Molecular Diagnostics and Theranostics

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UPMC LIFE CHANGING MEDICINE

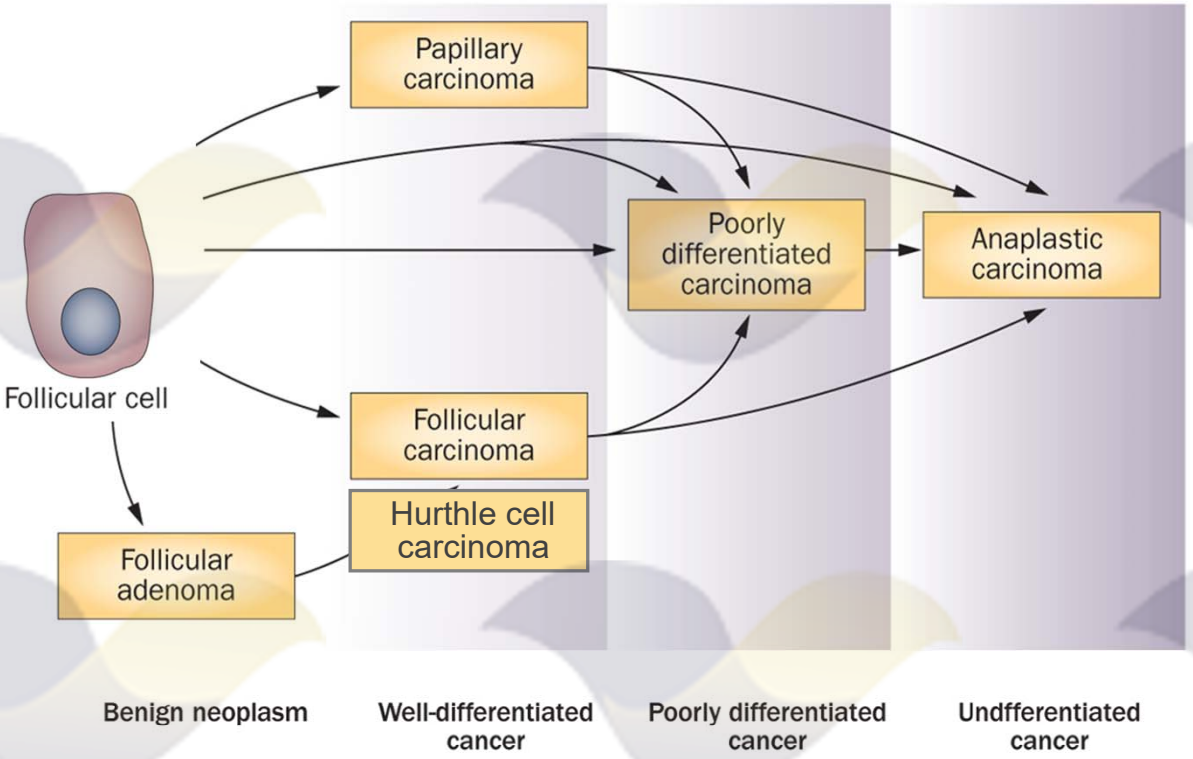
Disclosures

- Own IP related to ThyroSeq through University of Pittsburgh (royalties)
- Consultant to Sonic Healthcare USA (consultant fees)

Outlines

- Molecular classification based on early driver alterations: BRAF-like, RAS-like, CNA-driven tumors
- Impact of late driver mutations (TERT) on differentiation
- Frequency of molecular groups
- Genetic variability of primary and metastatic tumors

