# Advances in molecular genetics of thyroid cancer: Impact on cancer classification, diagnosis and patient management

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Director, Division of Molecular & Genomic Pathology
Co-Director, Multidisciplinary Thyroid Center
University of Pittsburgh Medical Center

UPMC LIFE CHANGING MEDICINE

# Disclosures

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

# Objectives

- To provide an overview of molecular genetics of main types of thyroid cancer
- To discuss the impact of new genetic information on cancer classification
- To discuss the use of molecular markers for cancer diagnosis, prognostication, and targeted therapy

**“No classification is more difficult to establish than that of thyroid carcinomas…Of all cancers, they teach, perhaps, the greatest lessons of humility to histopathologists.”**

Prof. Pierre Masson (1880–1959)

# 42 yo female with thyroid mass, FNA suspicious for cancer, BRAF mutation +

Dr. Yuri Nikiforov

**RE:** [redacted] **(DOB 4/8/1976)**
[redacted] **accession:** [redacted]**18-20100**

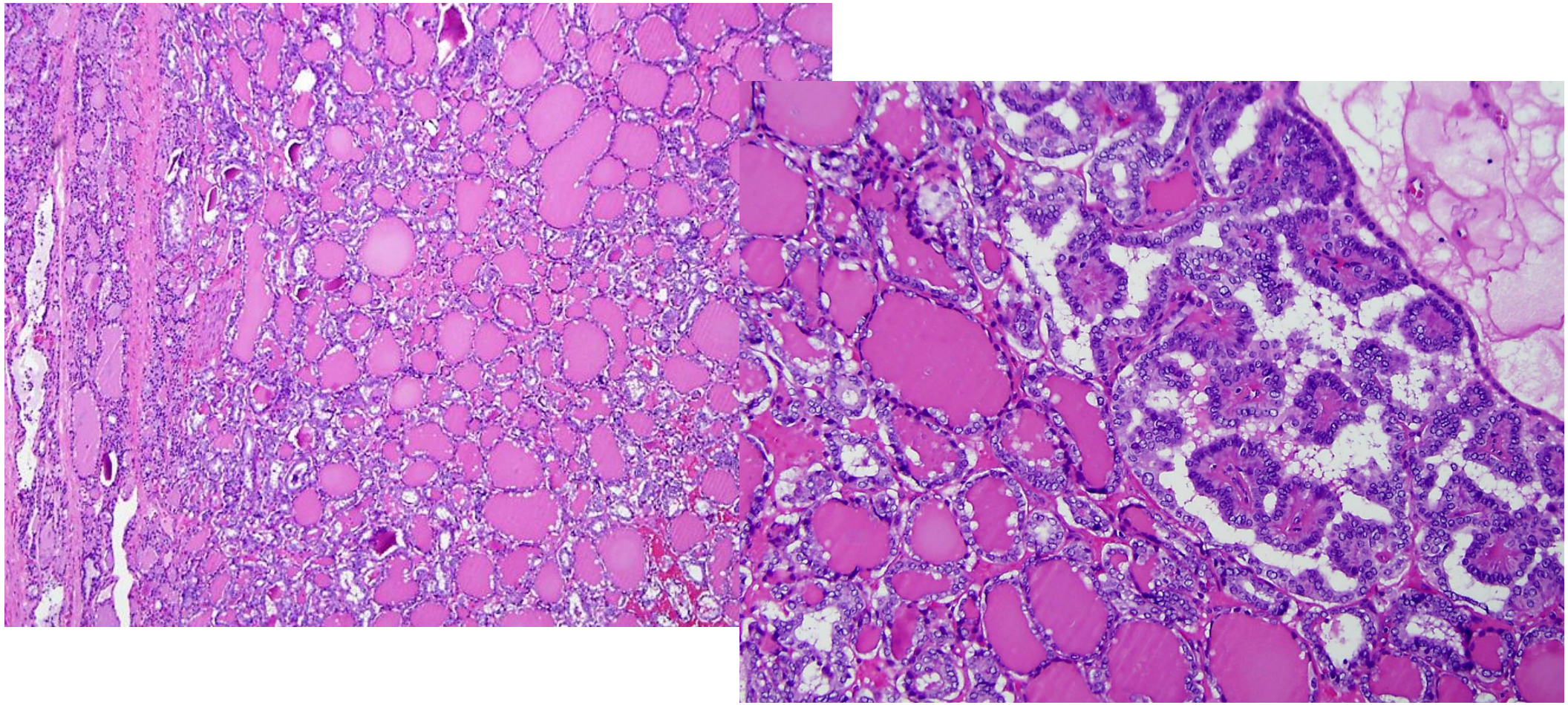
Enclosed are 17 recut slides and 1 block from the above patient's thyroidectomy.

By report this patient had a prior FNA interpreted as Bethesda category 5 at an outside institution, with molecular testing listed as pending. The thyroidectomy was performed at our hospital and we originally signed out the case as benign.

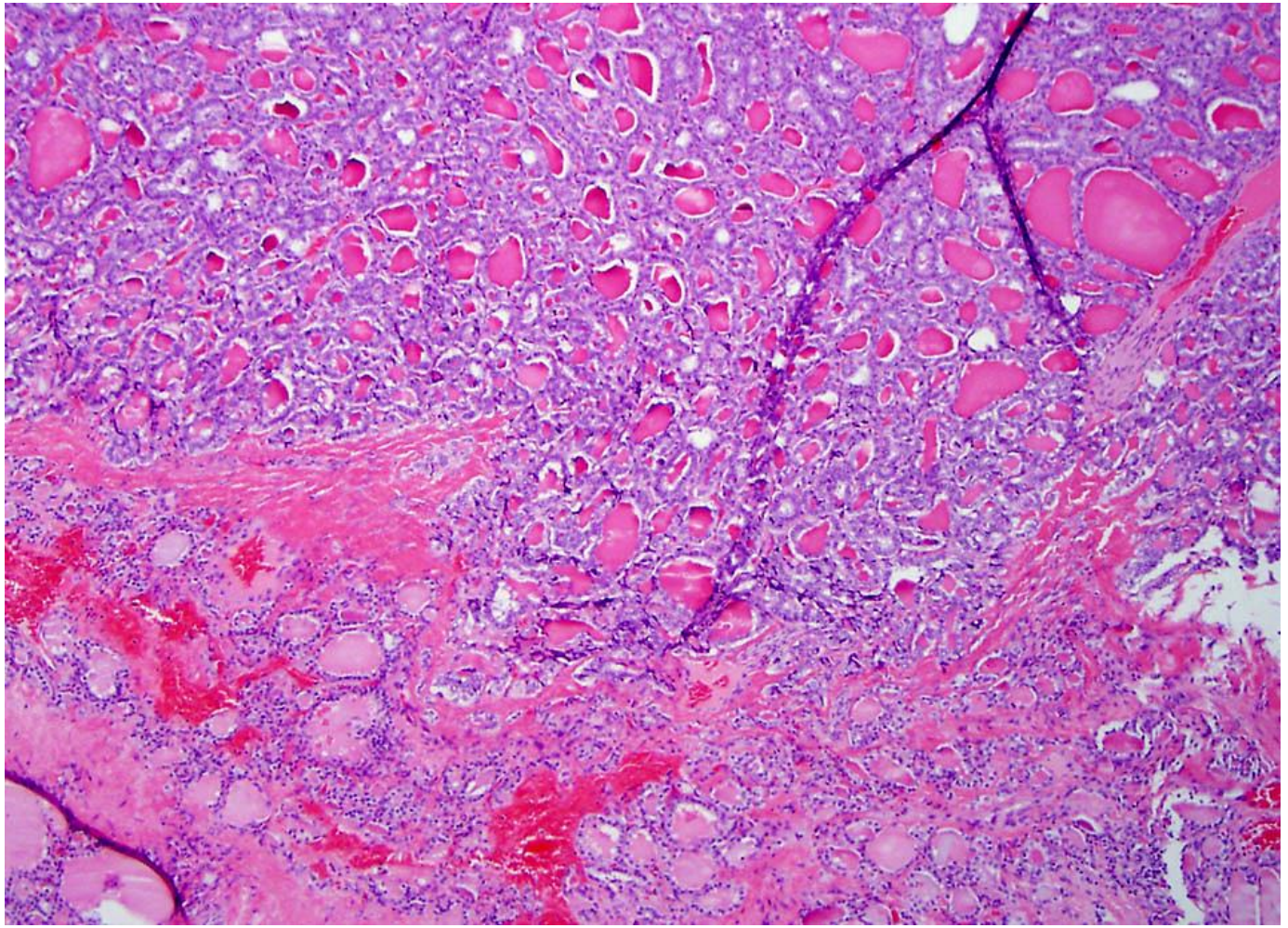
The molecular testing (ThyroSeq) was completed after the thyroidectomy and was reported as positive for BRAF V600E mutation. Based on this new finding we had the case reviewed by a consultant and a second diagnosis of NIFT-P was rendered. Given the misgivings with BRAF mutation in NIFT-P, your opinion is requested.

Thank you,

# 42 yo female with thyroid mass, FNA suspicious for cancer, BRAF mutation +



# 42 yo female with thyroid mass, FNA suspicious for cancer, BRAF mutation +



# 42 yo female with thyroid mass, FNA suspicious for cancer, BRAF mutation +

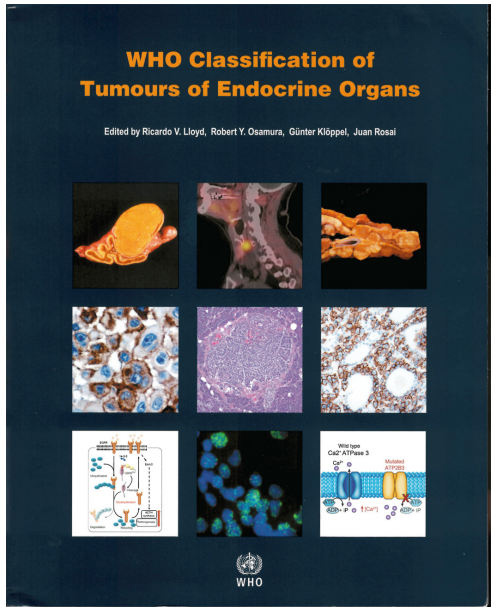
Pathology Diagnoses in this case:

Primary case pathologist: *Benign*

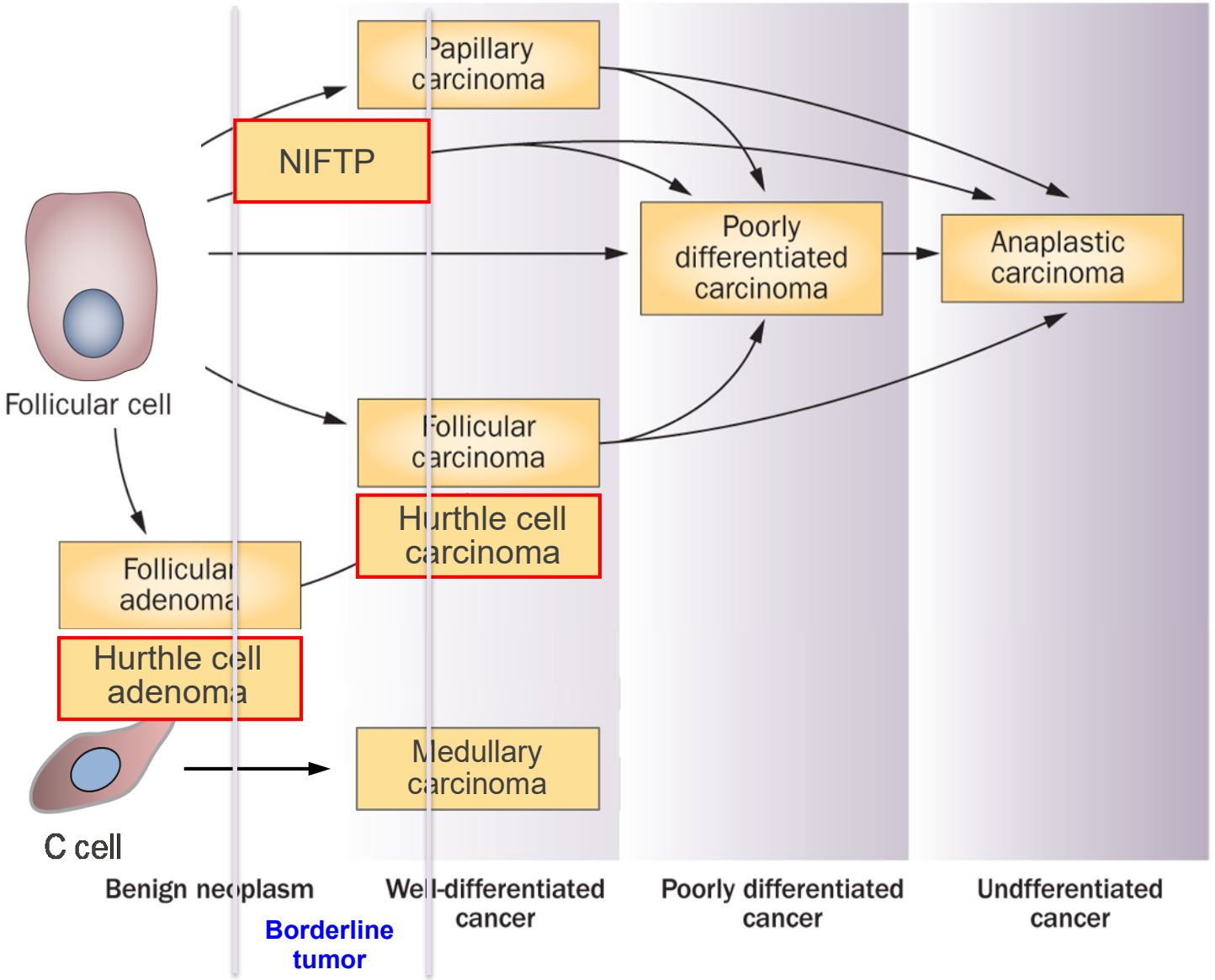
Consultant #1: *NIFTP*

Consultant #2: *PTC, classic papillary, partially encapsulate with infiltrative growth*

