

Integrating Genetics and Genomics into Multidisciplinary Care: Thyroid Cancer

American College of Surgeons Cancer Conference Phoenix, Arizona 2025

Jennifer E. Rosen, M.D., F.A.C.S.

Regional Chief of Endocrine Surgery, MedStar and Georgetown University School of Medicine



I have no disclosures except a deep and abiding love
for complex problem solving and for the well being of
my patients and colleagues.

Agenda



ILLUSTRATIVE PATIENT
EXAMPLE – THYROID
CANCER



BASIC CONCEPTS OF
GENETICS AND GENOMICS



CLINICAL CONUNDRUM IN
THYROID CANCER – WHERE
ARE THE PROBLEMS?



FUTURE OPPORTUNITIES –
ALL GOOD PROJECTS COME
FROM A QUESTION

Patient – case example

32 year old female with
a palpable 2 cm left
thyroid nodule

TSH is normal

Ultrasound
demonstrates a 2 cm
TIRADS5 nodule

Ultrasound guided fine
needle aspiration
biopsy – Bethesda
Category IV “suspicious
for follicular neoplasm”

How do we decide what thyroid nodules to biopsy?

Haugen B *et al. Thyroid* 2015

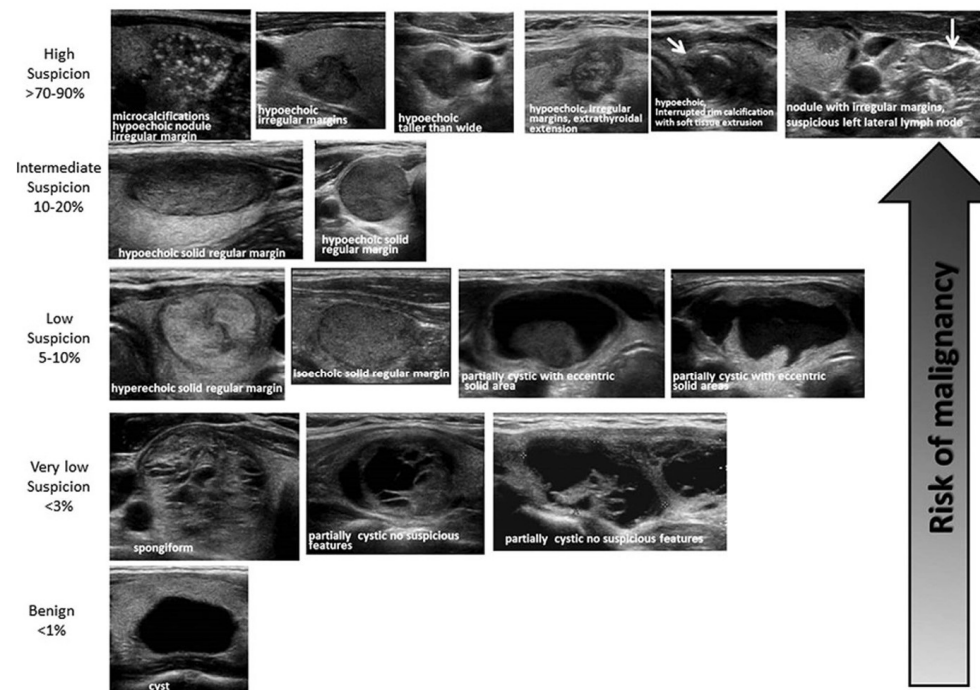
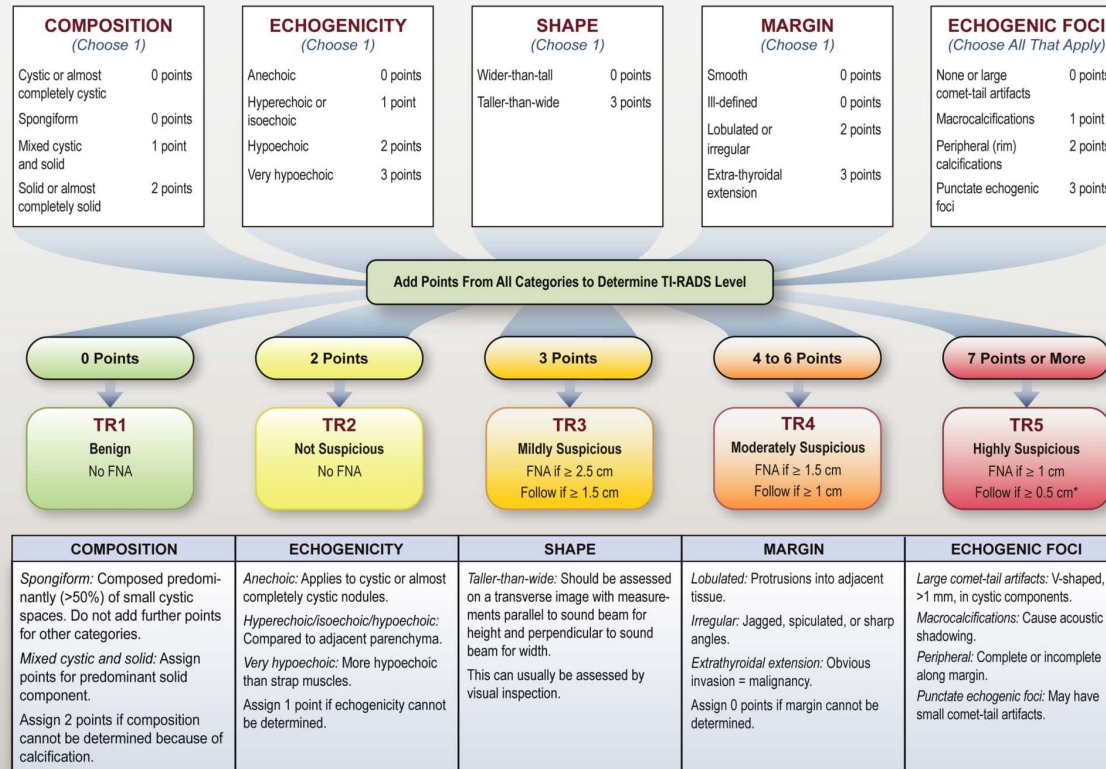


FIG. 2. ATA nodule sonographic patterns and risk of malignancy.