Thyroid Cancer



Papillary Thyroid Carcinoma

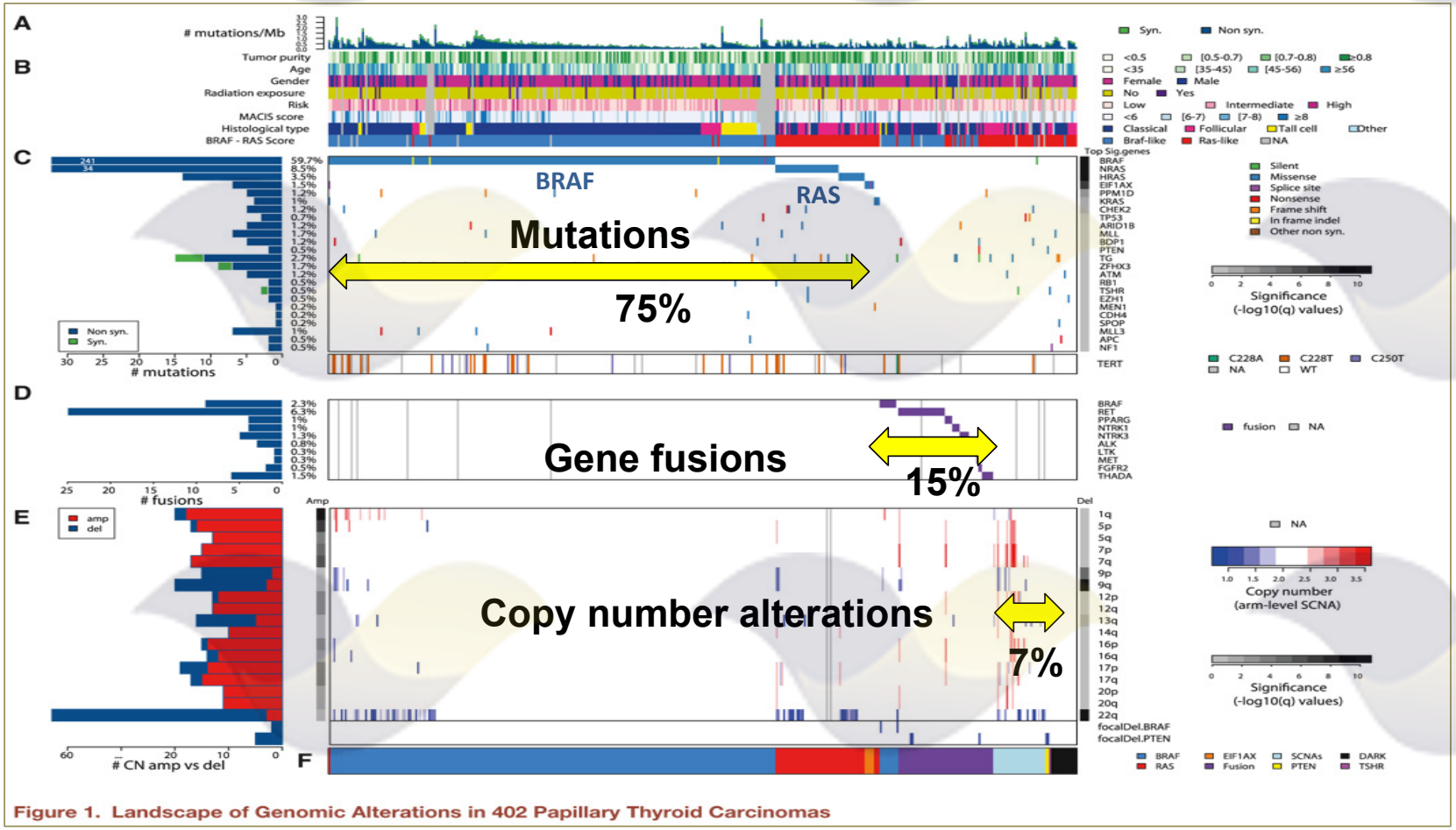
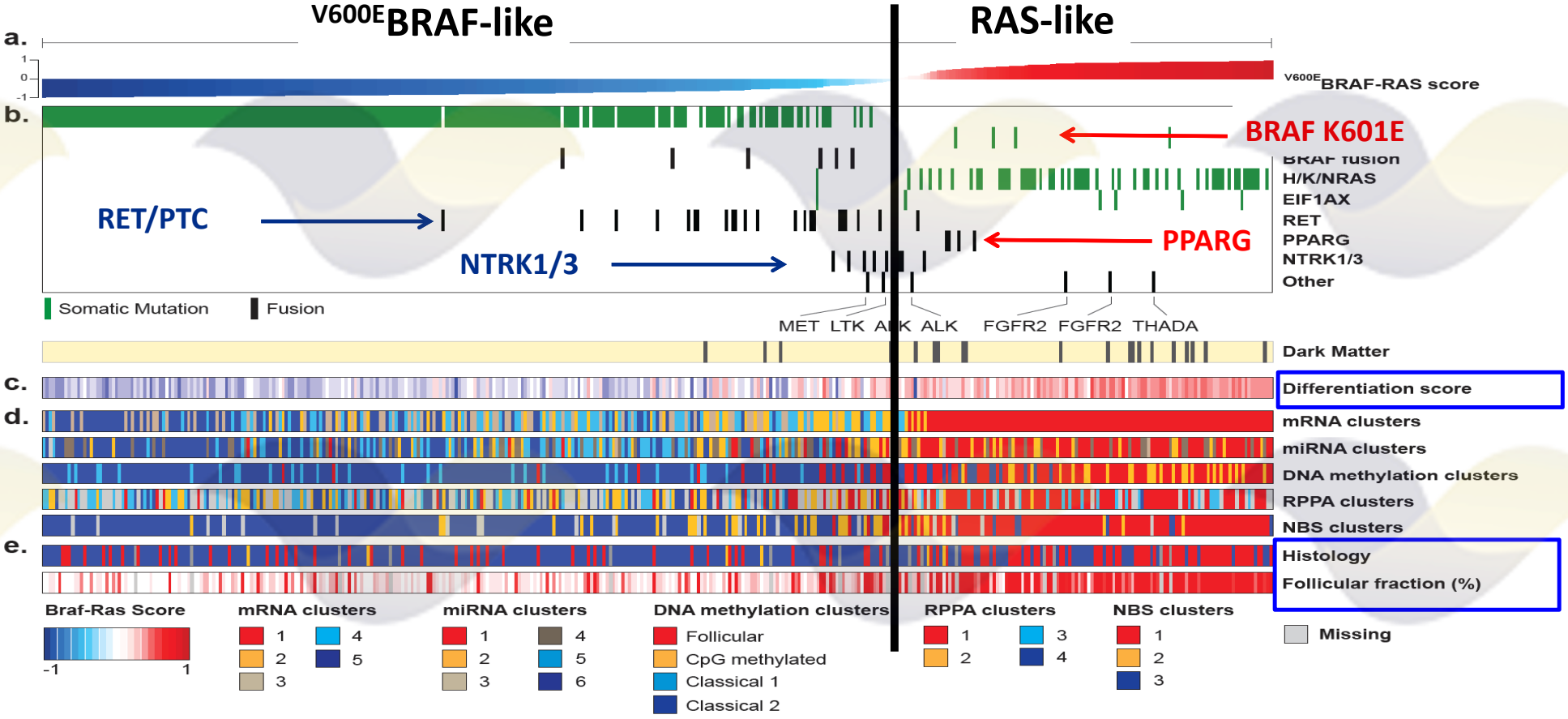


Figure 1. Landscape of Genomic Alterations in 402 Papillary Thyroid Carcinomas

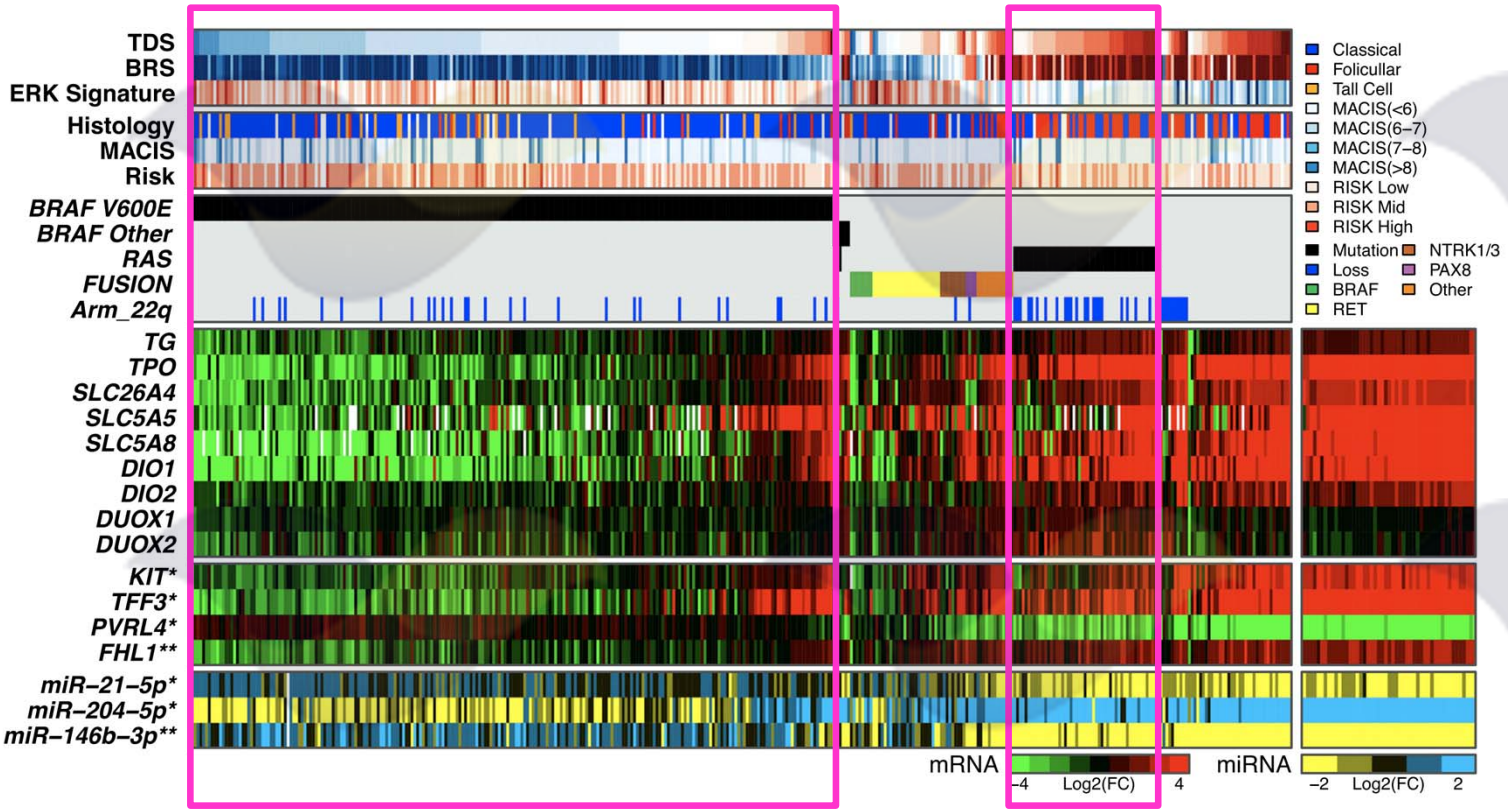
The Cancer Genome Atlas Research Network. *Cell* 159:676-690 (2014)