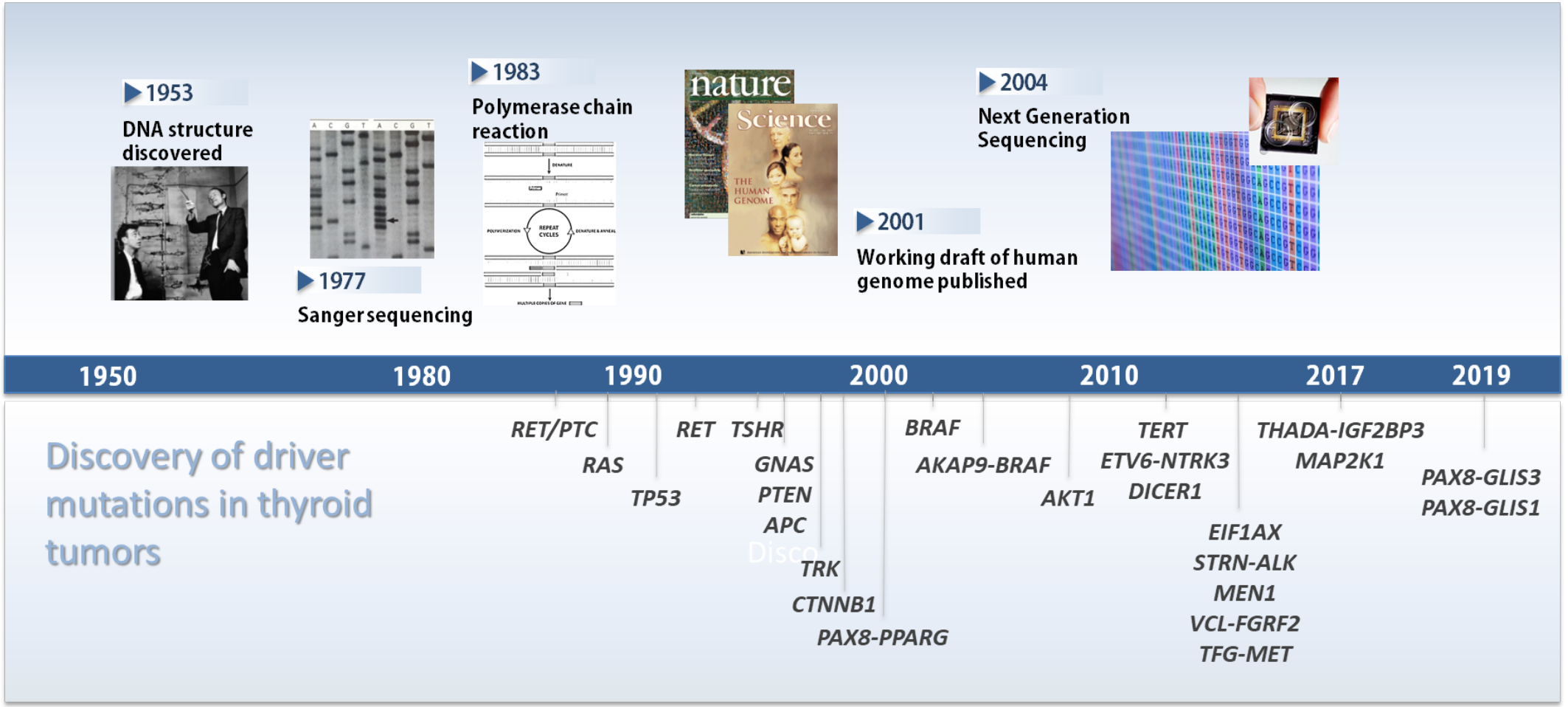
# Thyroid Tumors



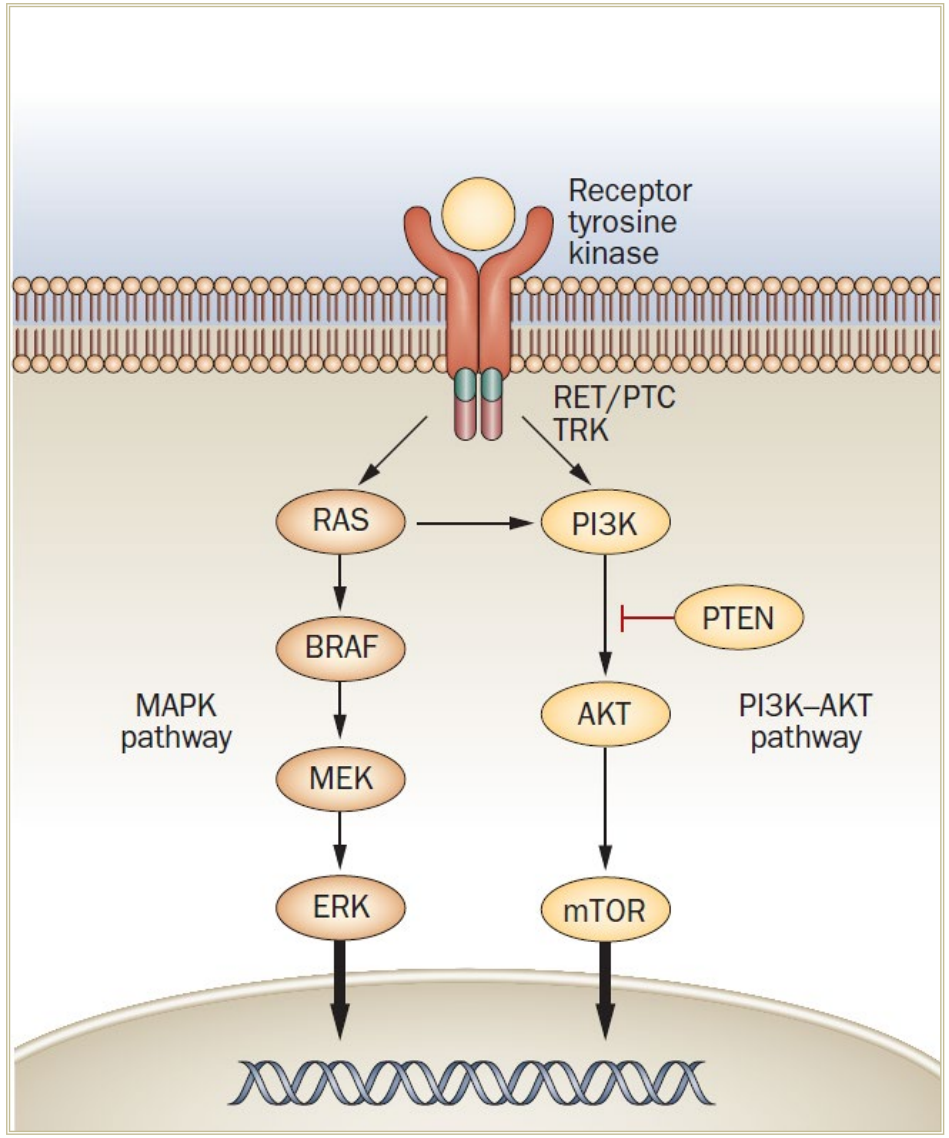

WHO Classification of Thyroid Tumors (2017)



# Progress in Understanding Cancer Genetics



# Molecular Pathogenesis of Thyroid Cancer




Types of genomic alterations in thyroid cancer:

- **Point mutations**
- **Gene fusions**
- **Copy number alterations (CNAs)**
- Gene expression alterations (GEAs)
- miRNA alterations

Nikiforov et al. *Nat Rev Endocrinol*. 2011

# Papillary Thyroid Carcinoma

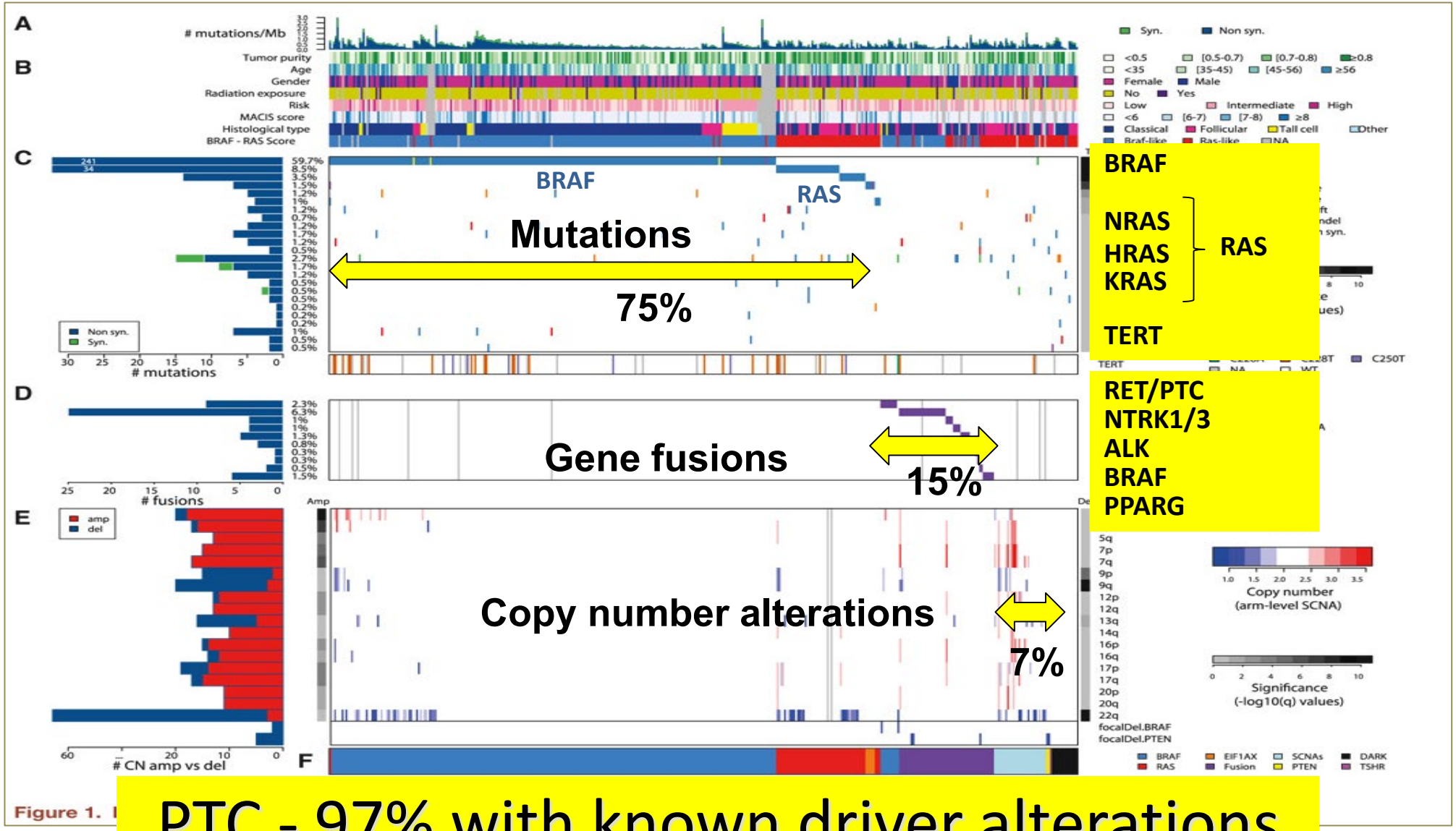
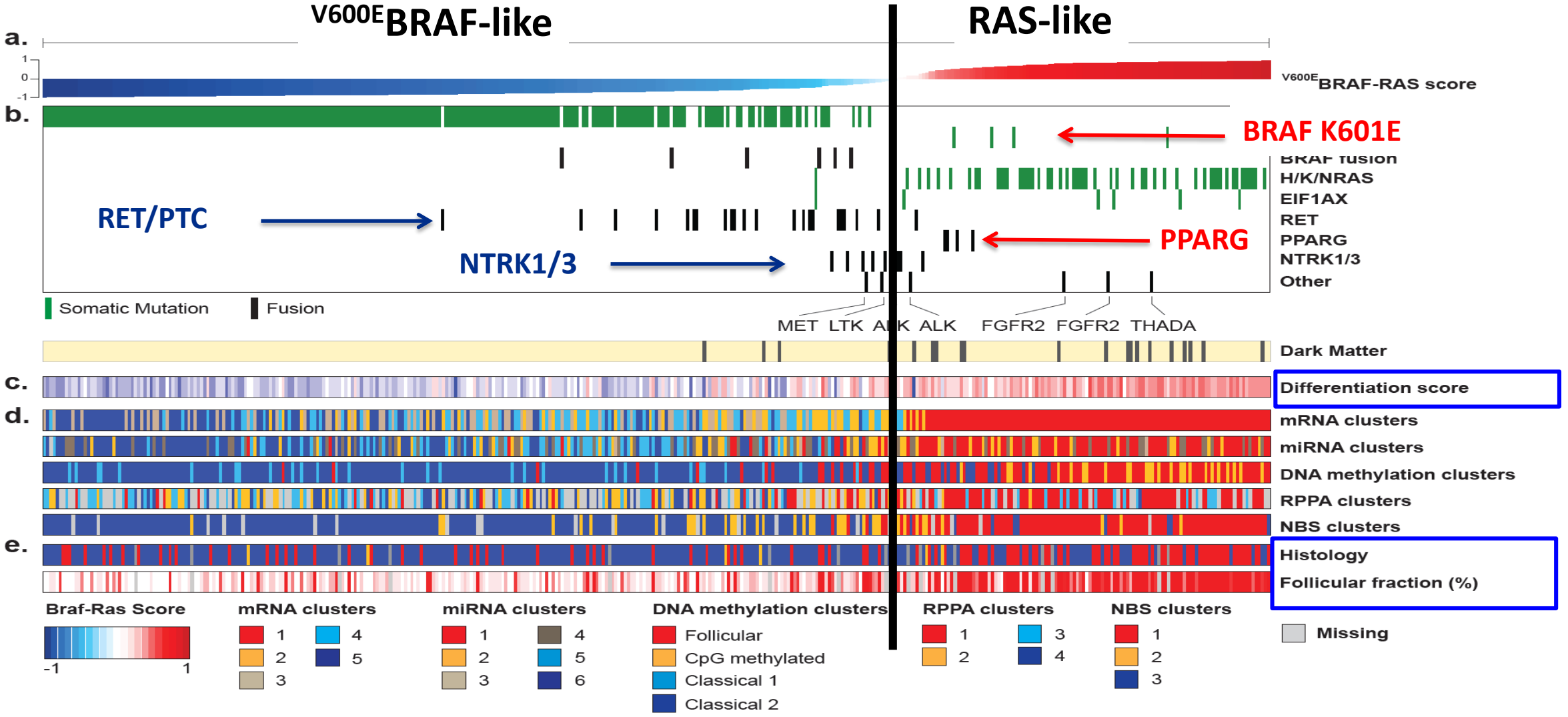



Figure 1.