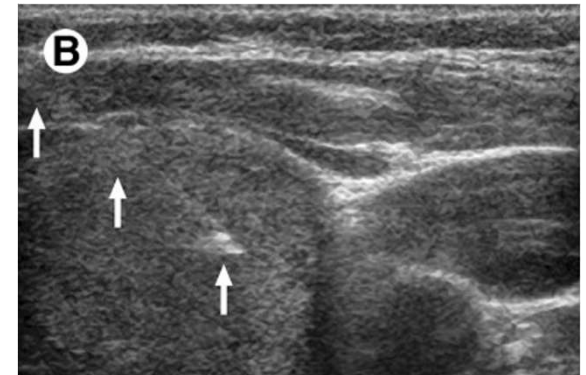
ACR TI-RADS



*Refer to discussion of papillary microcarcinomas for 5-9 mm TR5 nodules.

Fine Needle Aspiration Biopsy

Langer JE *et al.*, *Semin
Ultrasound CT MR.* 2012.

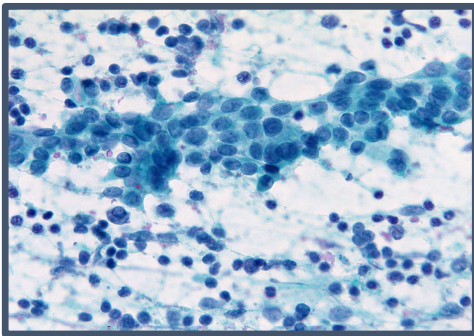


Thyroid biopsy results:

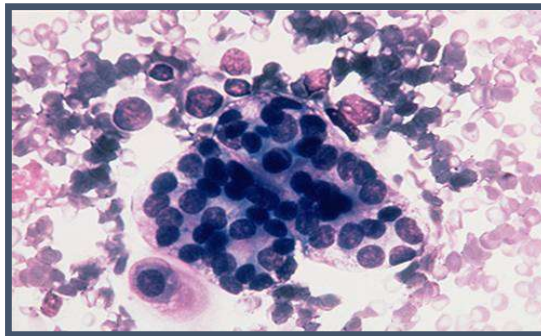
70% are benign

5% are cancer

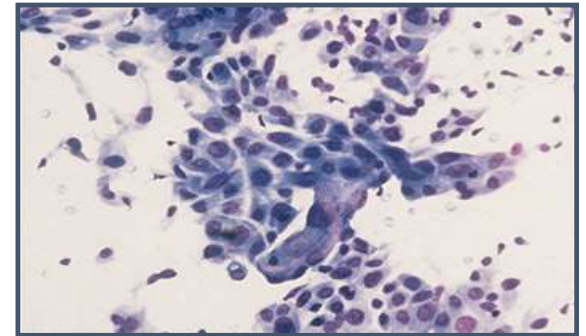
~25% thyroid FNAs are *suspicious or indeterminate* for malignancy



**Atypical cells of
undetermined
significance (AUS)**



**Follicular or Hürthle cell
neoplasm**



Suspicious for malignancy

The Bethesda System for Reporting Thyroid Cytopathology

<i>Diagnostic category</i>	<i>Estimated/predicted risk of malignancy by the Bethesda system, %^a</i>	<i>Actual risk of malignancy in nodules surgically excised, % median (range)^b</i>
Nondiagnostic or unsatisfactory	1–4	20 (9–32)
Benign	0–3	2.5 (1–10)
Atypia of undetermined significance or follicular lesion of undetermined significance	5–15	14 (6–48)
Follicular neoplasm or suspicious for a follicular neoplasm	15–30	25 (14–34)
Suspicious for malignancy	60–75	70 (53–97)
Malignant	97–99	99 (94–100)

Cibas et al 2009; Ali SZ et al 2023

Why so many indeterminate thyroid biopsies? And what can we do about it?

Bigger
needles

More
needles

PET/CT

CT

Elastography

Better
biopsiers

....

How can we harness the knowledge of genetics and genomics research for patient care?