BRAF-like and RAS-like Papillary Carcinomas



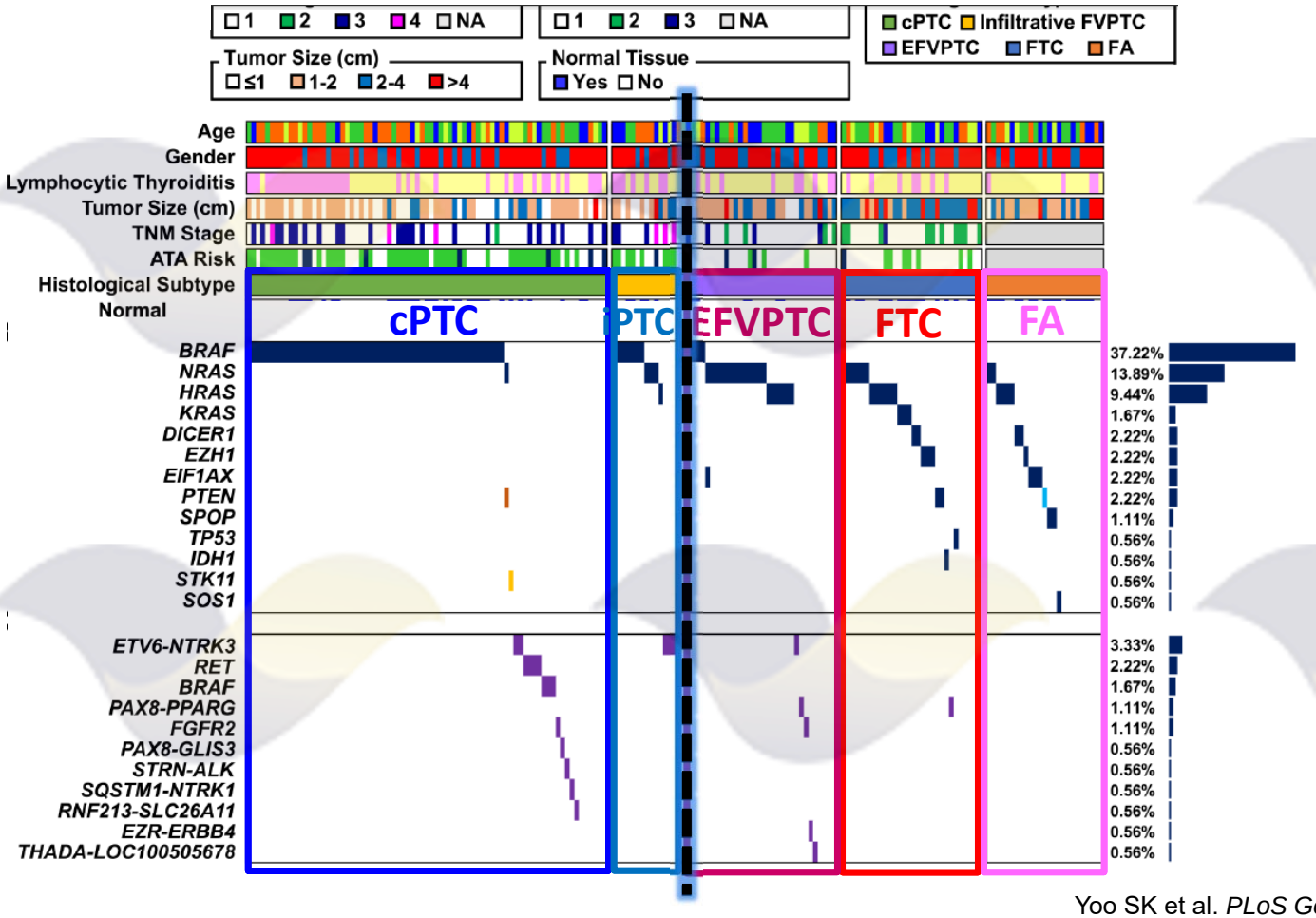
The Cancer Genome Atlas Research Network. *Cell* 159:676-690 (2014)