PTC - 97% with known driver alterations

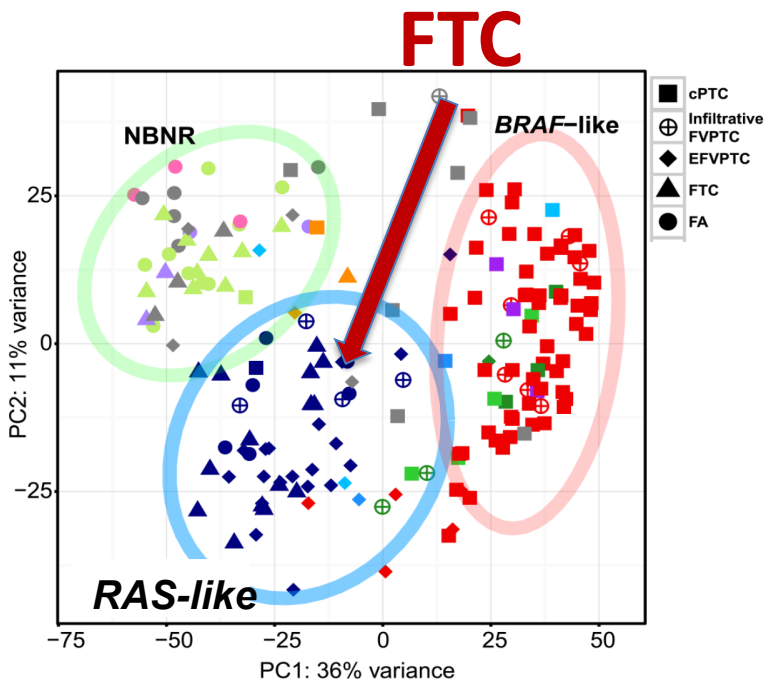
The Cancer Genome Atlas Research Network. *Cell* 159:676-690 (2014)

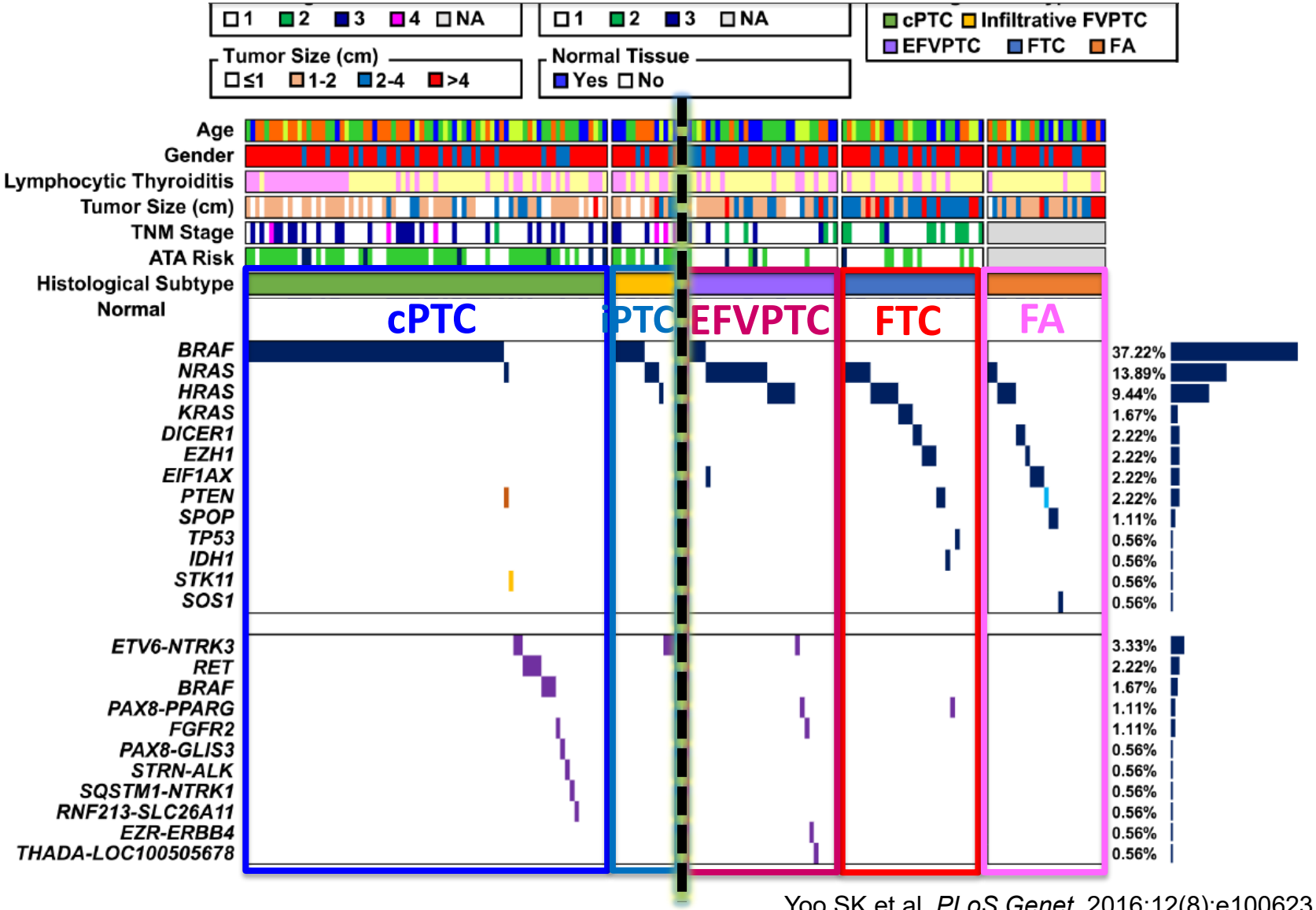
# BRAF-like and RAS-like Papillary Carcinomas




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

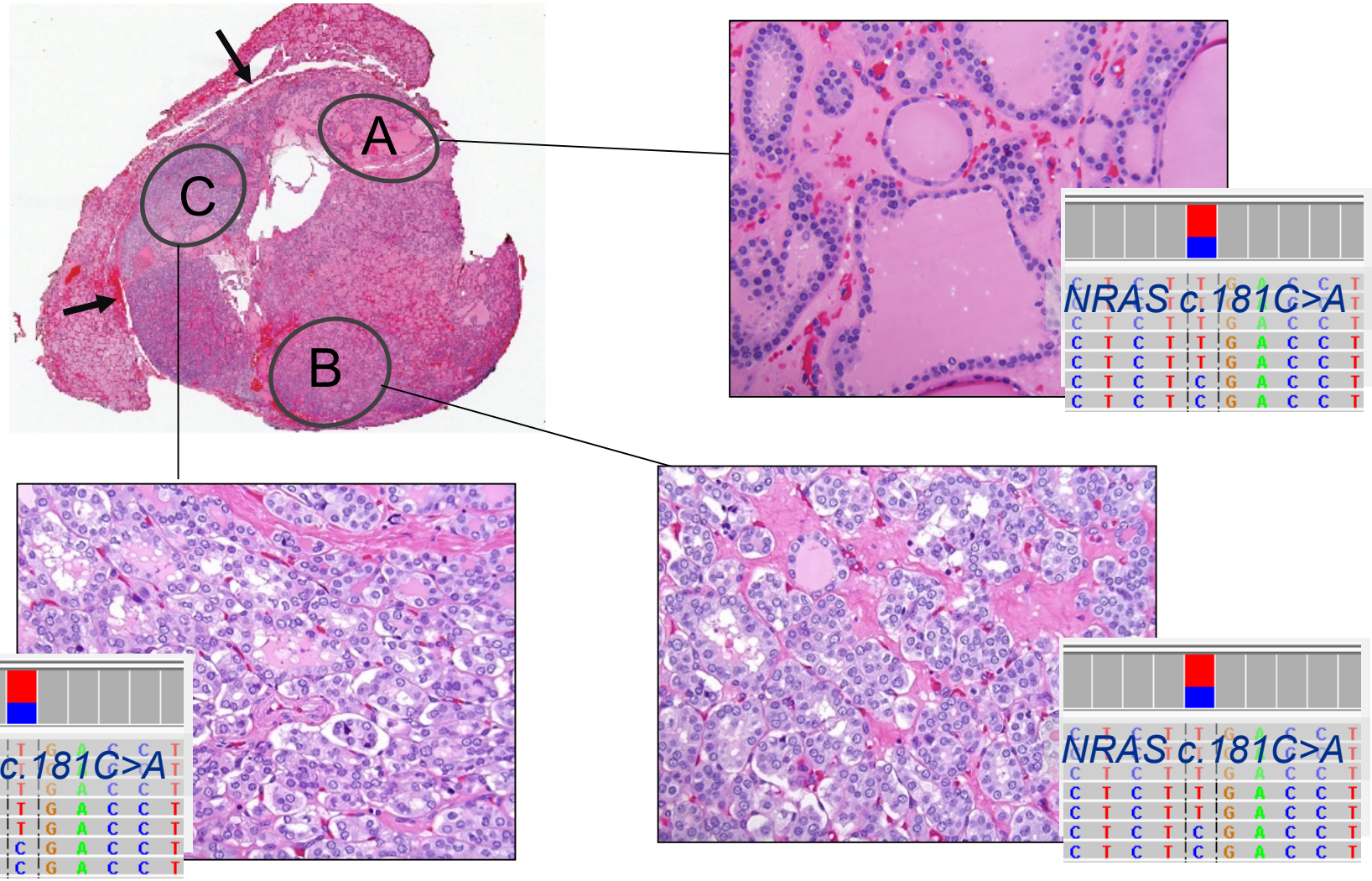
# Follicular Thyroid Carcinoma




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

# Molecular changes precede histological changes




Gupta M et al. *JCEM* (2013)

# NIFTP

## Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features

JAMA Oncology

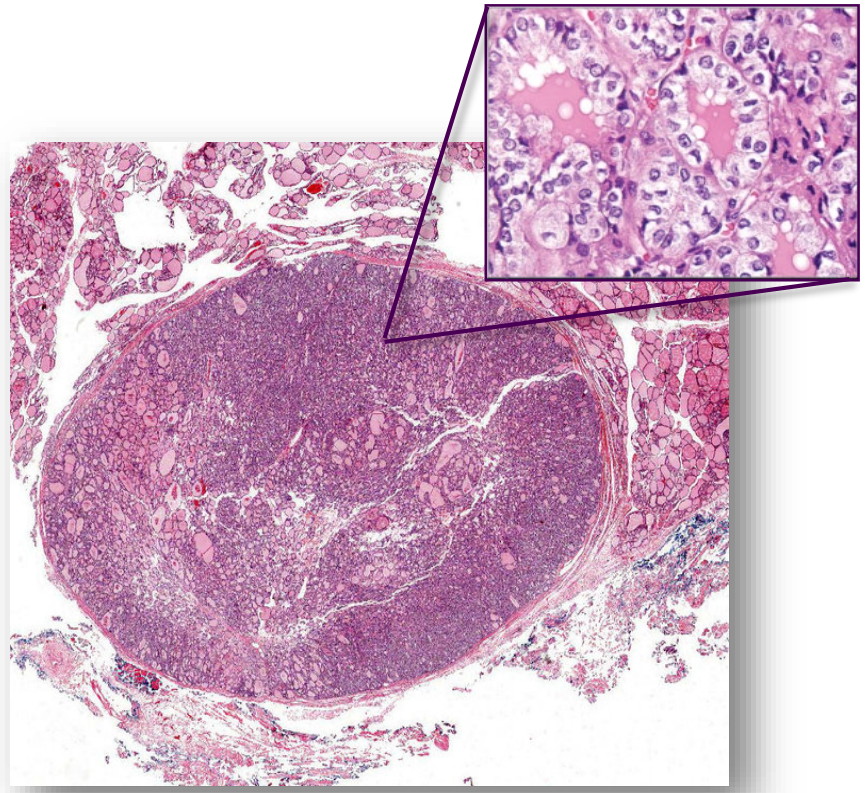
Research

Original Investigation

### Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD; Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD; Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD; Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Gooding, MS; Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD; Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD; Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. LiVolsi, MD; Gregory W. Randolph, MD; Ronald A. Ghossein, MD



Nikiforov et al. *JAMA Oncology* (2016)

# NIFTP

## Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features

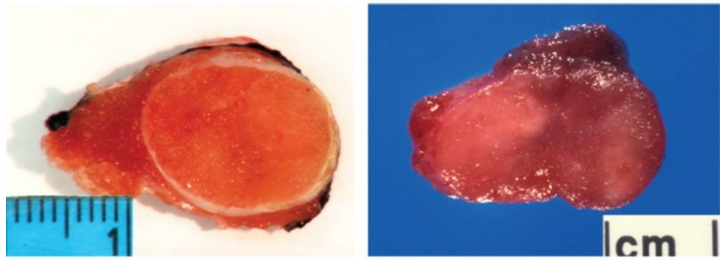
Diagnostic criteria:

1. Encapsulation or clear demarcation
2. Follicular growth pattern
   - < 1% papillae;
   - No psammoma bodies
   - < 30% solid/trabecular/insular
3. Nuclear features of PTC (nuclear score 2-3)
4. No invasion
5. No aggressive histology (necrosis, mitoses)

No true papillae!

Entire capsule must be examined!

1



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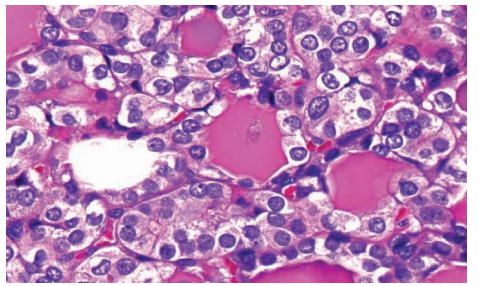
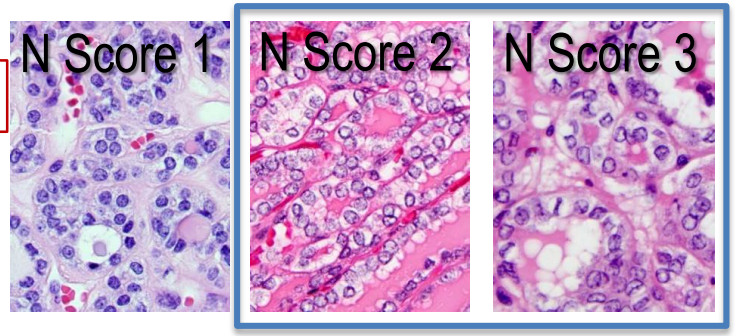


3




Nikiforov et al. *JAMA Oncology* (2016)

# Revised Diagnostic Criteria for NIFTP

**Primary**

- Encapsulation or clear demarcation[a]
- Follicular growth pattern with:
  - No well-formed papillae
  - No psammoma bodies
  - <30% solid/trabecular/insular growth pattern
- Nuclear score 2-3[b]
- No vascular or capsular invasion[c]
- No tumor necrosis or high mitotic activity[d]

