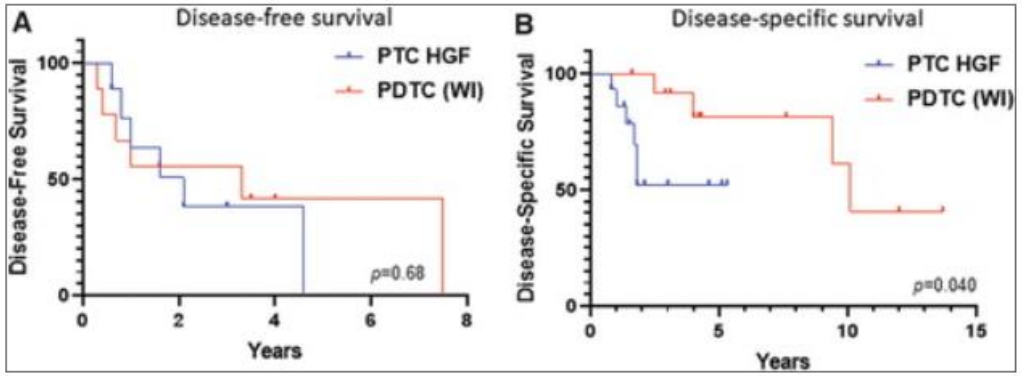


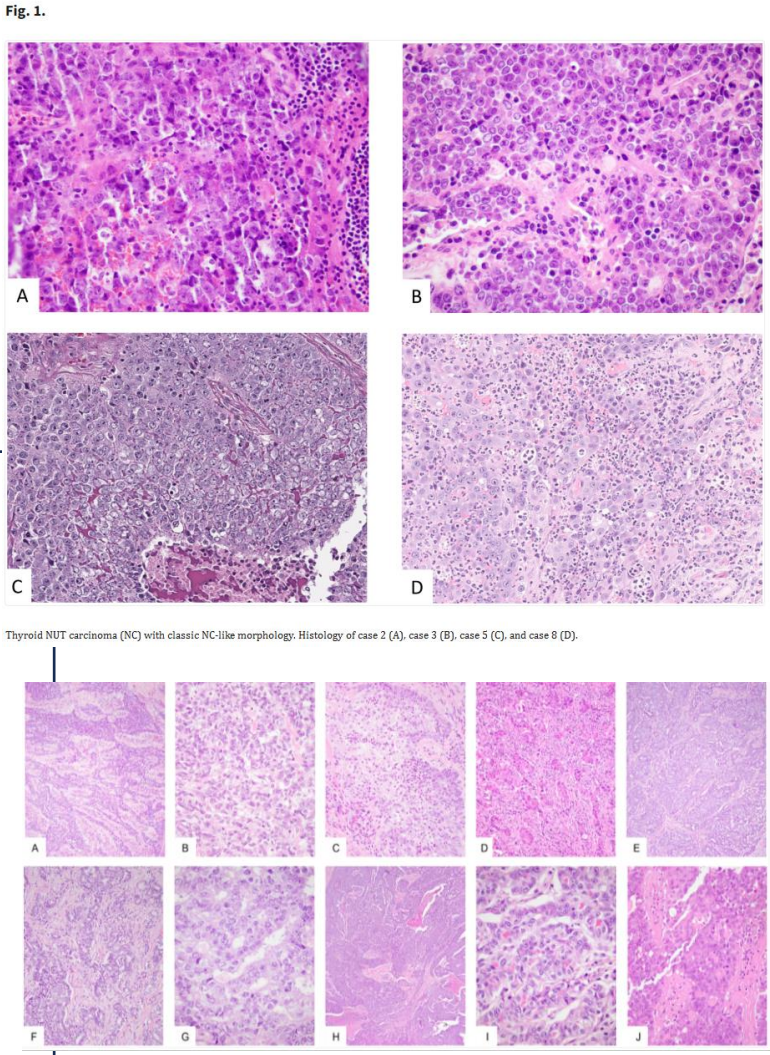
FIG. 4. DFS for patients with M0 disease with PTC HGF and widely invasive PDTC (**A**). DSS for patients with PTC HGF and widely invasive PDTC (**B**). Color images are available online.