BRAF-like and RAS-like PTC: Thyroid Differentiation Markers



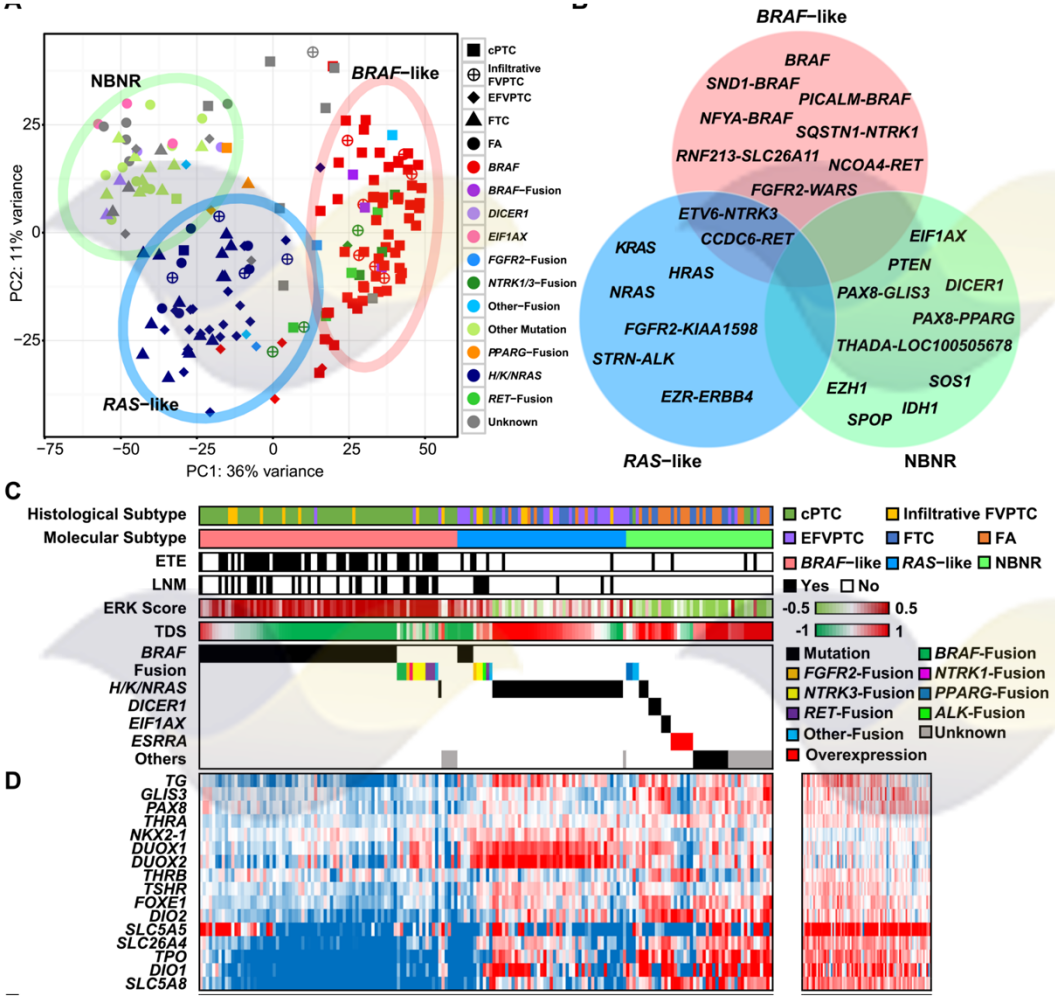
The Cancer Genome Atlas Research Network. *Cell* 159:676-690 (2014)

Follicular Thyroid Carcinoma



Yoo SK et al. *PLoS Genet*. 2016;12(8):e100623

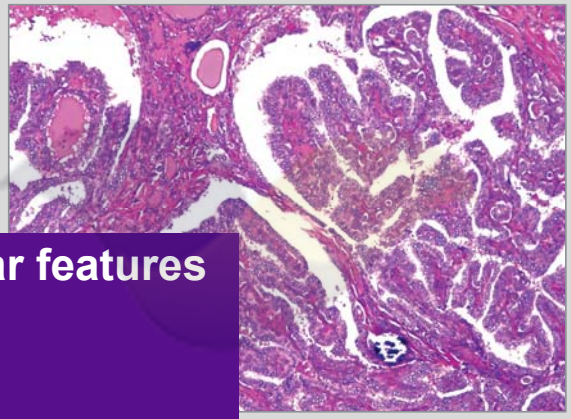
Follicular Thyroid Carcinoma



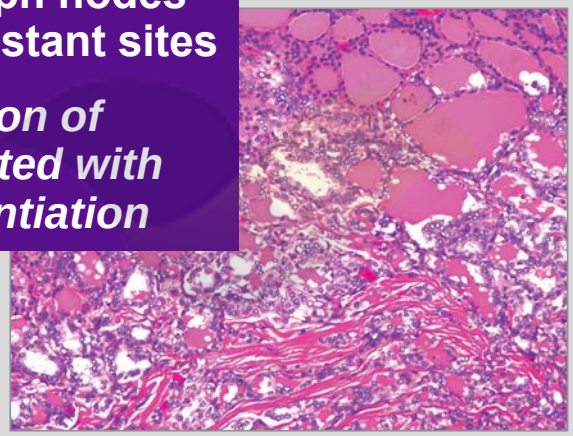
Yoo SK et al. *PLoS Genet*. 2016;12(8):e100623

BRAF-like tumors

cPTC



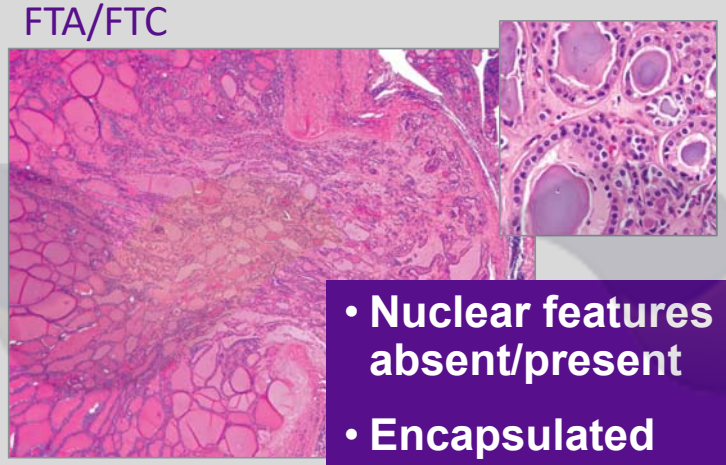
VPTC



- **Classic nuclear features of PTC**
- **Infiltrative**
- **Spread to lymph nodes first, later to distant sites**
- ***Lose expression of genes associated with thyroid differentiation***