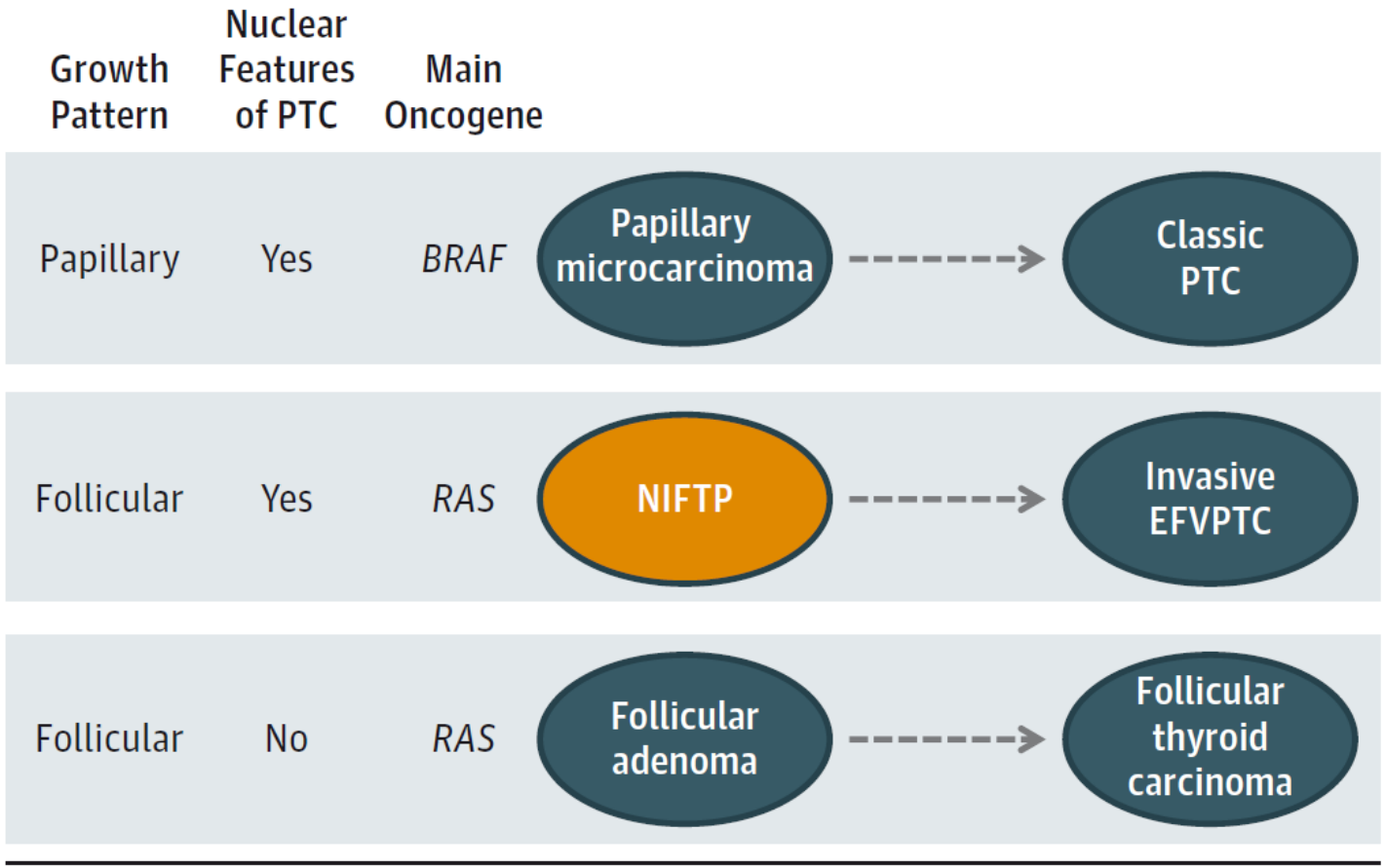
**Secondary[e]**

- Lack of *BRAF* V600E mutation detected by molecular assays or immunohistochemistry
- Lack of *BRAF* V600E-like mutations or other high-risk mutations (TERT, TP53)

Nikiforov et al. *JAMA Oncology* 2018

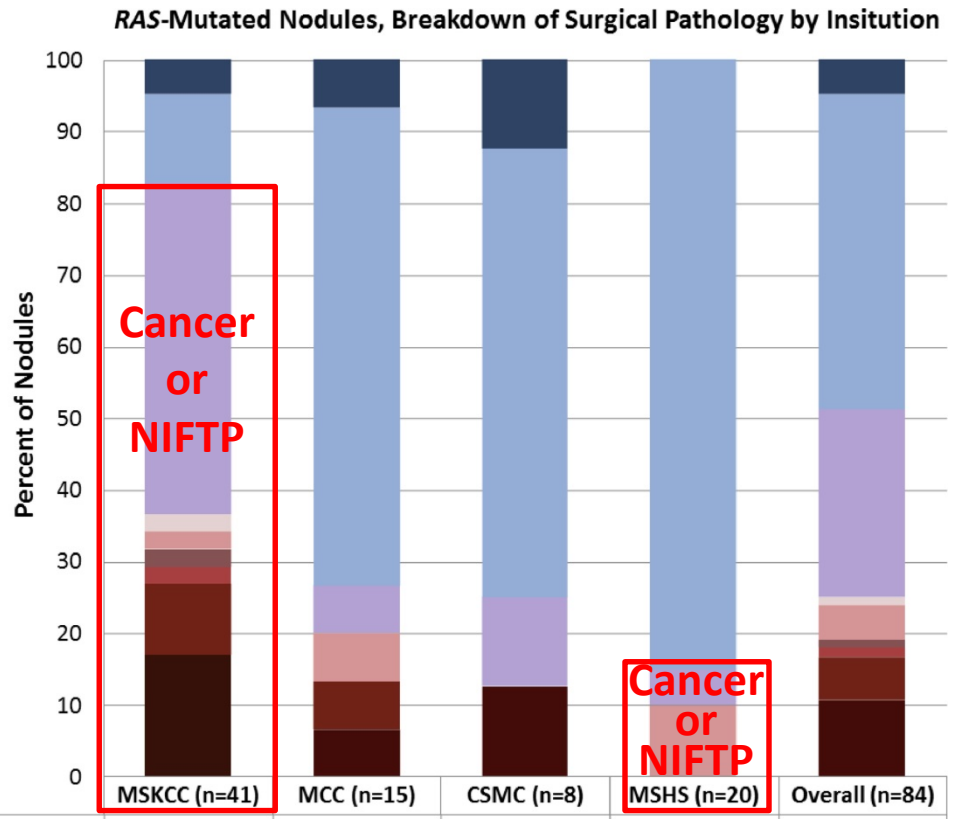
# Multistep Cancer Progression and Existence of Borderline Tumors: NIFTP

Figure 2. Putative Scheme of Thyroid Carcinogenesis

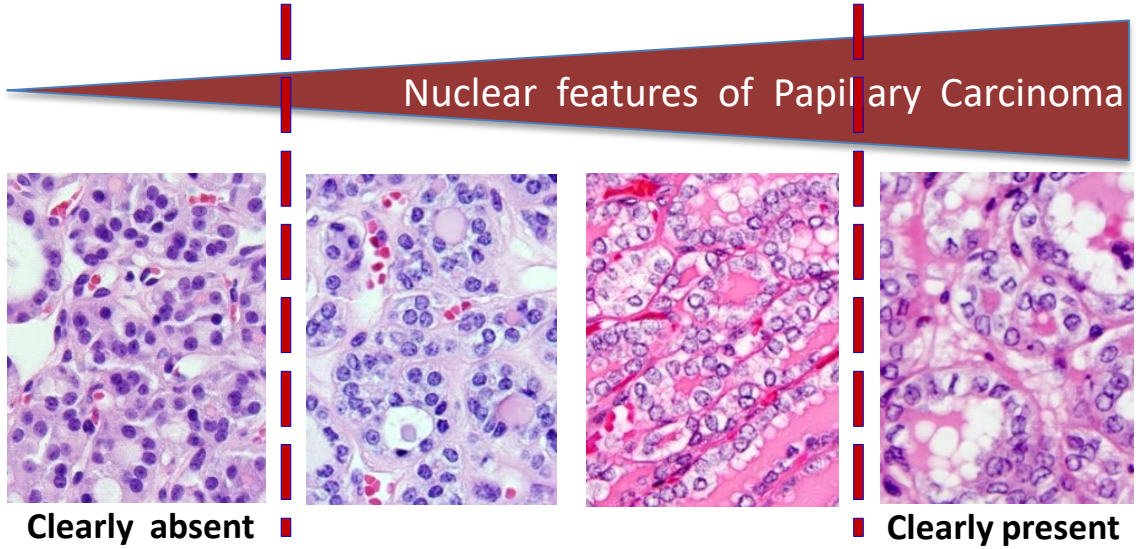



Nikiforov et al. *JAMA Oncology* 2016; 2:1023-9.

# Cancer incidence in RAS-positive nodules



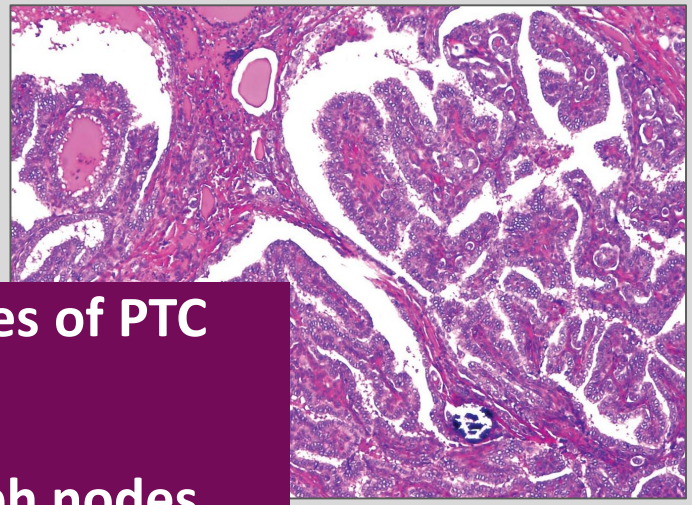

| | MSKCC (n=41) | MCC (n=15) | CSMC (n=8) | MSHS (n=20) | Overall (n=84) |
|---|---|---|---|---|---|
| Hurthle cell adenoma | 4.9 | 6.7 | 12.5 | 0 | 4.8 |
| Follicular adenoma / Nodular hyperplasia | 12.2 | 66.7 | 62.5 | 85.0 | 44.0 |
| NIFTP | 46.3 | 6.7 | 12.5 | 5.0 | 26.2 |
| Hurthle cell carcinoma | 2.4 | 0 | 0 | 0 | 1.2 |
| Follicular thyroid carcinoma | 2.4 | 6.7 | 0 | 10.0 | 4.8 |
| PTC solid variant | 2.4 | 0 | 0 | 0 | 1.2 |
| PTC classical and follicular variants | 2.4 | 0 | 0 | 0 | 1.2 |
| PTC follicular variant | 9.8 | 6.7 | 0 | 0 | 6.0 |
| PTC classical variant | 17.1 | 6.7 | 12.5 | 0 | 10.7 |




Marcadis AR et al. *Surgery* (2019)

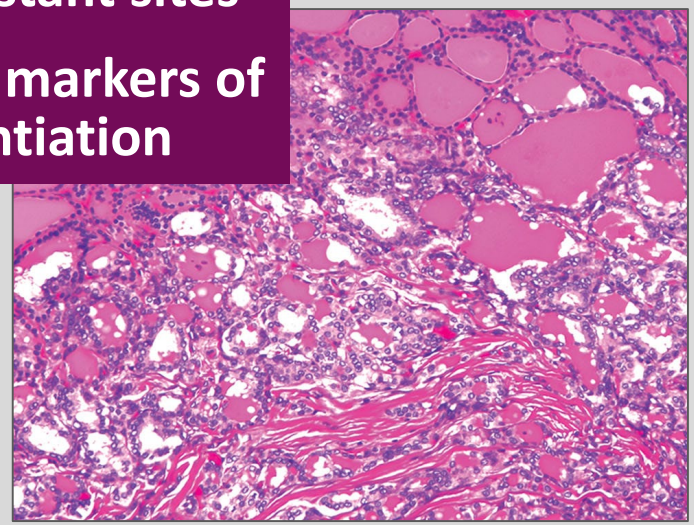
# BRAF-like tumors

cPTC



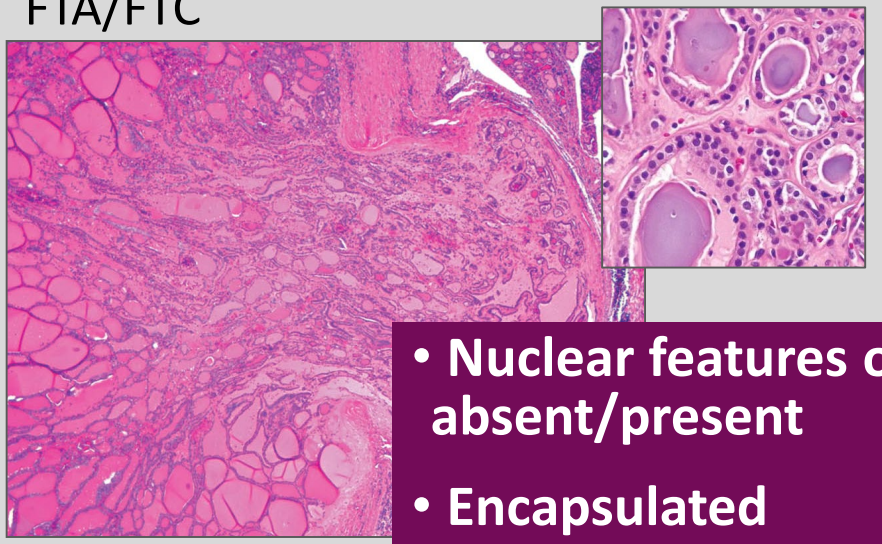
- Nuclear features of PTC
- Infiltrative
- Spread to lymph nodes first, later to distant sites
- Prone to loose markers of thyroid differentiation

VPTC



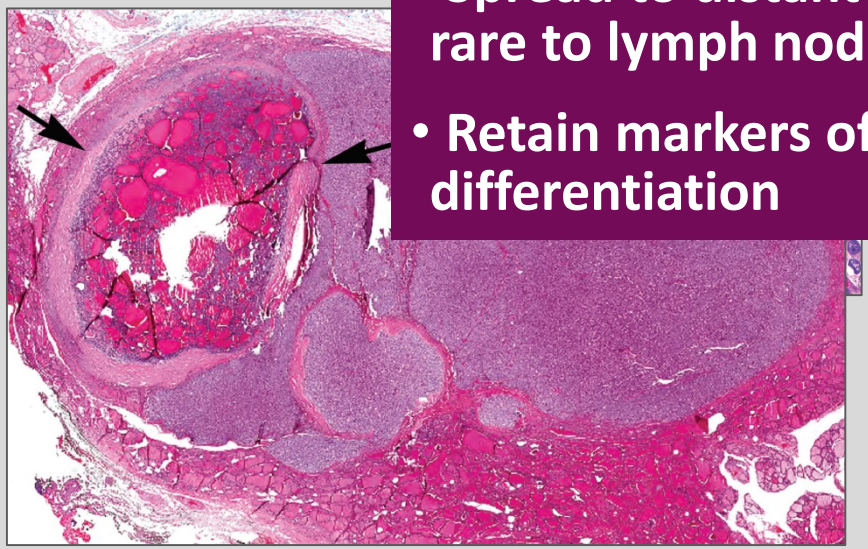
# RAS-like tumors

FTA/FTC

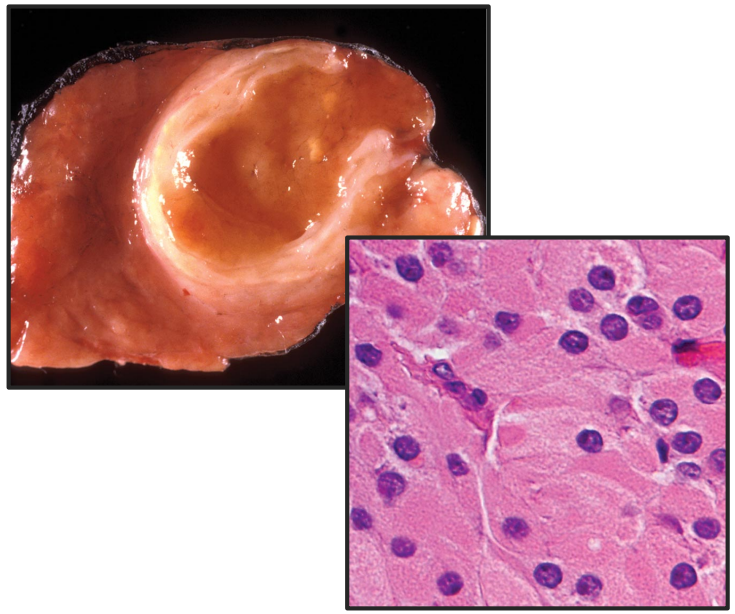


- Nuclear features of PTC absent/present
- Encapsulated
- Spread to distant sites, rare to lymph nodes
- Retain markers of thyroid differentiation