The Cancer Genome Atlas Giordano TJ *et al.*, *Cell*. 2014

Nature Communications

Yu et al 2019

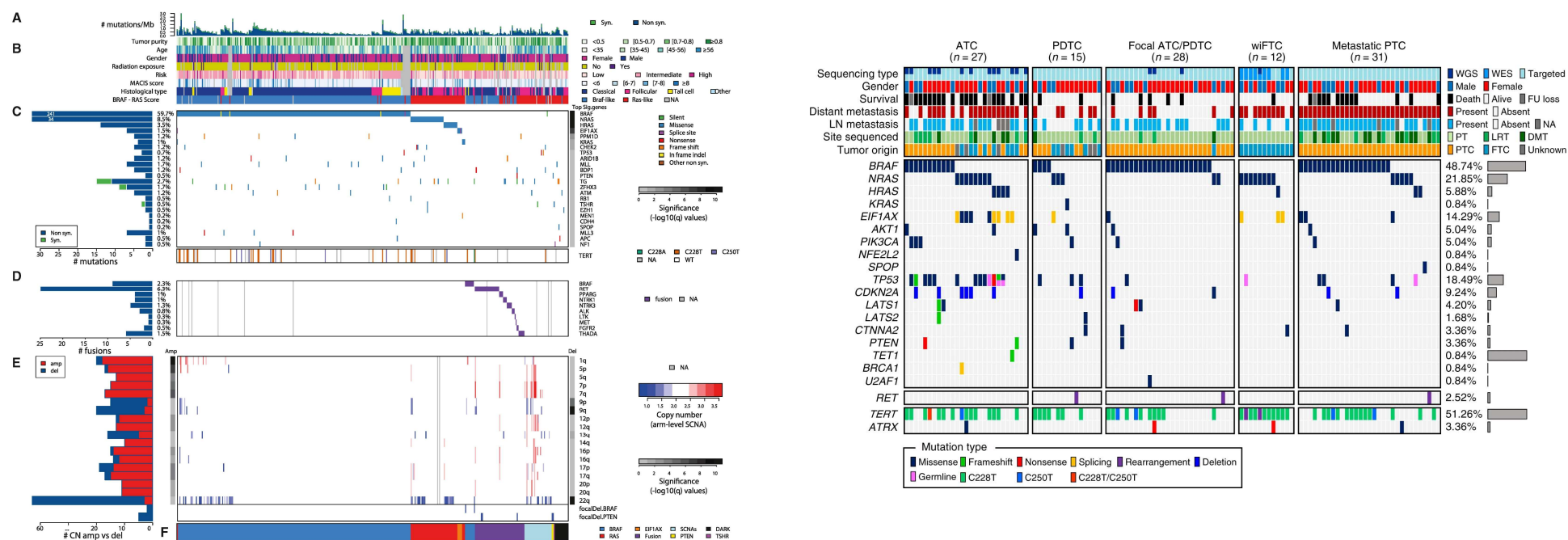
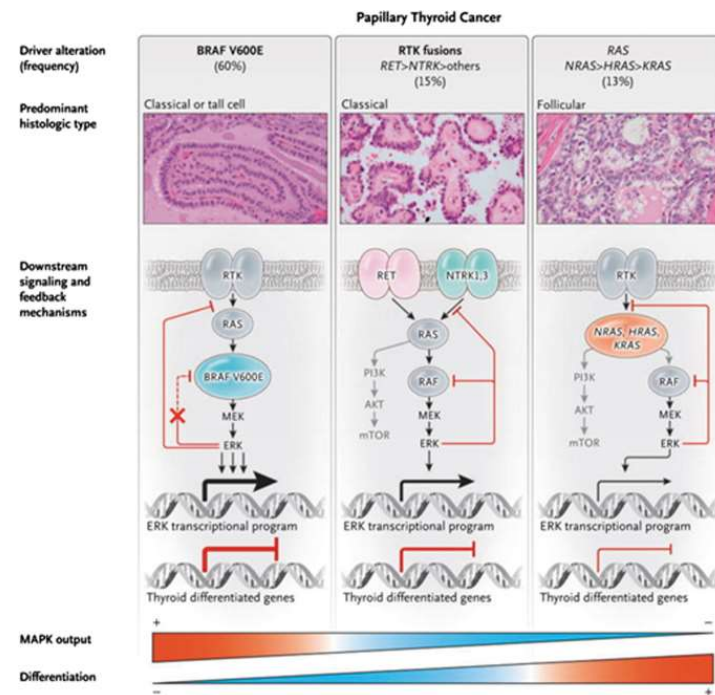
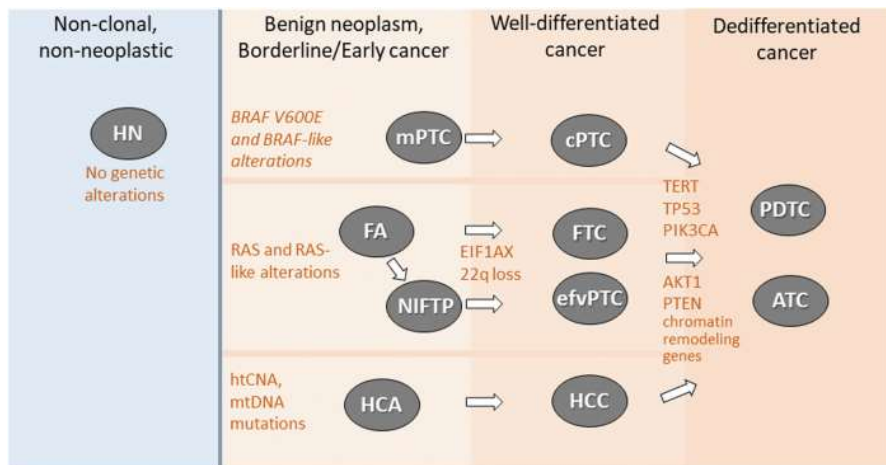


Figure 1. Landscape of Genomic Alterations in 402 Papillary Thyroid Carcinomas

Understanding the molecular progression of thyroid cancer...



Fagin J and Nikiforov Y, Thyroid 2024

Molecular testing for thyroid cytology...

- **ThyroSec v3 (\$3600):**
 - core alterations: BRAF V600E, NRAS, HRAS, KRAS, RET/PTC1, RET/PTC3, and PAX8/PPARG; 112 genetic alterations, gene fusions, copy number alterations, abnormal gene expression
- **Afirma Genomic Sequencing Classifier (GSC) (\$3600):**
 - 905 genomic variants and 235 fusion pairs from 593 genes
- **ThyGeNext (\$1266) & ThyraMiR v2 (\$3000):**
 - DNA mutation, RNA & miRNA expression panel

Molecular testing
for thyroid
“indeterminate”
yea or nay?

PRO

- May change decision to watch and wait
- May favor lobectomy over total thyroidectomy

CON

- Expensive
- May not alter management
- Patient decision

Patient Case Example

Molecular testing performed – suspicious/positive gene expression classifier, BRAF mutation

Bilateral lateral neck ultrasound for lymph node mapping – no worrisome lateral lymphadenopathy, did have several worrisome central lymph nodes

Opted for a total thyroidectomy with central neck evaluation

Final pathology: multifocal papillary thyroid cancer, dominant nodule 2.5 cm with lymphovascular invasion, 3/3 central lymph nodes positive for metastasis with no extranodal extension

AJCC pT2pN1M0 = Stage 1

Patient Case Example – so what now?

- Moderate risk for recurrence
- Opted for treatment with radioactive iodine
- ...Thyroglobulin was 20 postop with elevation to 43 with rhTSH stimulation
- ...I123 only demonstrated 0.38% remnant, no metastasis
- ...I131 treatment 75 mCi, posttherapy scan no metastasis

- One year later – Tg is now 40, up to 93 with rhTSH stimulation
- Low dose I131 scan is NEGATIVE
- PET/CT demonstrates multifocal central neck positivity, 2.5 cm nodule in the left lateral neck