RAS-like tumors

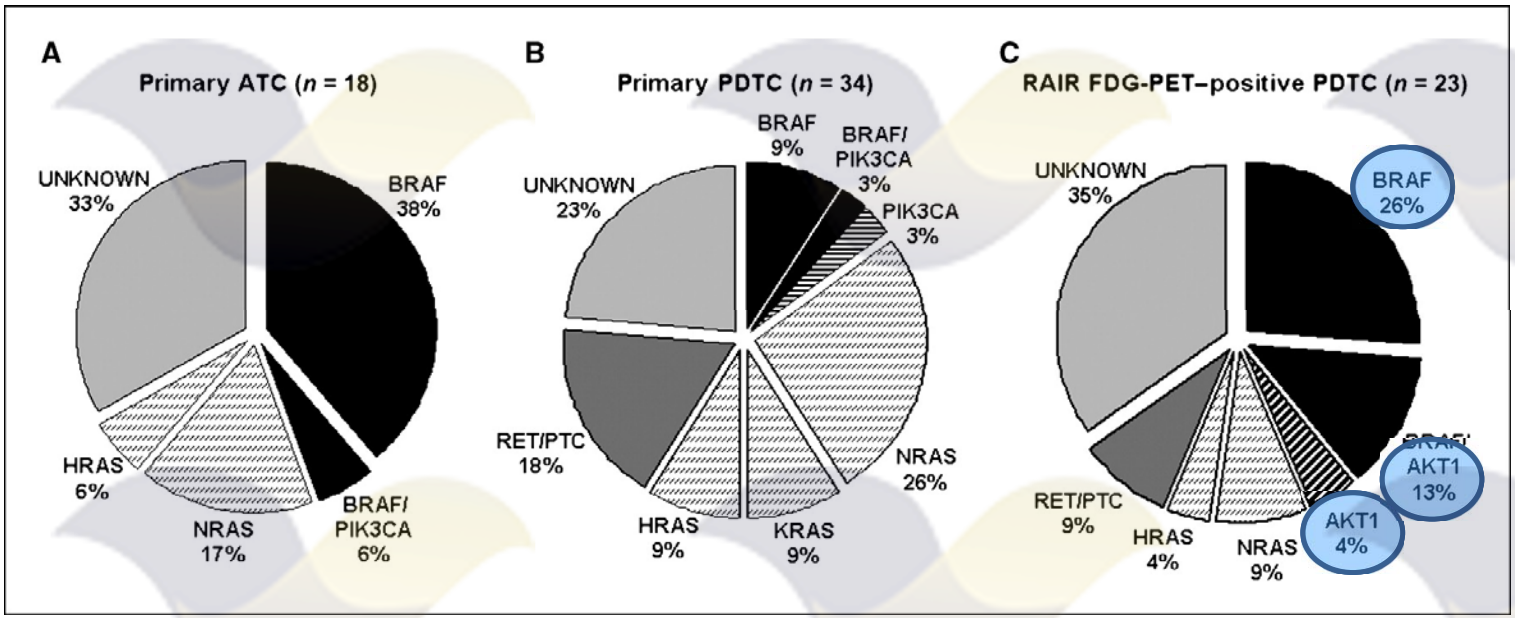
FTA/FTC



NIFTP Invasive

- **Nuclear features of PTC absent/present**
- **Encapsulated**
- **Spread to distant sites, rarely to lymph nodes**
- ***Retain expression of genes associated with thyroid differentiation***

^{131}I-Refractory Disease



Mutational frequency of BRAF, RET/PTC, NRAS, HRAS, KRAS, AKT1, and PIK3CA in (A) 18 primary ATC, (B) 34 primary PDTC, and (C) 23 RAIR, FDG-PET-positive PDTC.

Ricarte-Filho JC et al. Cancer Res 2009;69:4885-93

TERT Promoter Mutation Predicts Radioiodine-Refractory Character in Distant Metastatic Differentiated Thyroid Cancer

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Telomerase reverse transcriptase (*TERT*) promoter mutation has been reported to be associated with aggressive characteristics in differentiated thyroid cancer (DTC). This study examined the status of *TERT* mutation in distant metastatic DTC and evaluated the correlation between *TERT* mutation and radioiodine uptake, as well as that between *TERT* mutation and therapy response. **Methods:** *TERT* promoter and B-Raf proto-oncogene (*BRAF*) V600E mutation were retrospectively examined in primary tumors of 66 patients with mutation manifested a greater negative influence on radioiodine uptake. *TERT* mutation could also be used as an early predictor of radioiodine-refractory cases.

Key Words: differentiated thyroid carcinoma; *TERT* mutation; radioactive iodine therapy; therapy response

J Nucl Med 2017; 58:258–265
DOI: 10.2967/jnumed.116.180240

- 66 patients with distant metastatic DTC.
- Stimulated thyroglobulin (sTg),RAI uptake status (avid or nonavid), and other imaging evidence to evaluate therapy response.
- After a median follow-up of 46.5 mo (interquartile range, 29.0–70.5 mo), therapy response was classified as either disease control or refractory.
- TERT mutation significantly correlated with non–radioiodine avidity
- Patients with distant metastatic DTC with TERT mutation were more likely to lose radioiodine avidity at the
- initial radioiodine therapy

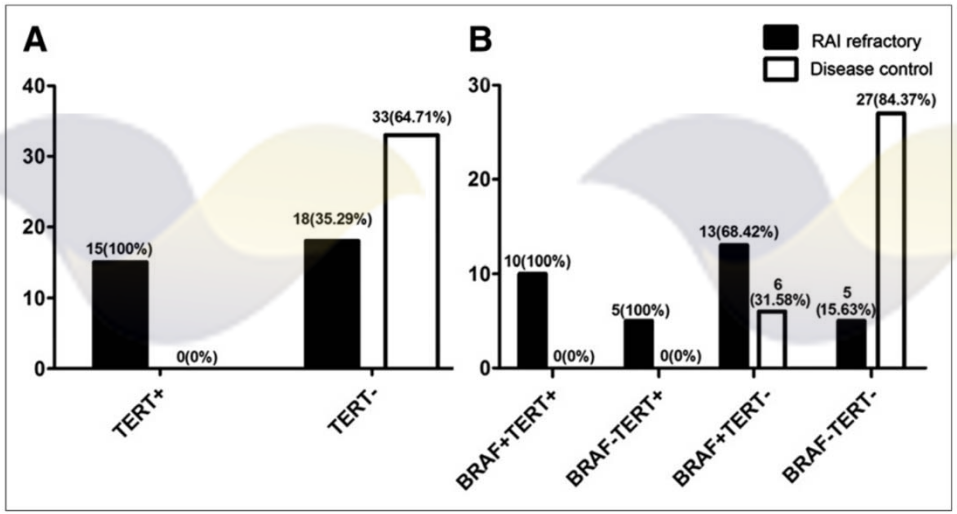


FIGURE 1. Association between *TERT*/*BRAF* mutation and radioiodine therapy response in distant metastatic DTC. (A) Association between *TERT* mutation and radioiodine therapy response (radioiodine-refractory or disease control). (B) Radioiodine responses of 4 different mutational scenarios. RAI = radioiodine.