NIFTP Invasive



# Genetics of Hurthle cell carcinoma



## 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,*]

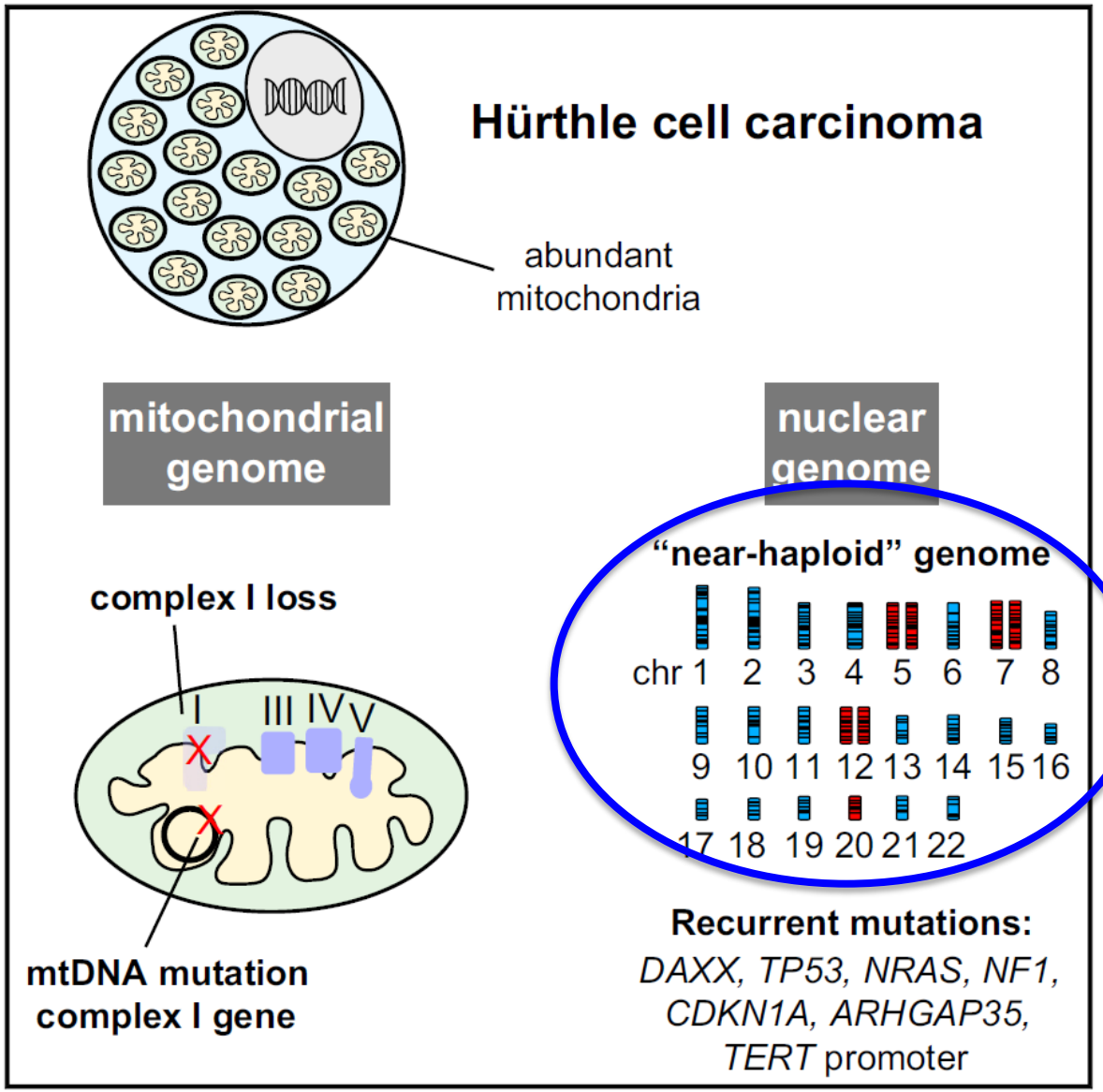
*Ganly et al. Cancer Cell 2018*

## 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

Endocrine-Related Cancer | W R Doerfler *et al.* | Molecular alterations in Hürthle cell tumors | **28**:5 | **301**–309

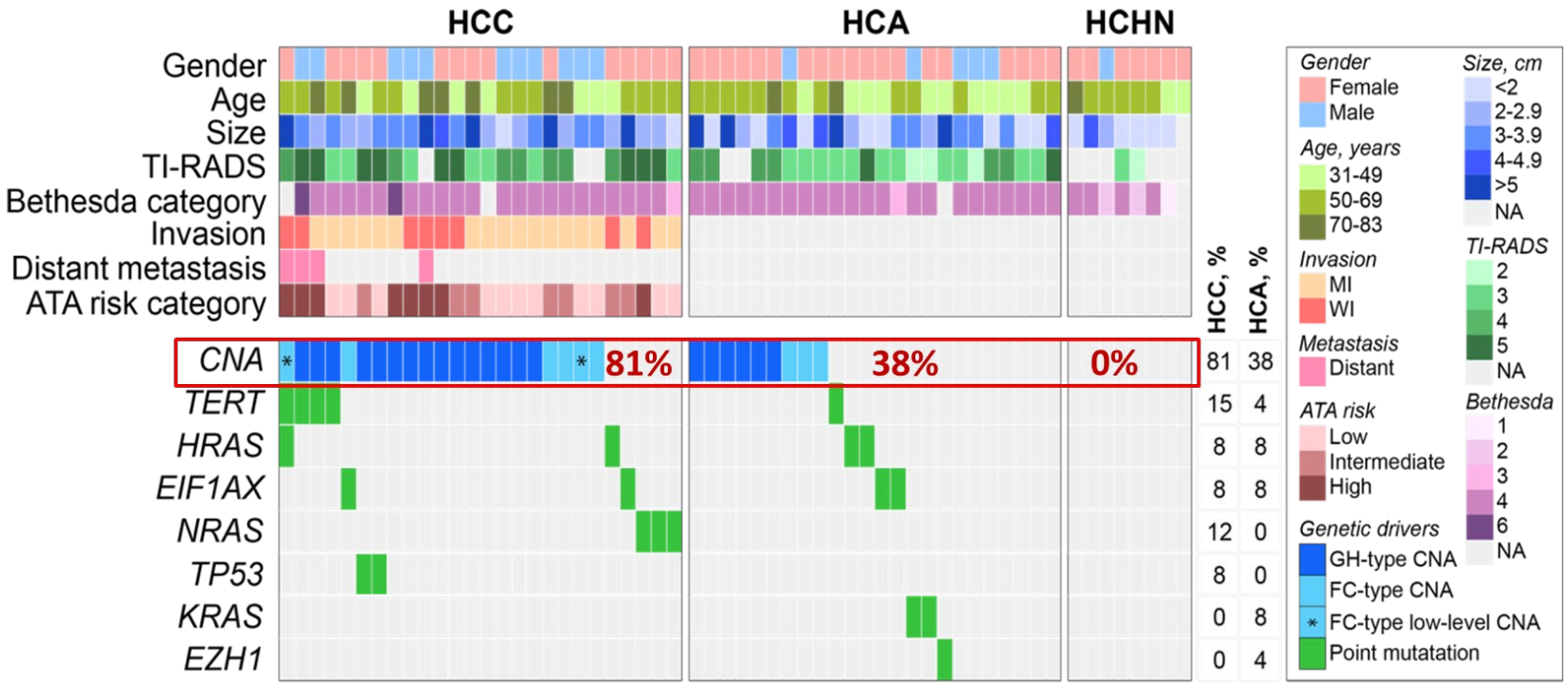
RESEARCH

# Molecular alterations in Hürthle cell nodules and preoperative cancer risk

**William R Doerfler[1], Alyaksandr V Nikitski[2], Elena M Morariu[1], N Paul Ohori[2], Simion I Chiosea[2], Michael S Landau[2], Marina N Nikiforova[2], Yuri E Nikiforov[2], Linwah Yip[3]** and **Pooja Manroa[1,4]**

[1]Division of Endocrinology and Metabolism, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[2]Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[3]Division of Endocrine Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[4]Division of Endocrinology, University of Texas Medical Branch, Galveston, Texas, USA

**Correspondence should be addressed to P Manroa:** pomanroa@utmb.edu




*Doerfler et al. Cancer 2021*

# Importance of thorough capsule examination in an encapsulated nodule

## *TERT* Promoter Mutation as an Early Genetic Event Activating Telomerase in Follicular Thyroid Adenoma (FTA) and Atypical FTA

Na Wang, MD[1]; Tiantian Liu, MD[2]; Anastasios Sofiadis, MD, PhD[1]; C. Christofer Juhlin, MD, PhD[1]; Jan Zedenius, MD, PhD[3,4]; Anders Höög, MD, PhD[1]; Catharina Larsson, MD, PhD[1]; and Dawei Xu, MD, PhD[2]

**TABLE 1.** Mutations and Follow-Up for the 58 Patients With a Primary FTA

| | Mutation | | | | | Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|---|
| Case No. | *TERT* Promoter | *RAS* Gene | Age at Diagnosis, y | Sex (M/F) | Primary Tumor | Disease Recurrence | Patient Outcome | Time, mo | Final Diagnosis |
| FTA-1 | wt | – | 55 | F | FTA | no | DWOD | 172 | FTA |
| FTA-2 | wt | – | 40 | F | FTA | no | AWOD | 316 | FTA |
| FTA-3 | wt | – | 52 | | | | | | |
| FTA-4 | wt | – | 32 | | | | | | |
| FTA-5 | wt | – | 46 | | | | | | |
| FTA-6 | wt | – | 40 | | | | | | |
| FTA-7 | wt | – | 46 | | | | | | |
| FTA-8 | wt | – | 50 | | | | | | |
| FTA-9 | wt | – | 25 | | | | | | |
| FTA-10 | wt | – | 61 | | | | | | |
| FTA-11 | wt | – | 55 | | | | | | |
| FTA-12 | wt | – | 50 | | | | | | |
| FTA-13 | wt | – | 32 | | | | | | |
| FTA-14 | wt | – | 64 | | | | | | |
| FTA-15 | wt | – | 37 | | | | | | |
| FTA-16 | wt | – | 62 | F | FTA | no | AWOD | 303 | FTA |
| FTA-17 | wt | – | 43 | M | FTA | no | AWOD | 303 | FTA |
| FTA-18 | wt | – | 54 | F | FTA | no | AWOD | 303 | FTA |
| FTA-19 | wt | – | 49 | M | FTA | no | AWOD | 302 | FTA |
| FTA-20 | wt | – | 78 | F | FTA | no | DWOD | 198 | FTA |
| FTA-21 | C228T | *NRAS* Q61R | 69 | F | FTA | yes, FTC | DOD | 250 | FTC |

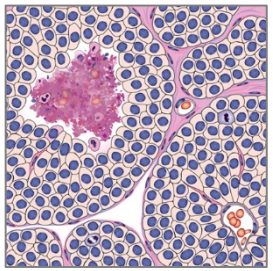
**TABLE 1.** Mutations and Follow-Up for the 58 Patients With a Primary FTA

| | Mutation | | | | | Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|---|
| Case No. | *TERT* Promoter | *RAS* Gene | Age at Diagnosis, y | Sex (M/F) | Primary Tumor | Disease Recurrence | Patient Outcome | Time, mo | Final Diagnosis |
| FTA-21 | C228T | *NRAS* Q61R | 69 | F | FTA | yes, FTC | DOD | 250 | FTC |

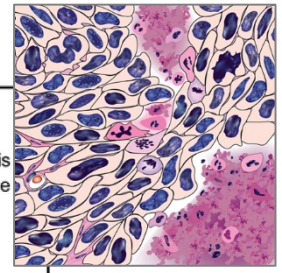
Wang N, et al. *Cancer*. 2014;120:2965-79

# Genetics of Dedifferentiated Thyroid Cancer

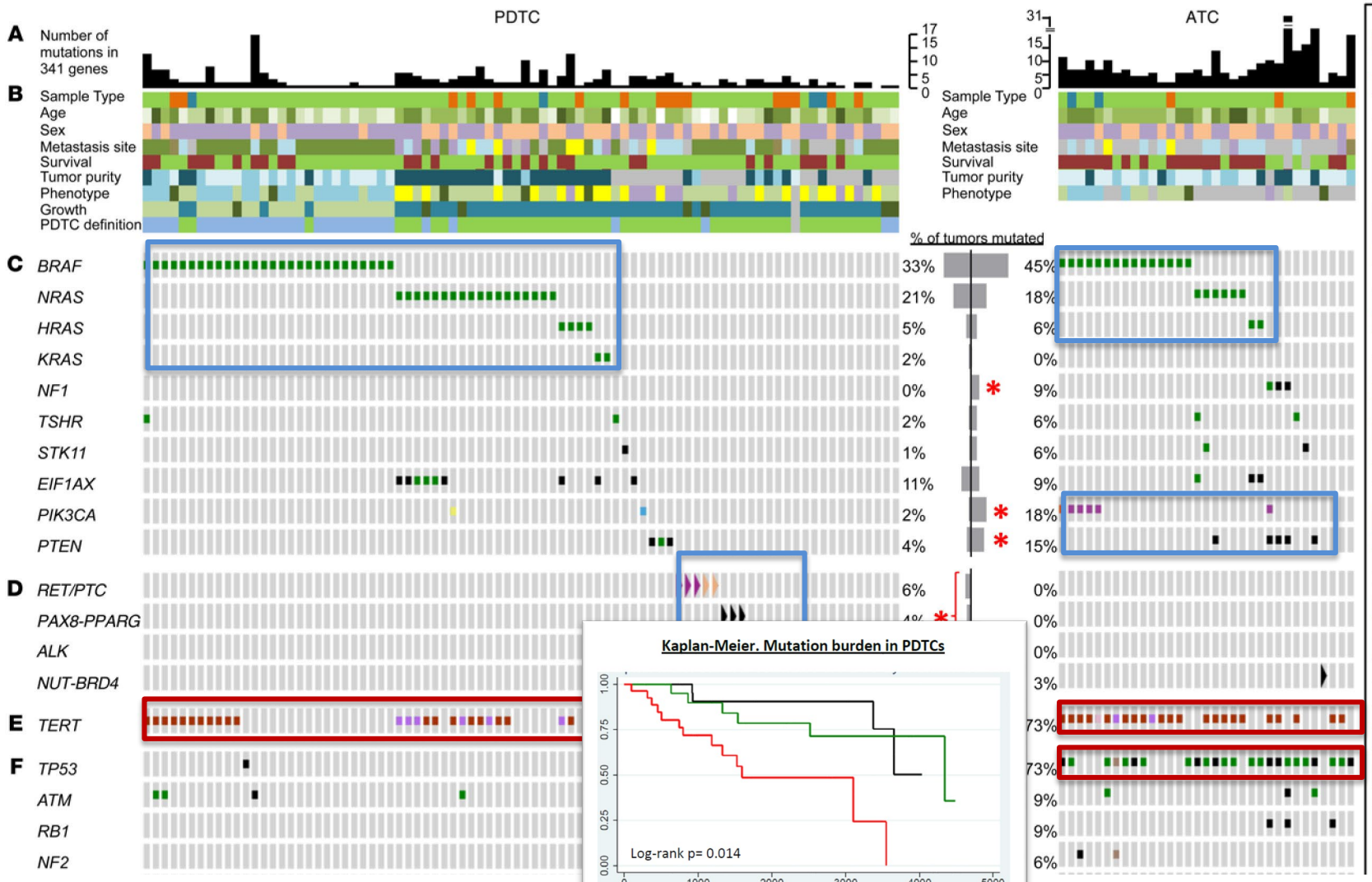
## *Progressive accumulation of mutations*