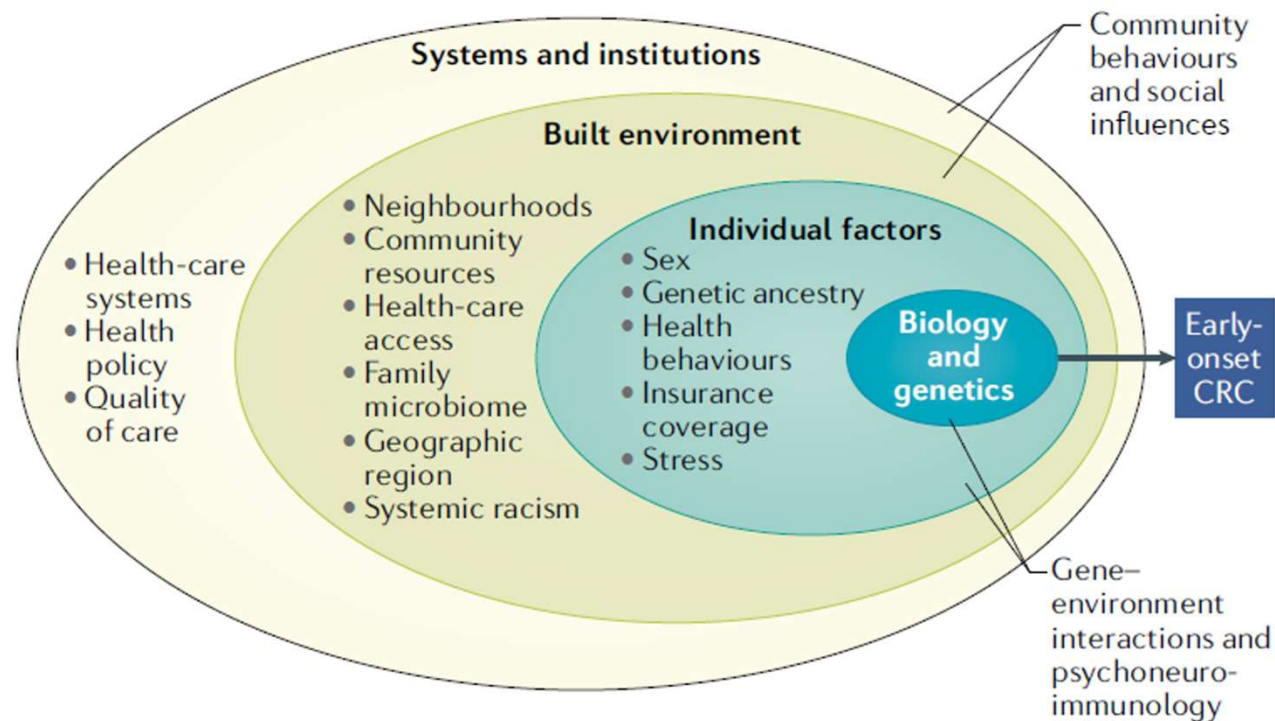
So what are
her options?
And why did
this happen?

- Radiofrequency ablation of all foci?
- Alcohol ablation of all foci?
- Chemotherapy?
- External beam radiation therapy?
- TSH suppressive therapy?
- Bilateral reoperative central neck dissection, left modified radical neck dissection?

....molecular fingerprinting

Influences on Cancer Incidence and Outcomes

A. Holowatyj et al Nature Reviews: Cancer 2021



CARIS Genotyping

MI Profile

- MI Profile™ comprehensive testing delivers whole exome sequencing (WES – DNA) and whole transcriptome sequencing (WTS – RNA) for 23,000+ genes, as well as protein analysis and AI-predictive algorithms.

MI Tumor Seek Hybrid

- MI Tumor Seek Hybrid™ is a high-throughput next generation sequencing (NGS)-based assay that simultaneously captures both DNA and RNA

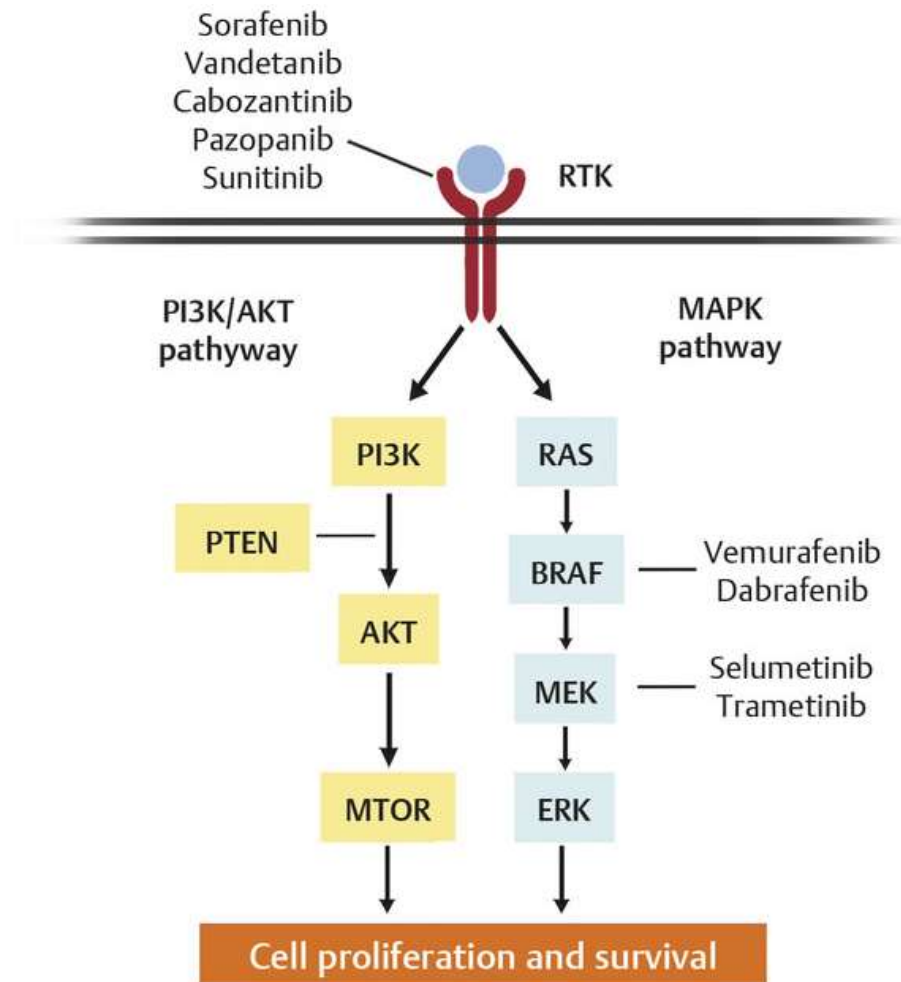
Caris Assure

- Whole Exome and Whole Transcriptome Sequencing from blood. This revolutionary, pan-cancer assay utilizes a novel circulating Nucleic Acid Sequencing (cNAS) approach.

To reiterate, I have NO financial or ethical conflicts of interest and do NOT receive support from CARIS. There are other companies that provide testing, this is what we currently use.

Oncohematol Key. 2017.

Molecular Targeted BRAF Pathway



Sipos JA & Ringel MD,
*Best Pract Res Clin
Endocrinol Metab.* 2023.