Ricarte-Filho JC et al. Cancer Res 2009;69:4885-93

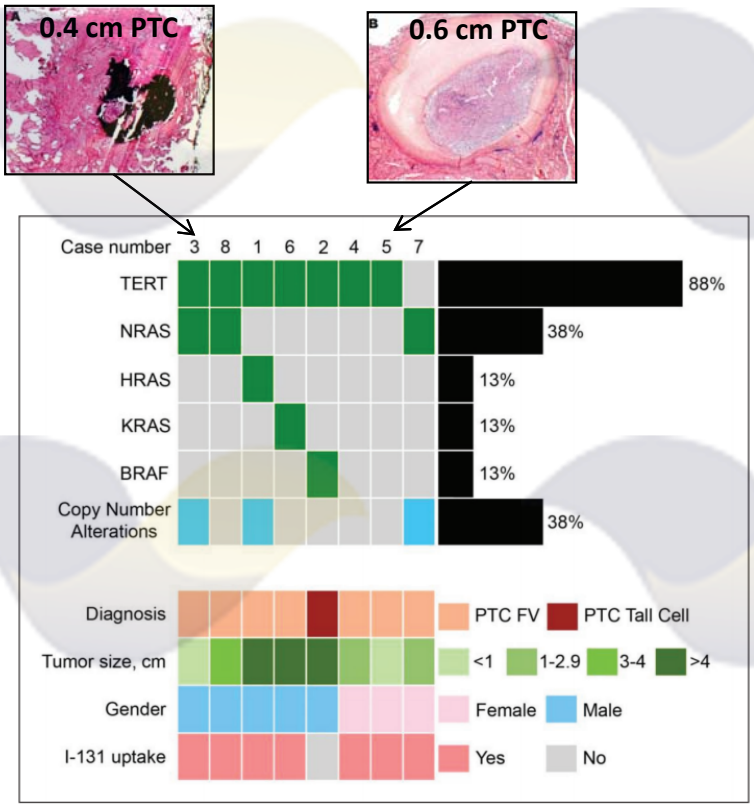
I-131 uptake in metastatic thyroid cancer with different molecular profiles

MOLECULAR PROFILE AND CLINICAL OUTCOMES IN DIFFERENTIATED THYROID CANCER PATIENTS PRESENTING WITH BONE METASTASIS

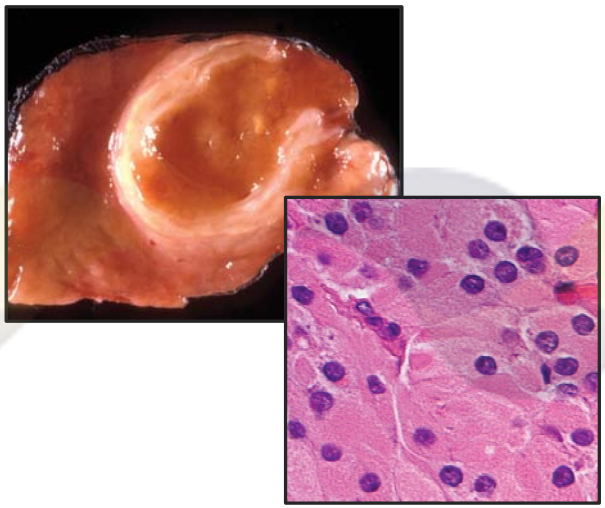
Nilma Malik, MD[1]; Alyaksandr V. Nikitski, MD, PhD[2]; Elie Klam, MD[3]; Jason Hunt, MD[4]; Benjamin Witt, MD[5]; Barbara Chadwick, MD[5]; Yuri E. Nikiforov, MD, PhD[2]; Devaprabu Abraham, MD, MRCP (UK)[1]

Malik N et al. *Endocr Pract*. 2019

- 8 patients presented with symptomatic bone metastasis from unknown primary
- Bone biopsy – thyroid cancer
- Thyroid surgery: 7 - follicular variant PTC; 1 - tall cell variant PTC
- Primary tumor size 0.4-7.5 cm



Hurthle cell tumors



Integrated Genomic Analysis of Hürthle Cell Cancer Reveals Oncogenic Drivers, Recurrent Mitochondrial Mutations, and Unique Chromosomal Landscapes

Ian Ganly,[1,2,*] Vladimir Makarov,[1,3] Shyamprasad Deraje,[1] YiYu Dong,[1] Ed Reznik,[4,5] Venkatraman Seshan,[4] Gouri Nanjangud,[6] Stephanie Eng,[1] Promita Bose,[1] Fengshen Kuo,[1] Luc G.T. Morris,[1,2] Inigo Landa,[1] Pedro Blecua Carrillo Albornoz,[1,3] Nadeem Riaz,[1,3] Yuri E. Nikiforov,[7] Kepal Patel,[8] Christopher Umbricht,[9] Martha Zeiger,[9] Electron Kebebew,[10] Eric Sherman,[11] Ronald Ghossein,[12] James A. Fagin,[1] and Timothy A. Chan[1,3,13,*]

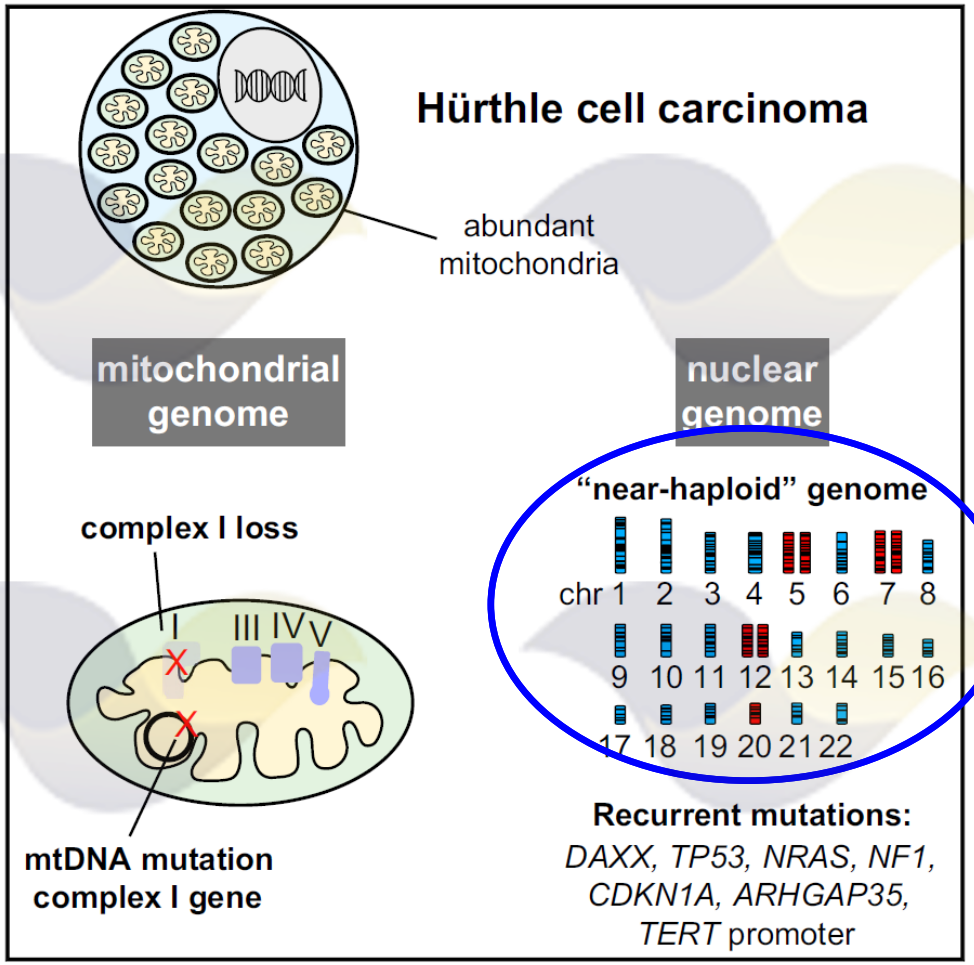
Ganly et al. Cancer Cell 2018

Widespread Chromosomal Losses and Mitochondrial DNA Alterations as Genetic Drivers in Hürthle Cell Carcinoma