**PDTC**

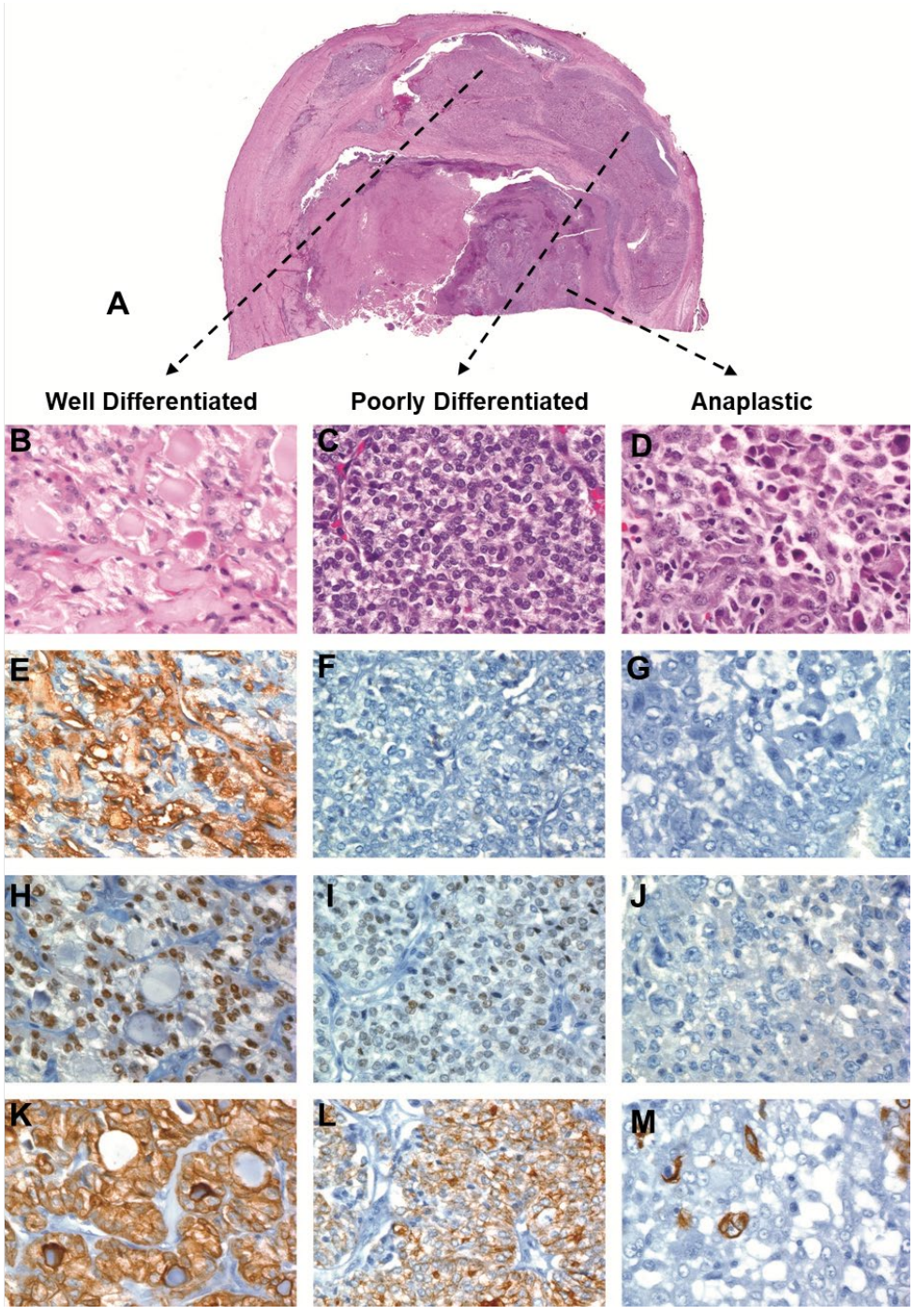


**ATC**




Landa I et al. *JCI*. 2016.

# Poorly Differentiated Carcinoma Anaplastic (Dedifferentiated) Carcinoma




(Nikiforov YE, Biddinger PW, Thompson, LDR; Editors. *Diagnostic Pathology and Molecular Genetics of the Thyroid*, 3rd Ed. 2019)

# Follicular Adenoma vs Hyperplasia

Atlas of Nontumor Pathology
AFIP 2002

Table 3-2

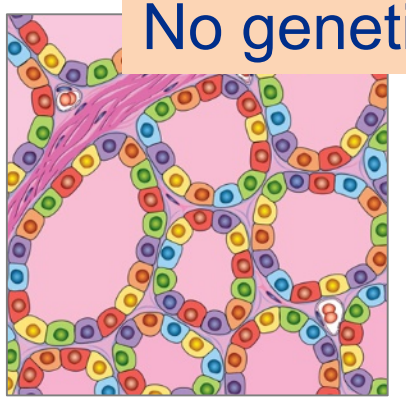
DIAGNOSTIC FEATURES DISTINGUISHING HYPERPLASTIC NODULES FROM ADENOMAS

| | |
|---|---|
| Variable cells in nodules without compression and similar to those outside nodule | Uniform lesion with compression of adjacent dissimilar thyroid |
| Polyclonal cell population | Monoclonal cell population |

**Finding a clonal (somatic) molecular alteration is diagnostic of a neoplasm, irrespective of microscopic appearance**

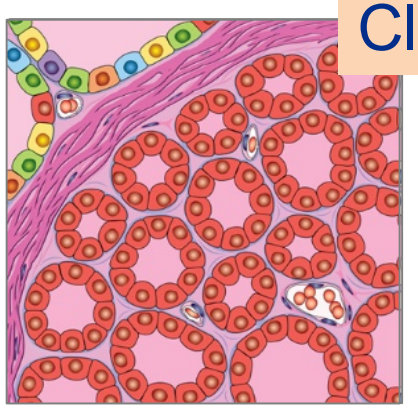
**Hyperplasia**

No genetic alterations



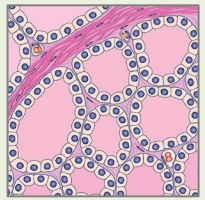
**FA**

Clonal gene mutation



# Molecular Classification of Follicular Cell-Derived Thyroid Cancer

Non-clonal
Non-neoplastic



Hyperplastic nodule

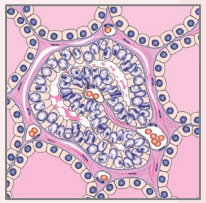
*No mutations*

I. Benign neoplasm
Borderline; Early cancer

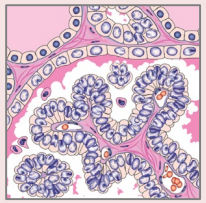
II. Well-differentiated cancer

III. Dedifferentiated cancer

*BRAF-like mutations*

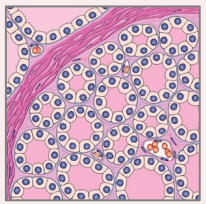


mPTC

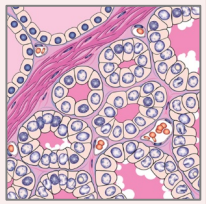


cPTC

*RAS-like mutations*

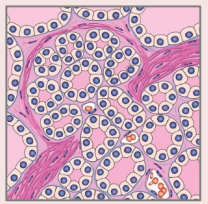


FA

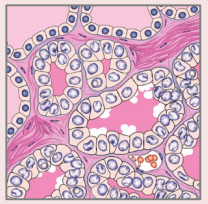


NIFTP

*EIF1AX, fcCNA*

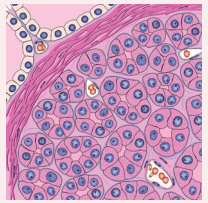


FTC

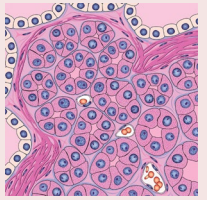


iefvPTC

*Copy Number Alterations*



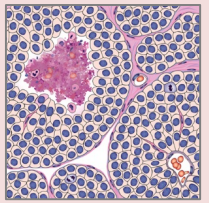
HCA



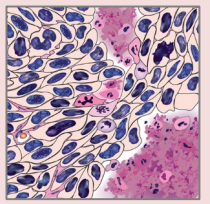
HCC

*TERT, TP53*

*AKT1, PIK3CA*



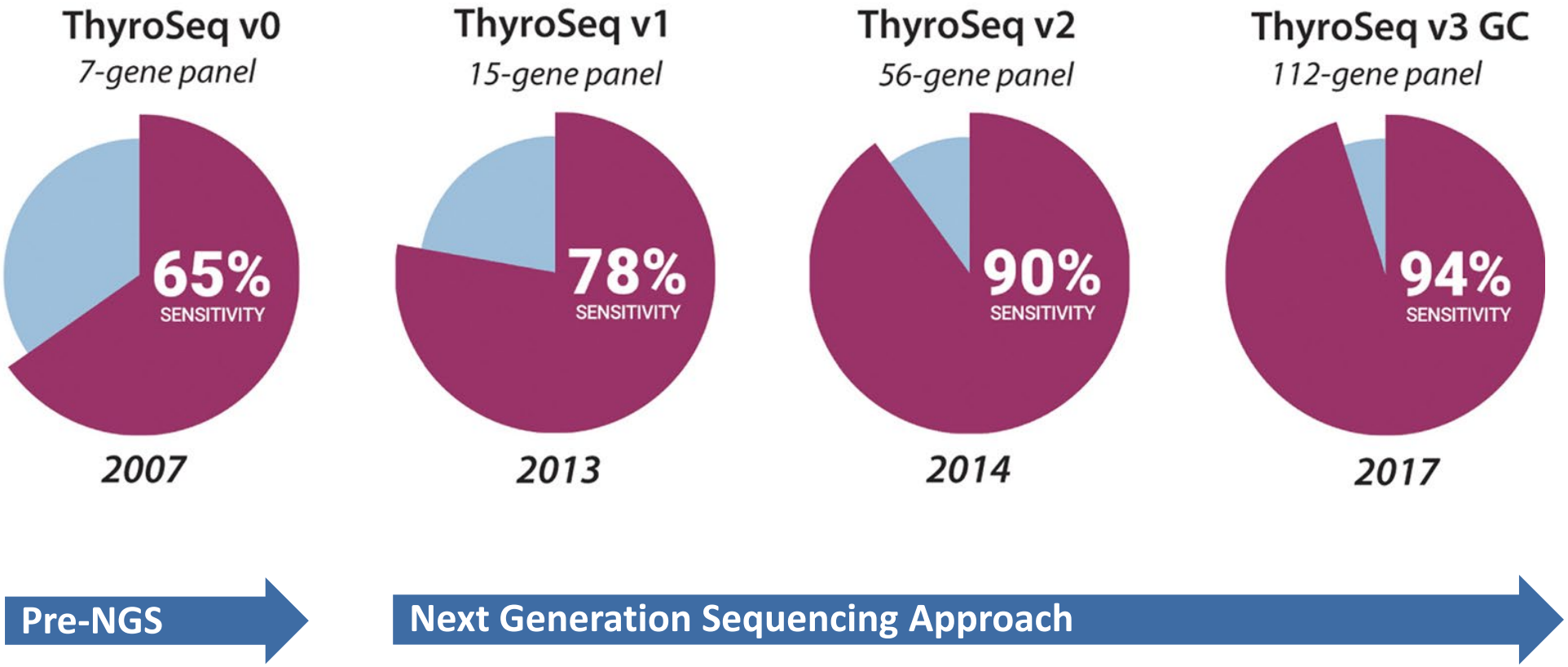
PDC



ATC

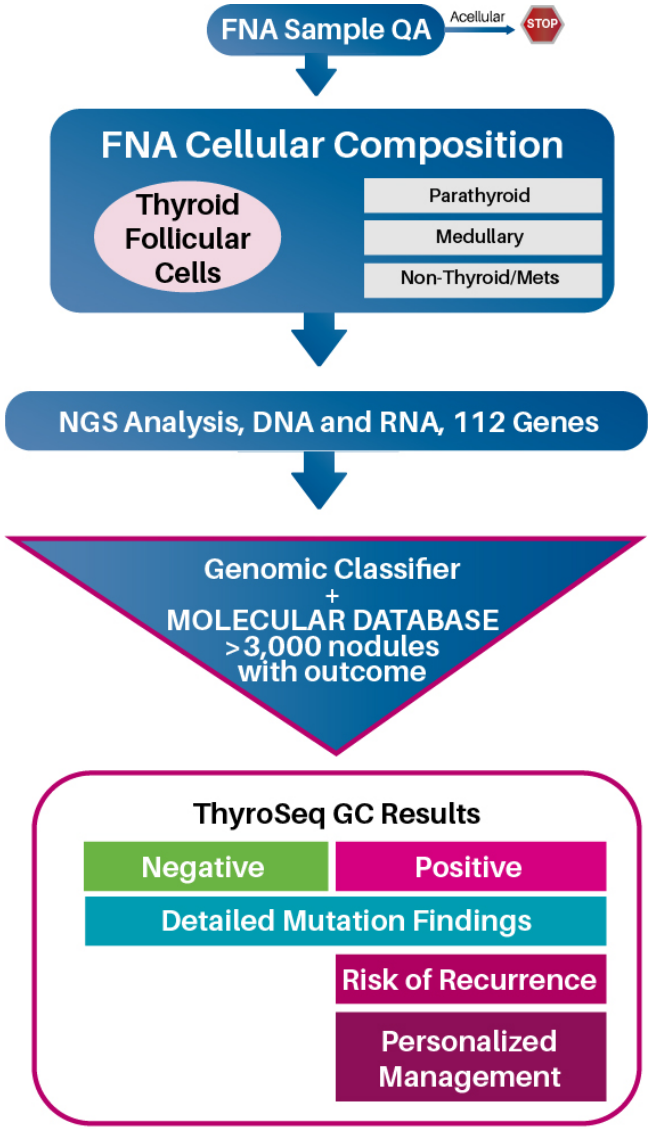
# Molecular Markers for Thyroid Nodules

# Evolution of ThyroSeq Test



# ThyroSeq v3 Genomic Classifier (GC)

- **Next-generation sequencing of DNA and RNA**
- **Determine FNA cellular composition** (follicular cells, MTC, parathyroid, mets to thyroid)
- Analysis of **112 thyroid-related genes** for:
  - Point mutations (>12,000 variants) and small indels (>500 variants)
  - Gene fusions (>150 types)
  - Copy number alterations
  - Gene expression alterations
- **Test result interpretation** based on molecular database of >3,000 FNAs results with known surgical outcome
- Every case evaluated and **reported by a licensed molecular pathologist**
- Reports:
  - Positive or Negative, plus all detected alterations
  - Provides assessment of **specific cancer probability** and **risk of cancer recurrence**
  - Provides potential **clinical management**