FDA-approved Treatment for Advanced Thyroid Cancer

Compound	Biomarkers	Tumor Indication
Immune Checkpoint Inhibitors	High Tumor Mutation Burden and/or mismatch repair deficient or tumors with microsatellite instability	Any solid tumor with biomarker
Dabrafenib + Trametinib Selpercatinib or Pralsetinib	BRAF V600E mutation Ret mutations and RET fusions	Anaplastic Thyroid Cancer Progressive FCDTC ^a or medullary thyroid cancer
Larotrectinib or Entrectinib Lenvatinib, Sorafenib, and Cabozantinib ^b	NTRK fusions No specific molecular biomarker	Any progressive solid tumor with biomarker Progressive metastatic non anaplastic FCDTC
Vandetanib and Cabozantinib	No specific molecular biomarker	Progressive medullary thyroid cancer

^a Follicular cell derived thyroid cancer.

^b Approved as second-line therapy following prior VEGF-targeted treatment.

The Cancer Genome Atlas (TCGA) and bias

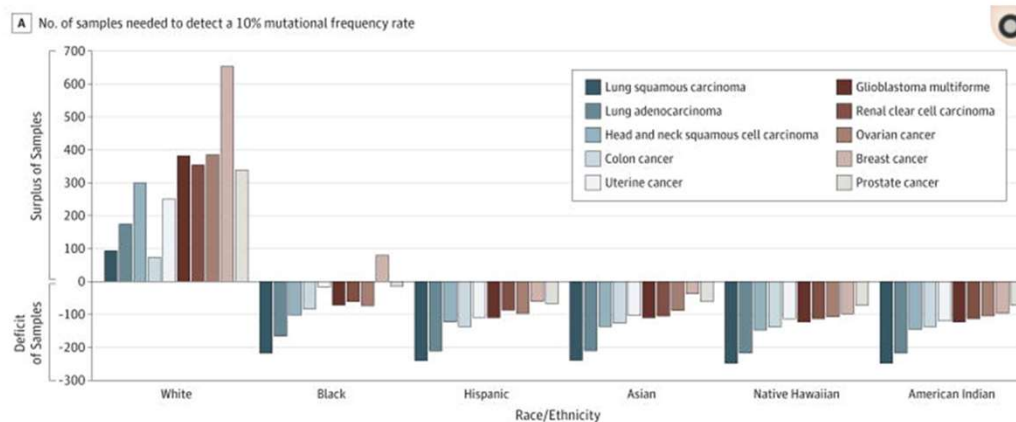
- Most cancer type cohorts were >80% non-Hispanic white
- NOT because cancers have lower incidence
- Severely limits our ability to test for enriched mutations

Characteristic	Cancer, %												Total, No. (%)
	Prostate		Breast	Lung AC	Lung SCC	Colon	Uterine	Ovarian	HNSCC	Kidney	GBM		
	495	1085	521	495	453	540	591	423	533	593			
Race ^a													
White	83	69	75	69	47	69	83	106	87	85	4389	(77)	
Black	12	16	10	6	12	19	6	11	10	9	660	(12)	
Asian	2	6	2	2	2	4	3	3	2	2	173	(3)	
Native Hawaiian	0	0	0	0	0	2	0	0	0	0	10	(0.2)	
American Indian	0	0	0	0	0	1	1	0	0	0	13	(0.2)	
NA	3	9	13	23	38	5	7	4	1	4	584	(10)	
Ethnicity ^a													
Hispanic	1	4	1	2	0	3	2	6	5	2	149	(3)	
Non-Hispanic	78	80	74	63	59	69	57	109	66	82	4234	(74)	
NA	21	16	24	36	41	28	41	9	29	16	1446	(25)	
Median somatic mutation frequency (per Mb)	0.7	1.2	8.1	9.9	3.1	2.5	1.7	3.9	1.9	2.2			

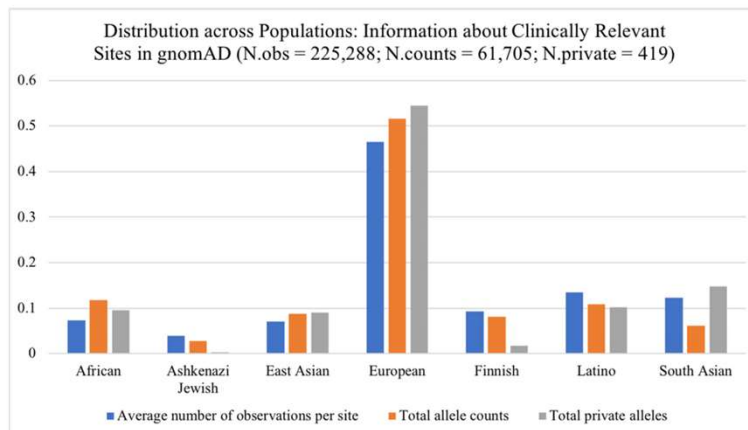
Abbreviations: AC, adenocarcinoma; GBM, glioblastoma multiforme; HNSCC, squamous cell carcinoma; NA, not available; SCC, squamous cell carcinoma; TCGA, The Cancer Genome Atlas.

Ethnic Disparities in Genomic Sequencing

Jpratt, MD, Tiffany Chan, MA, Levi Waldron, PhD, Corey Speers, MD, Felix Y. n O. Ogunwobi, MD, PhD, and Joseph R. Osborne, MD, PhD



gnomAD - Clinical genetics – great promise but incomplete data



Published in final edited form as:

Hum Mutat. 2018 November ; 39(11): 1713–1720. doi:10.1002/humu.23644.

“The Clinical Imperative for Inclusivity: Race, Ethnicity, and Ancestry (REA) in Genomics”

Alice B. Popejoy^{1,*}, Deborah I. Ritter², Kristy Crooks³, Erin Currey⁴, Stephanie M. Fullerton⁵, Lucia A. Hindorf⁴, Barbara Koenig⁶, Erin M. Ramos⁴, Elena P. Sorokin¹, Hannah Wand¹, Mathew W. Wright¹, James Zou¹, Christopher R. Gignoux³, Vence L. Bonham⁴, Sharon E. Plon², and Carlos D. Bustamante¹ Clinical Genome Resource (ClinGen) Ancestry and Diversity Working Group (ADWG)

- gnomAD = Genome Aggregation database
- European ancestral databases constituted the majority of observations (55.8%); allele counts (59.7%), and private alleles (56.1%)
- Genetic Information Nondiscrimination Act (GINA) – not signed into law until May 21, 2008

DANCE-Th: Prospective Thyroid Cancer Cohort at Georgetown University School of Medicine and MedStar Health