- Barletta JA, Gilday S, Afkhami M, Bell D, Bocklage T, Boisselier P, Chau NG, Cipriani NA, Costes-Martineau V, Ghossein RA, Hertzler HJ, Kramer AM, Limaye S, Lopez CA, Ng TL, Weissferdt A, Xu B, Zhang S, French CA. **NUTM1 - rearranged Carcinoma of the Thyroid : A Distinct Subset of NUT Carcinoma Characterized by Frequent NSD3 - NUTM1 Fusions. Am J Surg Pathol. 2022;46(12):1706-15. PMID: 36040068.**

NUTM1 rearrangements by gene fusions are a defining event in NUT-carcinoma and are more commonly reported in the thoracic cavity, and head and neck region.

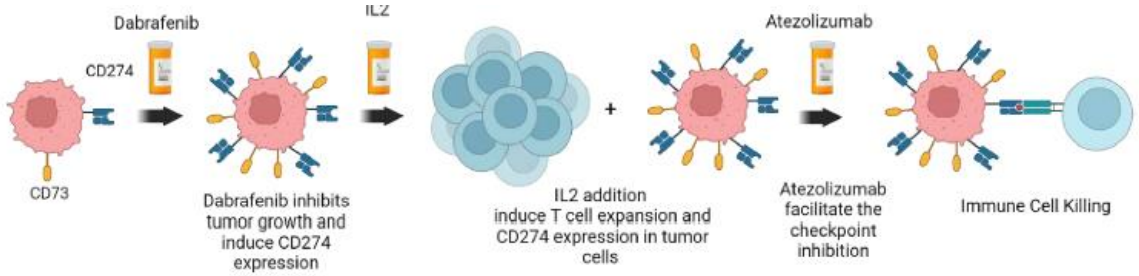
NUT carcinoma (NC) is a rare subtype of squamous cell carcinoma defined by *NUTM1* rearrangements encoding NUT fusion oncoproteins (the most frequent fusion partner being *BRD4*) that carries a very poor prognosis, with most patients dying in under 1 year.

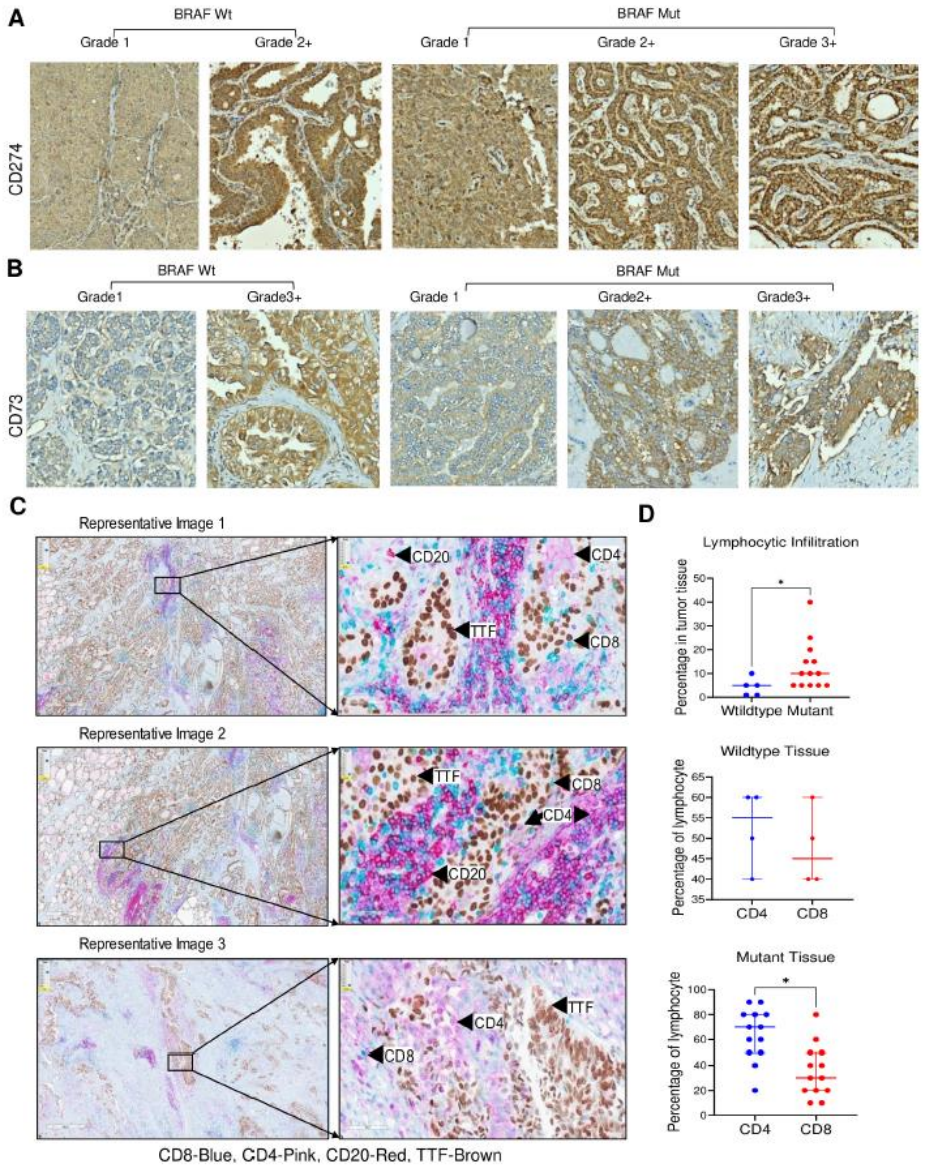
Our study shows that NC of the thyroid can mimic other thyroid primaries, has a high rate of *NSD3 - NUTM1* fusions, and an overall more protracted clinical course compared with non-thyroid primary NC.