# Performance of ThyroSeq v3 Test in Thyroid Nodules

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

- Prospective double-blind multicenter study
- Bethesda III-V cytology with surgical outcome
- 10 study centers; patient recruitment 01/2015-12/2016
- Central pathology review by a panel of 3 pathologist
- Primary outcome: accuracy of detection of cancer+NIFTP

**Performance in Bethesda III and IV nodules (n = 247; disease prevalence 28%)**

| Result | Cancer+NIFTP (n = 68) | Benign (n = 179) | Result |
|---|---|---|---|
| Positive | 64 | 33 | Sensitivity, 94 (86-98) |
| Negative | 4 | 146 | Specificity, 82 (75-87) |
| | | | NPV, 97 (93-99) |
| | | | PPV, 66 (56-75) |

Steward DL et al. *JAMA Oncology* (2019)

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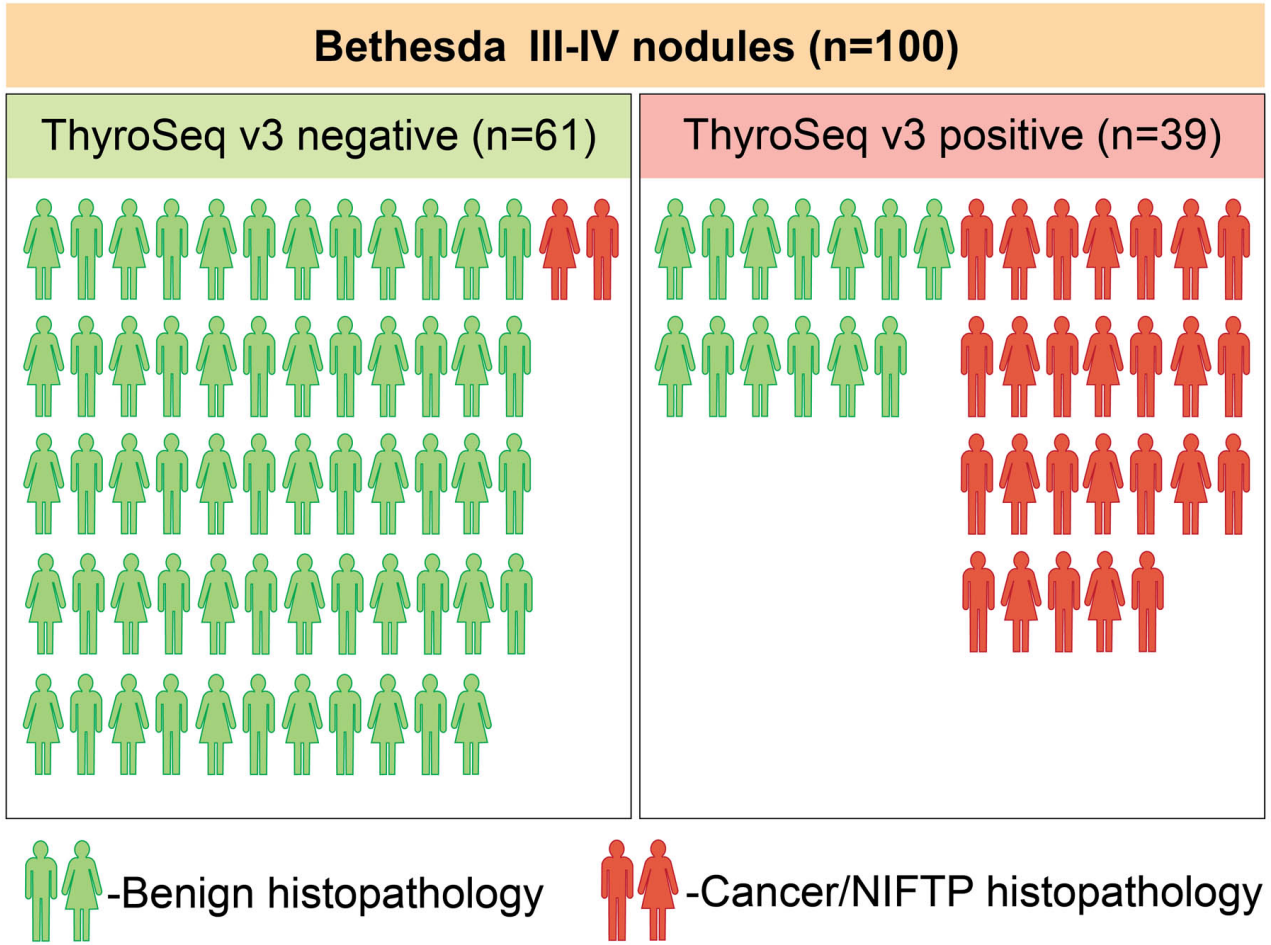
Steward DL et al. JAMA Oncology (2019)

# Clinical Utility: *Avoidance of Diagnostic Surgeries*

61% avoidable surgeries

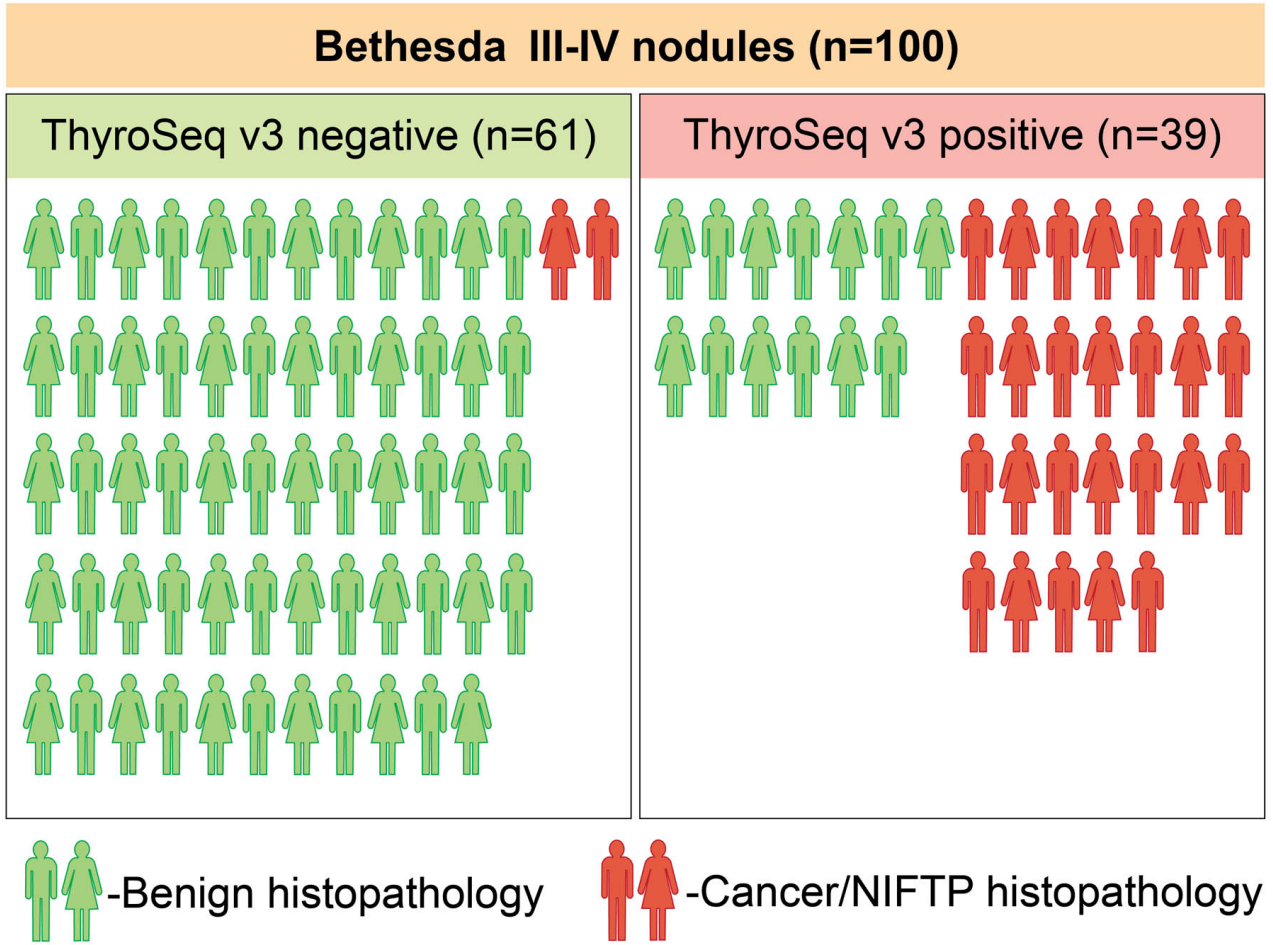
**82% of histologically benign nodules**




Disease prevalence 28%

Steward DL et al. *JAMA Oncology* (2019)

# Clinical Utility:
## *Individualizing Approach to Test-Positive Nodules*




39% require surgery

Disease prevalence 28%

Steward DL et al. *JAMA Oncology* (2019)

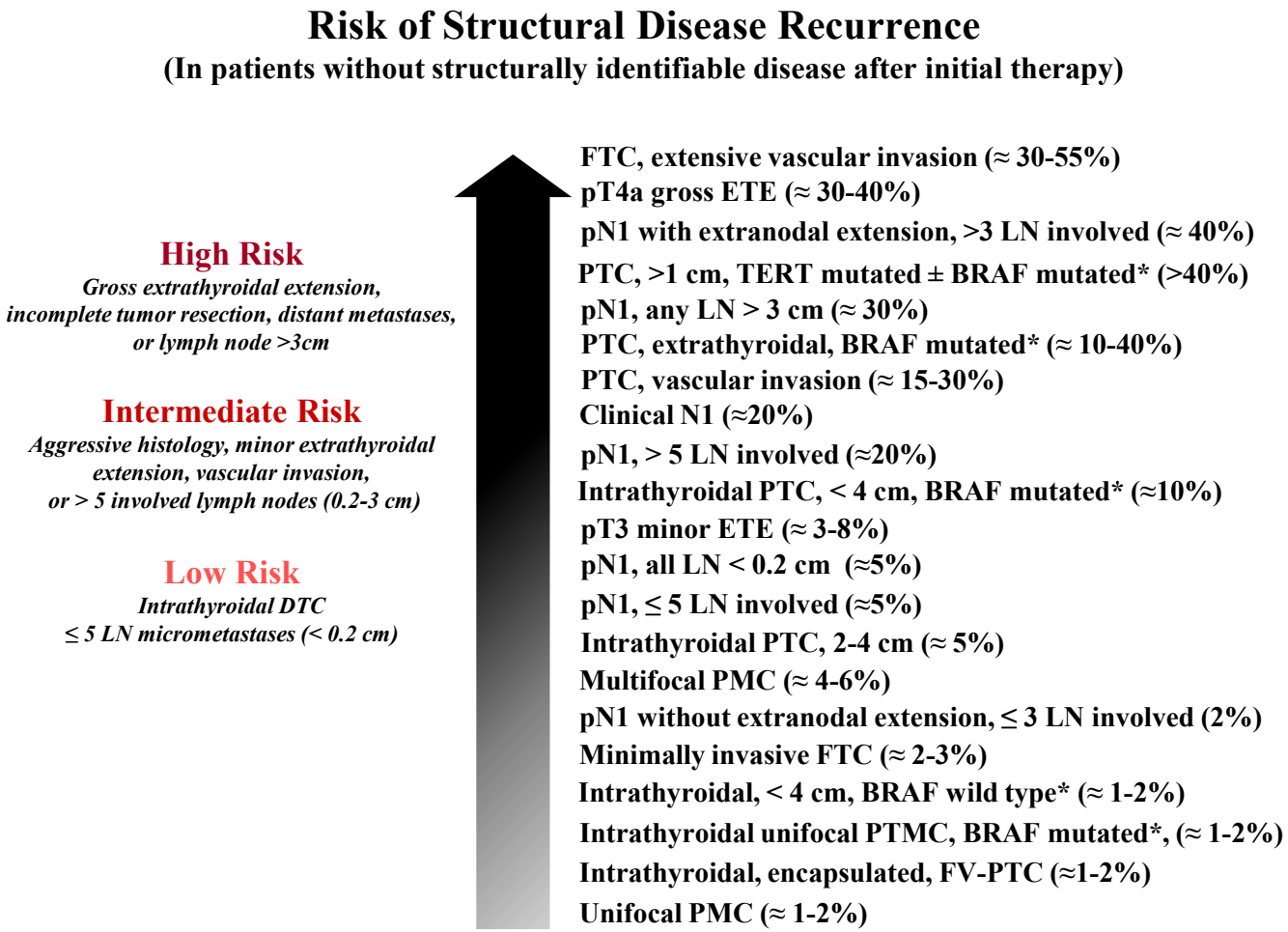
# Test-positive Nodules: Specific molecular alterations predict cancer type and risk of recurrence

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)<br>*TP53* (and *MEN1*) (1) | 2 (2) | 100 | 0 | Papillary carcinoma (50)<br>Follicular variant papillary carcinoma (8)<br>***High-Risk Cancer*** |
| *BRAF*-like group | *BRAF V600E* (9)<br>*NTRK3* fusions (2)<br>*RET* fusions (1)<br>*BRAF* fusions (1) | 13 (12) | 100 | 0 | Classical papillary carcinoma (92)<br>Follicular variant papillary carcinoma (8)<br>***Classic PTC*** |
| *RAS*-like group | *NRAS* (21)<br>*HRAS* (18)<br>*KRAS* (5)<br>*EIF1AX* (5)<br>*BRAF K601E* (3)<br>*PTEN* (1)<br>*IDH2* (1)<br>*DICER1* (1)<br>*PPARG* fusions (4)<br>*THADA* fusions (4) | 60 (57) | 62<br>Cancer/ NIFTP | 38<br>Benign tumors (not HN!) | Follicular variant papillary carcinoma (22)<br>Papillary carcinoma, other variants (17)<br>NIFTP (13)<br>Follicular carcinoma (3)<br>Hürthle cell carcinoma (5)<br>***EFVPTC, NIFTP*** |
| Copy number alterations group | Copy number alterations | 22 (21) | 59 | 41 | Hürthle cell carcinoma (32)<br>Follicular variant papillary carcinoma (14)<br>Papillary carcinoma, other variants (9)<br>NIFTP (5)<br>***HCC*** |
| Gene expression alterations group | Gene expression alterations | 8 (8) | 75 | 25 | Classical papillary carcinoma (37)<br>NIFTP (13)<br>Other cancers (MTC, mRCC) (25)<br>***MTC, mets*** |