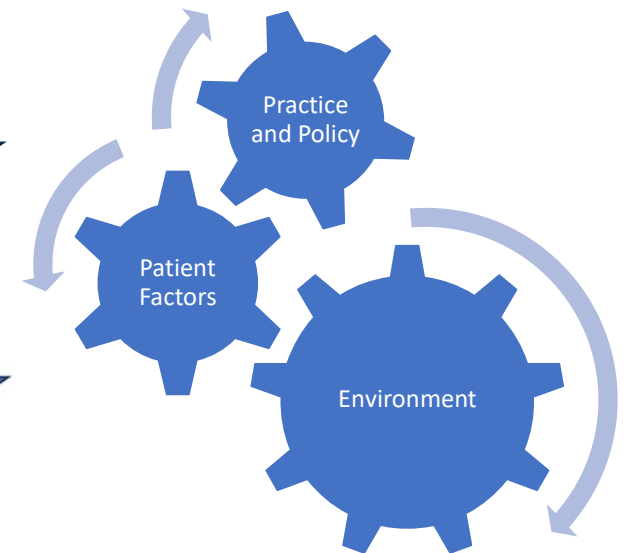
Inclusion: Patients with thyroid cancer
undergoing surgery

Goal: Highly diverse set of patients with
differentiated thyroid cancer

Plan:
Comprehensive initial evaluation along with a
genetic counselor
Genetic testing – blood, saliva, tissue biobank
Yearly evaluation

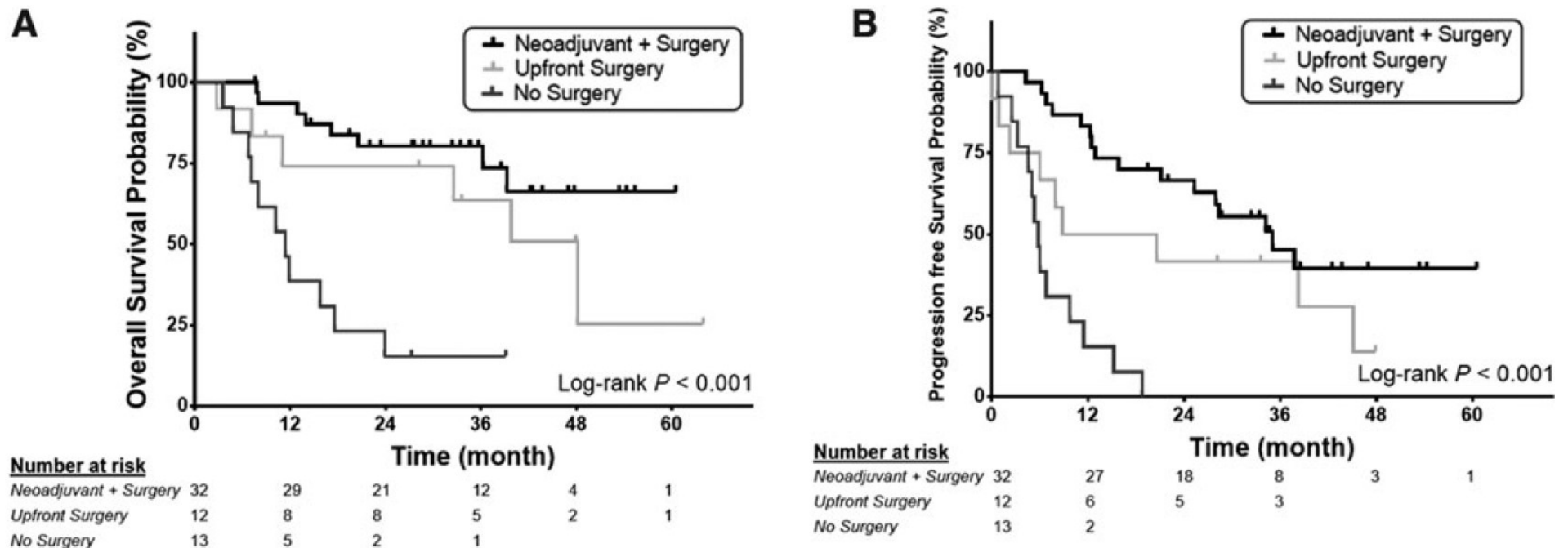
Outcomes:
Medical outcomes
Patient reported outcomes
Genetic epidemiology, genotype/phenotype
correlation

International Collaboration for Data Sharing
and Tissue Genotyping

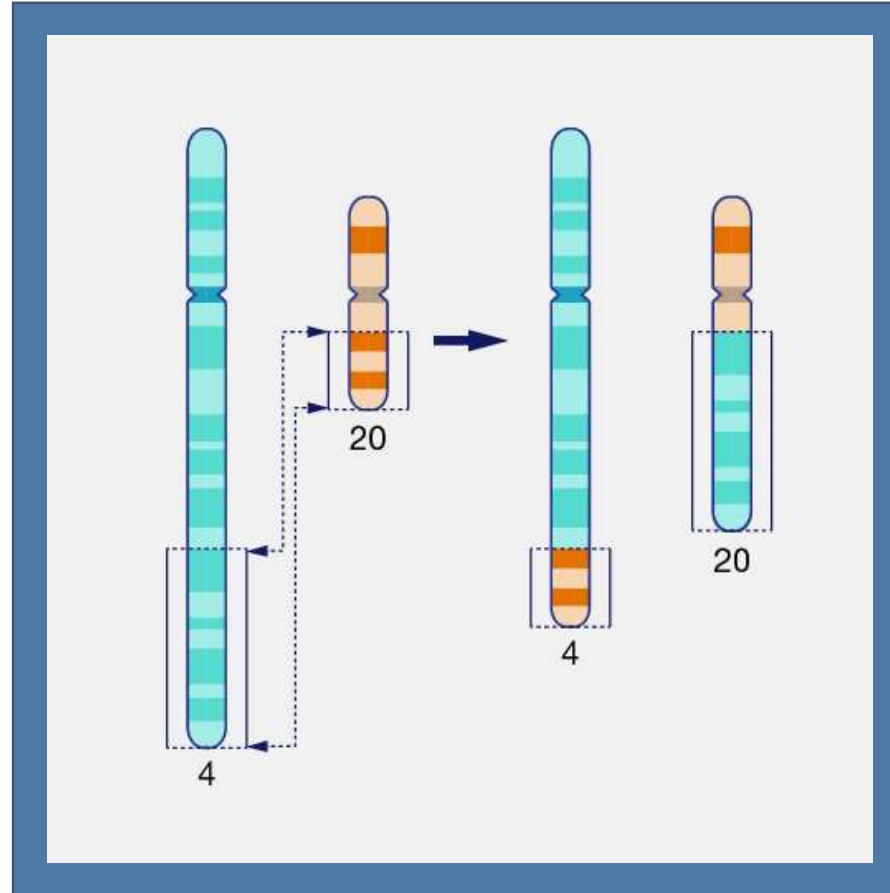


As of 3/14/2025 we have 5000
patients in our retrospective
database... recruiting now for
prospective study!