Raj K. Gopal,[1,2,6,8,9,11,19] Kirsten Kübler,[2,8,11,19] Sarah E. Calvo,[6,8,9] Paz Polak,[2,4,8,11,16] Dimitri Livitz,[8] Daniel Rosebrock,[8] Peter M. Sadow,[2,4,11] Braidie Campbell,[1,2] Samuel E. Donovan,[1,2] Salma Amin,[2,5] Benjamin J. Gigliotti,[1] Zenon Grabarek,[6,8,9] Julian M. Hess,[8] Chip Stewart,[8] Lior Z. Braunstein,[8,17] Peter F. Arndt,[8,18] Scott Mordecai,[4] Angela R. Shih,[4,11] Frances Chaves,[4] Tiannan Zhan,[7] Carrie C. Lubitz,[2,5,7,11] Jiwoong Kim,[14] A. John Iafrate,[4,11] Lori Wirth,[1,2,11] Sareh Parangi,[2,5,11] Ignaty Leshchiner,[8] Gilbert H. Daniels,[1,2,3,11] Vamsi K. Mootha,[1,6,8,9,10,20] Dora Dias-Santagata,[4,11,20] Gad Getz,[2,4,8,11,20,*] and David G. McFadden[1,3,12,13,15,20,21,*]

Gopal et al. Cancer Cell 2018

Genetics of Hurthle cell carcinoma



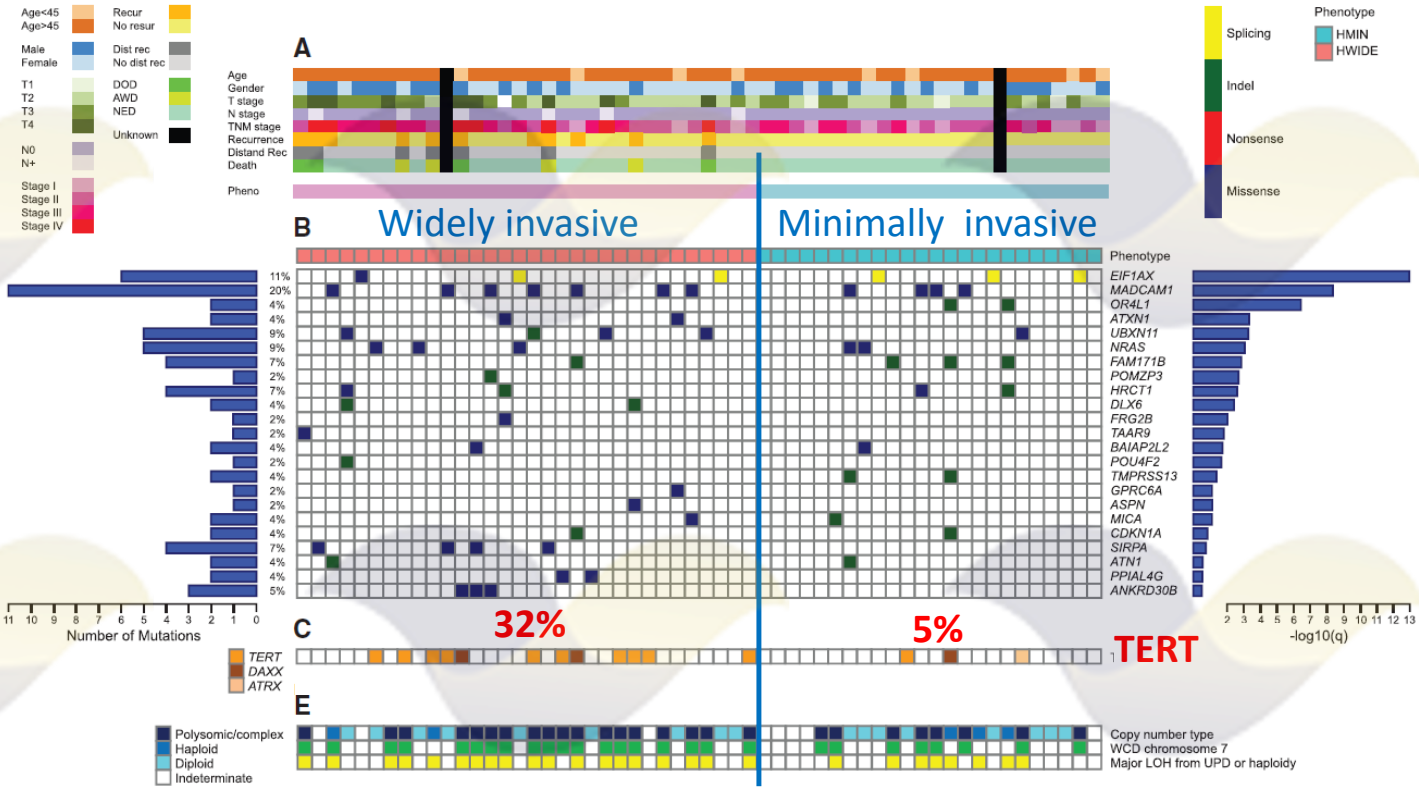
Mitochondrial DNA mutations

Chromosomal copy number alterations (CNA)

Nuclear DNA mutations

Gopal et al. Cancer Cell 2018

Hurthle cell carcinomas



- No *BRAF* V600E mutations
- <10% *RAS* mutations

Ganly et al. *Cancer Cell* 2018

Molecular profiles of thyroid nodules detected preoperatively

- Prospective double-blind multicenter study
- Bethesda III-V cytology with surgical outcome
- Primary outcome: accuracy of detection of cancer+NIFTP
- 257 nodules
- 68 cancers/NIFTP

Table 3. Probability of Cancer/NIFTP in Specific Molecular Alteration Groups

Group	Molecular Alterations, No.	Prevalence in Test-Positive Samples, No. (%)	Histopathologic Diagnosis, %		Cancer Type/ NIFTP (%)
			Cancer/ NIFTP	Benign	
High-risk group	*TERT* (and *HRAS*) (1) *TP53* (and *MEN1*) (1)	2 (2)	100	0	Papillary carcinoma (50) Follicular carcinoma (50)
BRAF-like group	*BRAF V600E* (9) *NTRK3* fusions (2) *RET* fusions (1) *BRAF* fusions (1)	13 (12)	100	0	Classical papillary carcinoma (92) Follicular variant papillary carcinoma (8)
RAS-like group	*NRAS* (21) *HRAS* (18) *KRAS* (5) *EIF1AX* (5) *BRAF K601E* (3) *PTEN* (1) *IDH2* (1) *DICER1* (1) *PPARG* fusions (4) *THADA* fusions (4)	60 (57)	62	38	Follicular variant papillary carcinoma (22) Papillary carcinoma, other variants (17) NIFTP (15) Follicular carcinoma (3) Hürthle cell carcinoma (5)
Copy number alterations group	Copy number alterations	22 (21)	59	41	Hürthle cell carcinoma (32) Follicular variant papillary carcinoma (14) Papillary carcinoma, other variants (9) NIFTP (5)
Gene expression alterations group	Gene expression alterations	8 (8)	75	25	Classical papillary carcinoma (37) NIFTP (13) Other cancers (MTC, mRCC) (25)