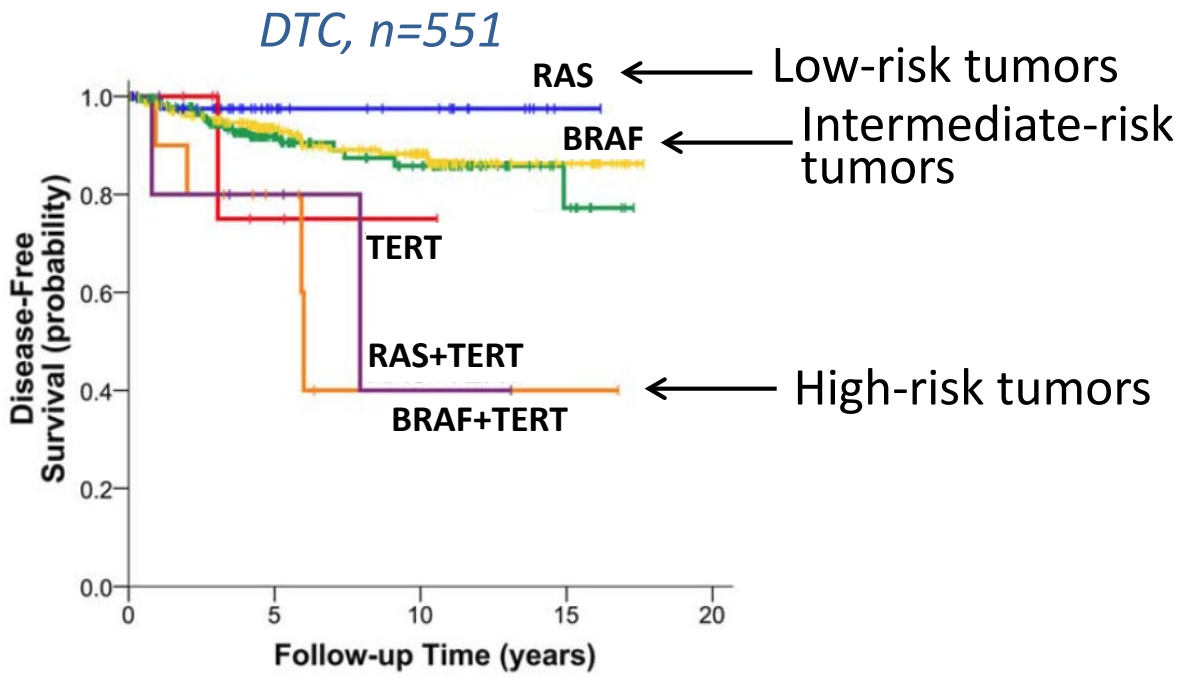
Steward DL et al. *JAMA Oncol.* 2019;5:204-212

# Thyroid Cancer Risk Stratification

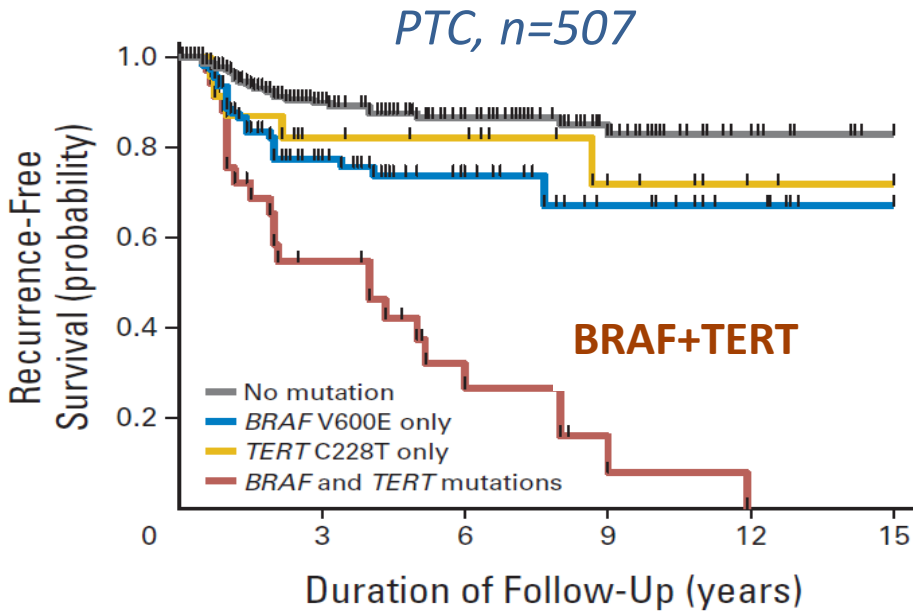



Haugen BR et al. *Thyroid*. 2016, 26:1-133

# Molecular Markers for Cancer Risk Stratification




Song YS et al. *Cancer* (2016)




Xing M et al. *JCO* (2014)

# Molecular Markers for Cancer Risk Stratification

**Risk of Structural Disease Recurrence**
**(In patients without structurally identifiable disease after initial therapy)**

**High Risk**
*Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node >3cm*

**Intermediate Risk**
*Aggressive histology, minor extrathyroidal extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm)*

**Low Risk**
*Intrathyroidal DTC ≤ 5 LN micrometastases (< 0.2 cm)*

- FTC, extensive vascular invasion (≈ 30-55%)
- pT4a gross ETE (≈ 30-40%)
- pN1 with extranodal extension, >3 LN involved (≈ 40%)
- PTC, >1 cm, TERT mutated ± BRAF mutated* (>40%)
- pN1, any LN > 3 cm (≈ 30%)
- PTC, extrathyroidal, BRAF mutated* (≈ 10-40%)
- PTC, vascular invasion (≈ 15-30%)
- Clinical N1 (≈20%)
- pN1, > 5 LN involved (≈20%)
- Intrathyroidal PTC, < 4 cm, BRAF mutated* (≈10%)
- pT3 minor ETE (≈ 3-8%)
- pN1, all LN < 0.2 cm (≈5%)
- pN1, ≤ 5 LN involved (≈5%)
- Intrathyroidal PTC, 2-4 cm (≈ 5%)
- Multifocal PMC (≈ 4-6%)
- pN1 without extranodal extension, ≤ 3 LN involved (2%)
- Minimally invasive FTC (≈ 2-3%)
- Intrathyroidal, < 4 cm, BRAF wild type* (≈ 1-2%)
- Intrathyroidal unifocal PTMC, BRAF mutated*, (≈ 1-2%)
- Intrathyroidal, encapsulated, FV-PTC (≈1-2%)
- Unifocal PMC (≈ 1-2%)

| Genetic Profile | | ThyroSeq 5-year risk of distant metastasis |
|---|---|---|
| *BRAF+TERT, RAS+TERT*<br>*Multiple driver mutations (eg. NRAS and PIK3CA or TP53)*<br>*TERT* | | *High-risk profile (20-35%)* |
| *ALK fusions*<br>*NTRK1 fusions*<br>*NTRK3 fusions*<br>*BRAF V600E*<br>*RET/PTC* | BRAF V600E-like mutations | *Intermediate-risk profile (5-10%)* |
| *RAS*<br>*BRAF K601E*<br>*PAX8/PPARG* | RAS-like mutations | *Low-risk profile (<1%)* |

Yip L et al. *Cancer* (2021)

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

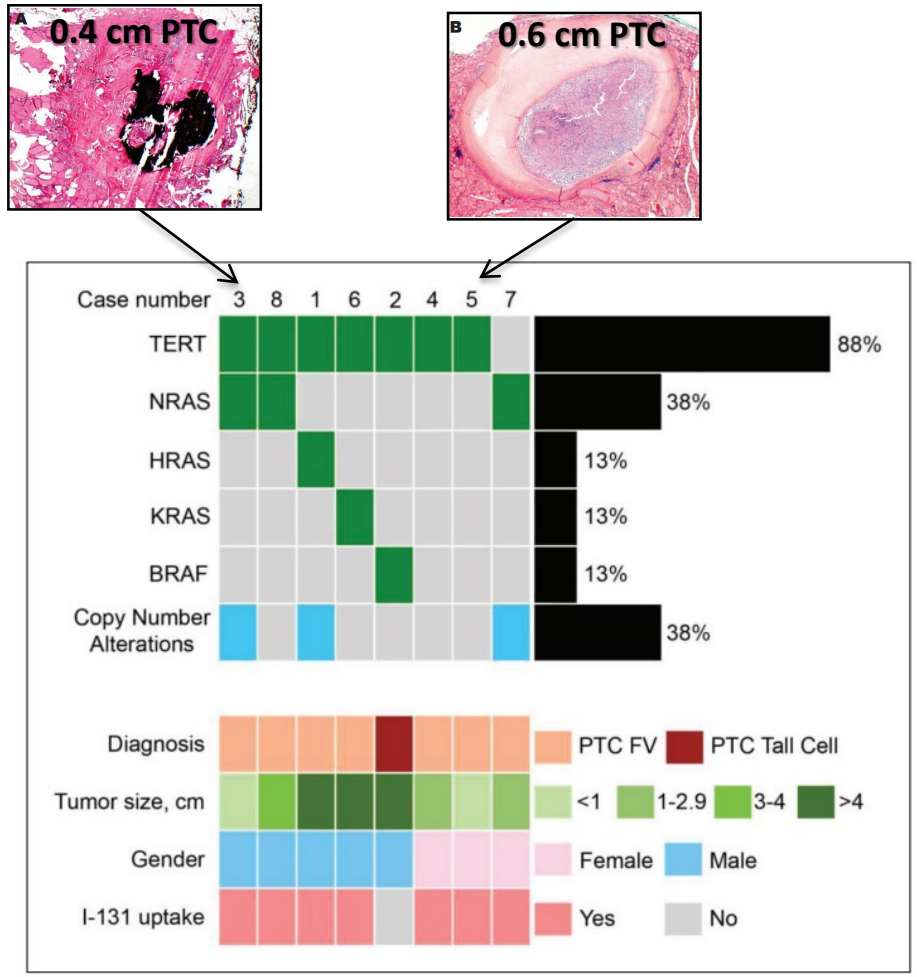
# Are high-risk thyroid cancers large and clinically apparent?

**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



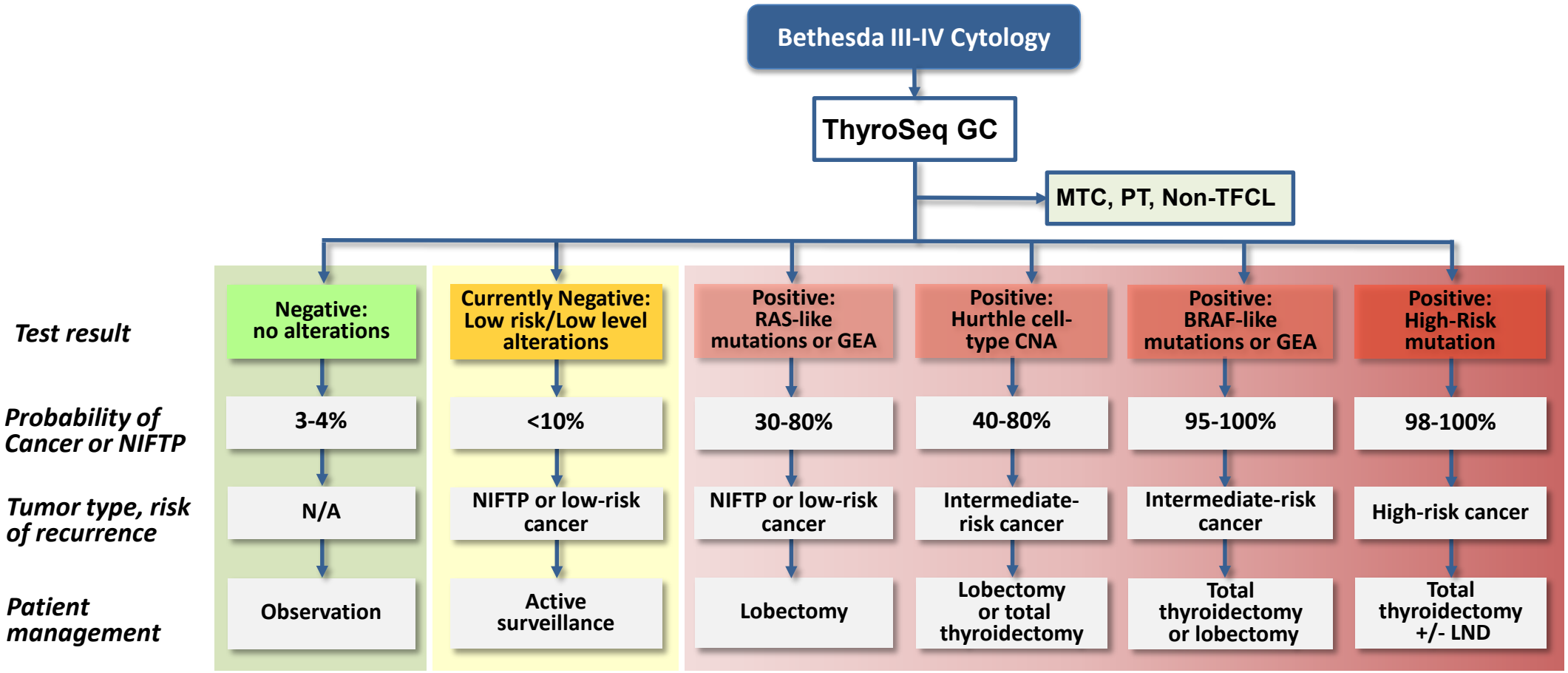
# Molecular Markers for Therapeutics of Advanced Thyroid Cancer

| Genetic Alteration | Tumor Type | Available Targeted Therapeutics |
|---|---|---|
| **BRAF V600E** | PTC, ATC | Vemurafenib, Debrafenib+Trametinib* |
| **HRAS** | PTC, FTC (OFTC), PDTC, ATC | Farnesyltransferase inhibitor tipifarnib |
| **PAX8/PPARG** | FTC (OFTC) | Pioglitazone |
| **ALK fusions** | PTC, ATC, PDTC | Crizotinib, ceritinib |
| **NTRK1/2/3 fusions** | PTC, ATC, PDTC | Entrectinib*, Larotrectinib* |
| **RET** | MTC, PTC, other | Vandetanib, cabozantinib, Selpercatinib* |

**approved by the FDA*

Bible KC and Ryder M. 2016 *Nat Rev Clin Oncol* with modif.

# Individualized Patient Management Informed by ThyroSeq Testing




Abbreviations: MTC, medullary thyroid cancer; PT, parathyroid; Non-TFCL, non-thyroid follicular cell lesion; GEA, gene expression alterations; CNA, copy number alterations; LND, lymph node dissection

Based on data reported in Steward et al. *JAMA Oncology* (2019)

# Summary

- Genetic drivers for most types of thyroid tumors have been uncovered
- Thyroid nodules carrying clonal (somatic) genetic alterations are neoplasms (adenomas or carcinomas) and not hyperplasia
- Many thyroid cancers develop from pre-existing benign or borderline tumors through multiple stages
- Molecular alterations define biological properties of thyroid tumors/ tumor lineage and clinical behavior
- Histopathology is essential to determine stage of tumor progression

# Summary

- Molecular testing:
  - ✓ Allows for safe avoidance of diagnostic surgeries
  - ✓ Provides prognostic information preoperatively – tailored surgery
  - ✓ Detects therapeutic targets for advanced thyroid cancer
- *Informs more individualized management of patients with thyroid nodules and cancer*

# Thank you!