Overall Survival and Progression Free Survival for Patients in Relation to Surgery After BRAF-directed Therapy

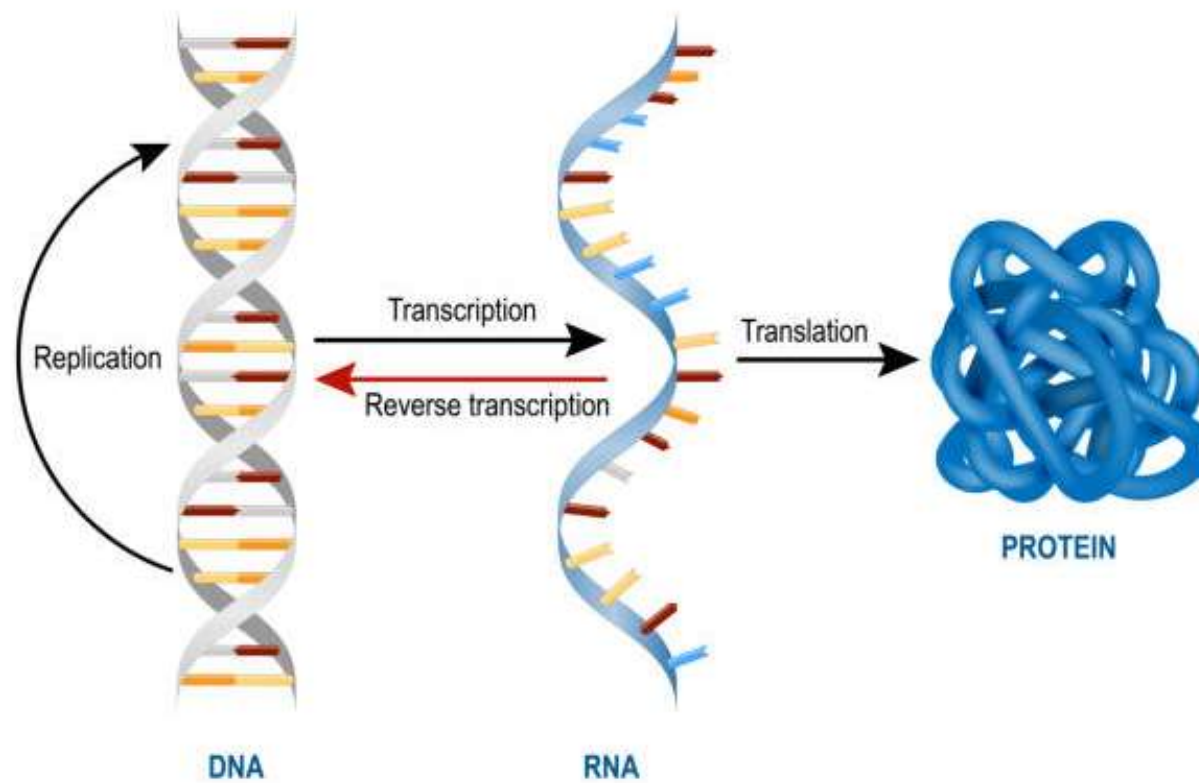


DNA Translocation

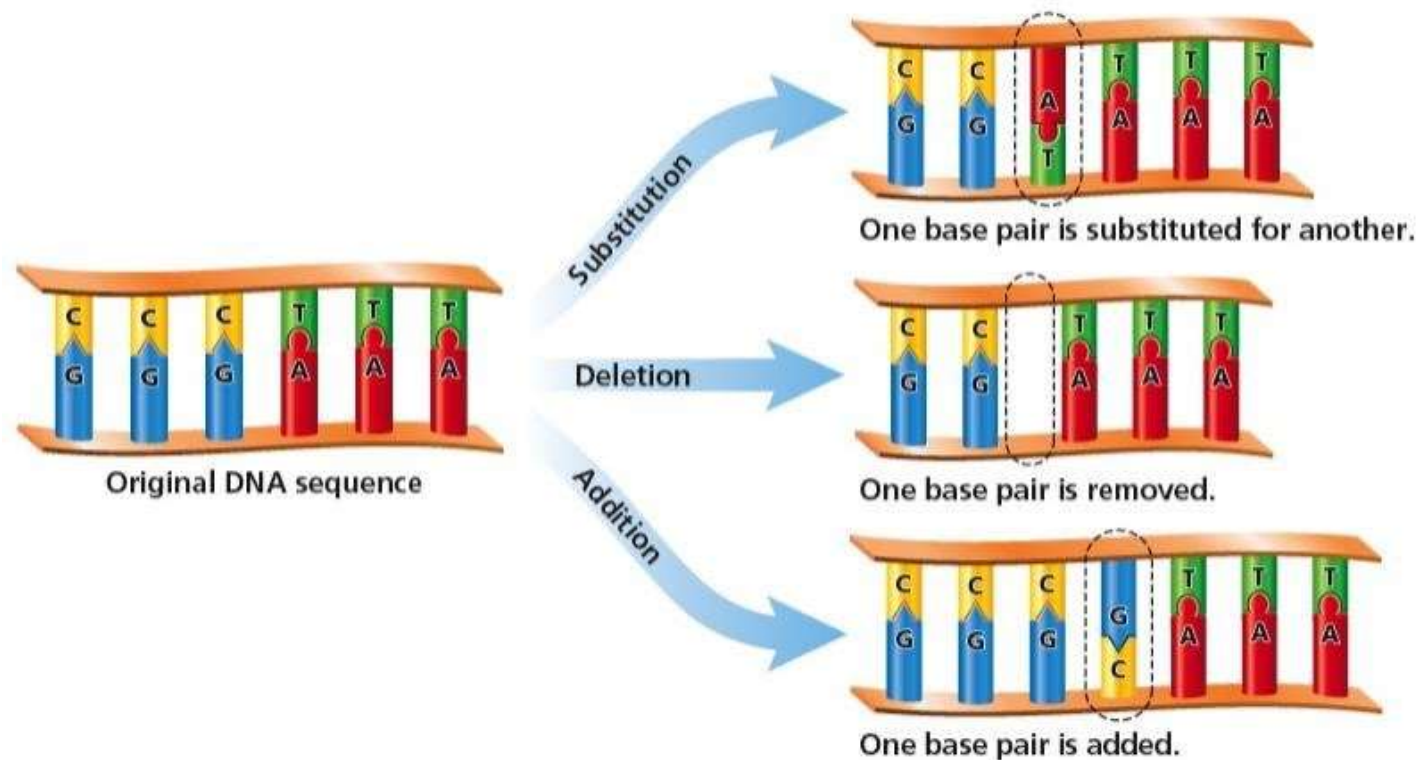


National Human Genome Research Institute. 2023.