Mohanty A, Afkhami M, Reyes A, Pharaon R, Yin H, Sun J, Nam A, Chang S, Gernon T, Kang R, Amini A, Sampath S, Vora N, Pillai R, Salgia R, Maghami E, Massarelli E. Exploring markers of immunoresponsiveness in papillary thyroid carcinoma and future treatment strategies. J Immunother Cancer. 2024;12(7):e008505.

- **Our study found that PTC cases with *BRAF* mutations had higher expression of immune checkpoint markers CD274 and CTLA4, as well as higher tumor-infiltrating lymphocytes, particularly CD4+ T cells.**
- **Additionally, the study identified immunosuppressive markers expressed by tumor cells like CD73, CD276, and CD200 that could be targeted for immunotherapy.**
- **Further experiments using PTC cell lines lead to the conclusion that CD274 expression correlates with *BRAF* activity and that inhibitors of *BRAF* could potentially be used in combination with immunotherapy to treat PTC.**





Future Direction: Digital Pathology and AI for Prediction of biomarkers and Therapy

- "third generation sequencing" – e.g. oxford nanopore
- Optical genomic mapping - e.g. Bionano
- Digital spatial profiling
- Digital imaging and machine learning
- Others...

Review > Ann Oncol. 2024 Jan;35(1):29-65. doi: 10.1016/j.annonc.2023.10.125. Epub 2023 Oct 23.

Artificial intelligence for predictive biomarker discovery in immuno-oncology: a systematic review

A Prelaj [1], V Miskovic [2], M Zanitti [3], F Trovo [4], C Genova [5], G Viscardi [6], S E Rebuzzi [7], L Mazzeo [2], L Provenzano [8], S Kosta [3], M Favali [4], A Spagnoletti [8], L Castelo-Branco [9], J Dolezal [10], A T Pearson [10], G Lo Russo [8], C Proto [8], M Ganzinelli [8], C Giani [8], E Ambrosini [4], S Turajlic [11], L Au [12], M Koopman [13], S Delaloge [14], J N Kather [15], F de Braud [8], M C Garassino [10], G Pentheroudakis [16], C Spencer [17], A L G Pedrocchi [4]

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PMID: 37879443 DOI: 10.1016/j.annonc.2023.10.125

> Nat Commun. 2021 Mar 12;12(1):1613. doi: 10.1038/s41467-021-21896-9.

Human-interpretable image features derived from densely mapped cancer pathology slides predict diverse molecular phenotypes

James A Diao [# 1 2], Jason K Wang [# 1 2], Wan Fung Chui [# 1 2], Victoria Mountain [1], Sai Chowdary Gullapally [1], Ramprakash Srinivasan [1], Richard N Mitchell [2 3], Benjamin Glass [1], Sara Hoffman [1], Sudha K Rao [1], Chirag Maheshwari [1], Abhik Lahiri [1], Aaditya Prakash [1], Ryan McLoughlin [1], Jennifer K Kerner [1], Murray B Resnick [1 4], Michael C Montalto [1], Aditya Khosla [1], Ilan N Wapinski [1], Andrew H Beck [# 5], Hunter L Elliott [# 1], Amaro Taylor-Weiner [# 6]

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PMID: 33712588 PMCID: PMC7955068 DOI: 10.1038/s41467-021-21896-9