Steward DL et al. JAMA Oncology (2018)

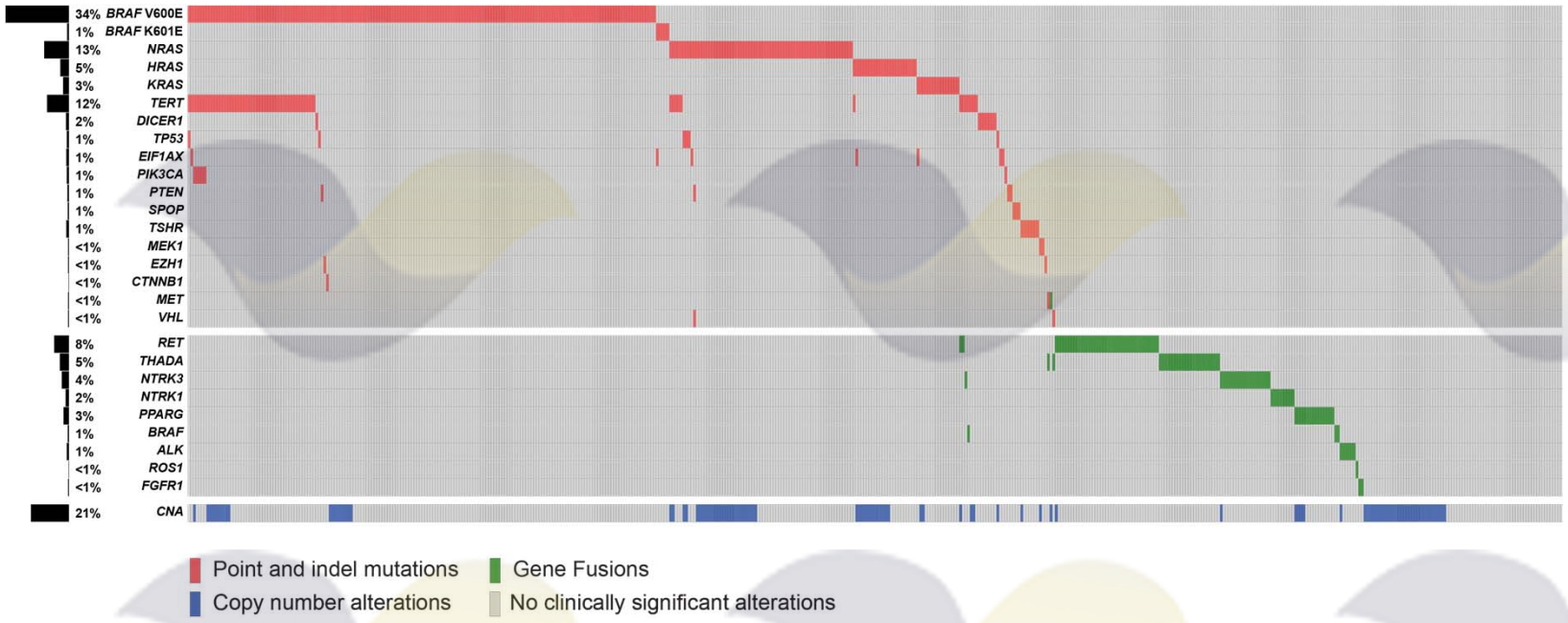
Molecular Landscape of Thyroid Tumors on FNA Testing

	AUS/FLUS (BC III), n (%)	FN/SFN (BC IV), n (%)	SFM (BC V), n (%)	Malignant (BC VI), n (%)	Total, n (%)
RAS	5615 (49)	1474 (40)	149 (9)	25 (8)	7263 (42)
BRAF V600E	1168 (10)	174 (5)	1071 (65)	229 (69)	2642 (15)
TERT	426 (4)	267 (7)	120 (7)	60 (18)	873 (5)
TP53	155 (1)	115 (3)	19 (1)	14 (4)	303 (2)

BRAF V600E+TERT - 7.3% of CA

Chiosea et al. ATA 2021 Abstract

Spectrum of genetic alterations in PTC (n=512)



BRAF V600E+TERT – 10.3% of PTC

Nikitski A, Condello V, Wald A, Nikiforova M, Chiosea S, Nikiforov Y. Abstract of "Genetic Profiling Of 900 Thyroid Tumors And Hyperplastic Nodules By Thyroseq V3 Confirms Tumor Clonality, Detects Therapeutic Targets, And Supports Molecular Tumor Classification". Thyroid, Volume: 31 Issue S1: 2021

Genetic heterogeneity of primary and metastatic thyroid cancers

Molecular Profiles of Primary Versus Metastatic Radioiodine Refractory Differentiated Thyroid Cancer

- 12 patients with radioiodine refractory metastases;
- median age at diagnosis of 61 years (range, 25-82).
- 9 – PTC
- 2 - HCC
- 1 – FTC
- Distant metastases:
  - lungs (n = 10)
  - bones (n = 4)
  - liver (n = 1)

	Primary	Metastases
Point mutations		
BRAF V600E	5	5
BRAF H542Y	1	1
NRAS Q61R	1	1
TP53 Q192X	0	1
ATM T2947N	1	1
ATM L2255P	0	1
MUTYH G393D	1	2
NTRK3 A631T	1	0
Gene fusions		
BRAF-CEP152	1	1
NTRK1-TPR	1	1
Immunohistochemistry (IHC)		
Positive PD-L1 expression	3/12	1/12
Tumor Mutational Burden (TMB)	4 -10/Mb	3 -10/Mb
Microsatellite Instability (MSI)	Stable	Stable

Cristiane J Gomes-Lima CJ et al. *Front Endocrinol*. 2021

Summary

- Thyroid differentiation status and RAI avidity can be predicted based on genomic profiles: early and late drivers
- Molecular profile of RAIR may be found in ~7-10% DTC, can be detected in FNA and core biopsy
- Expression of thyroid differentiation genes (TDS) may provide more accurate assessment
- Although some genetic heterogeneity between primary tumor and metastases exists, overall molecular profiles are expected to be similar

Thank you!

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