DNA → RNA → Protein



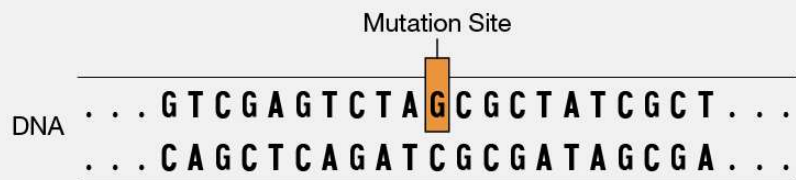
Types of DNA Mutation



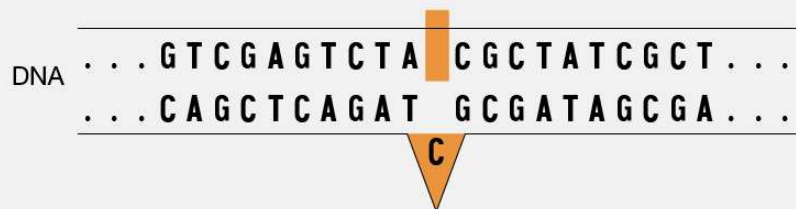
Frazer G, Arizona State University. 2019.

DNA Deletion

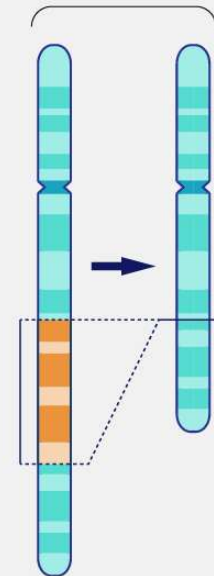
Microdeletion



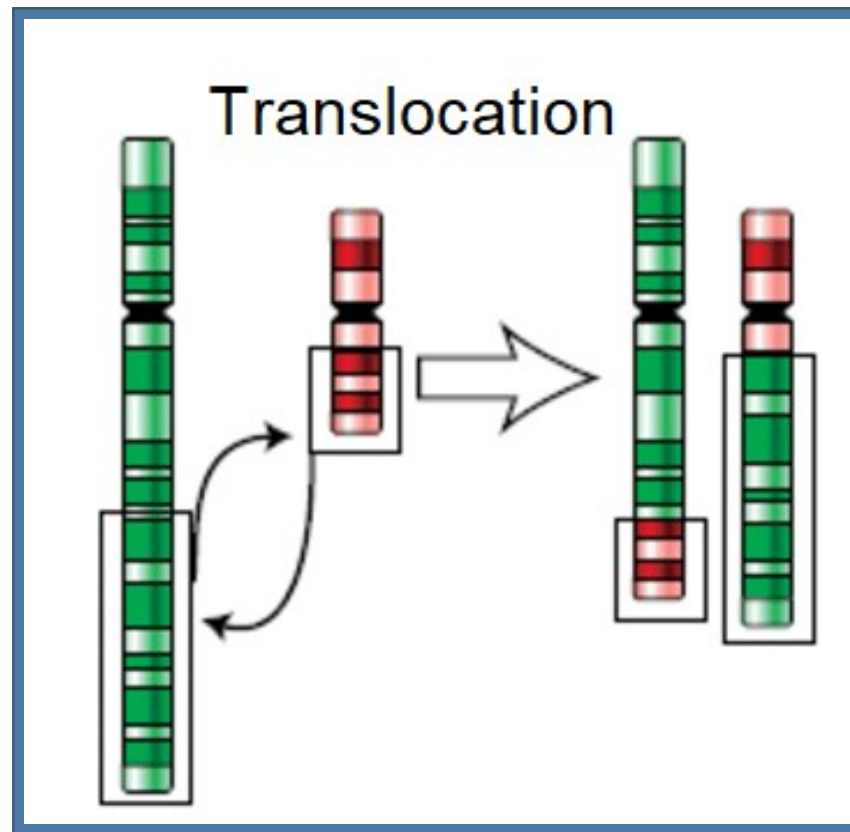
Deletion



Macrodeletion

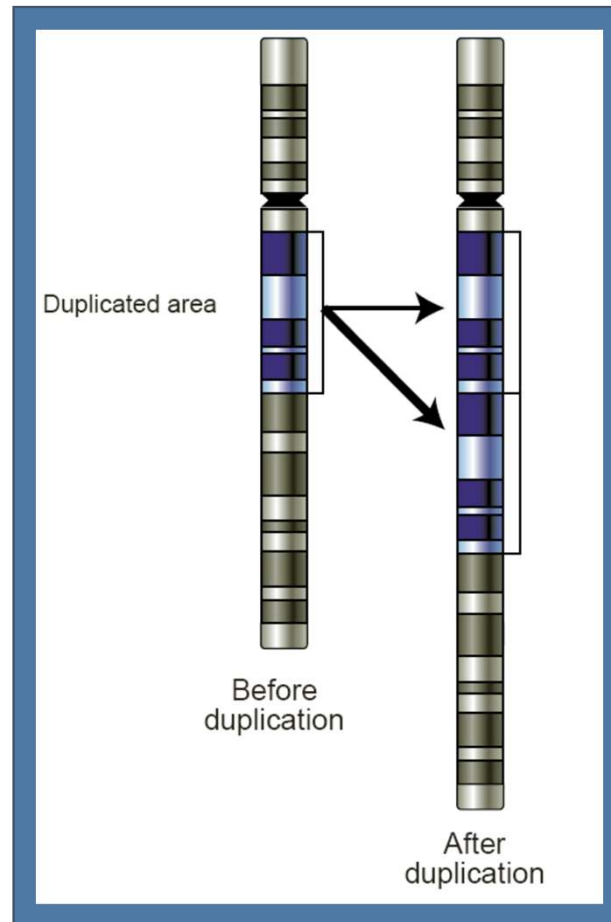


DNA Translocation



National Human Genome Research Institute. 2023.

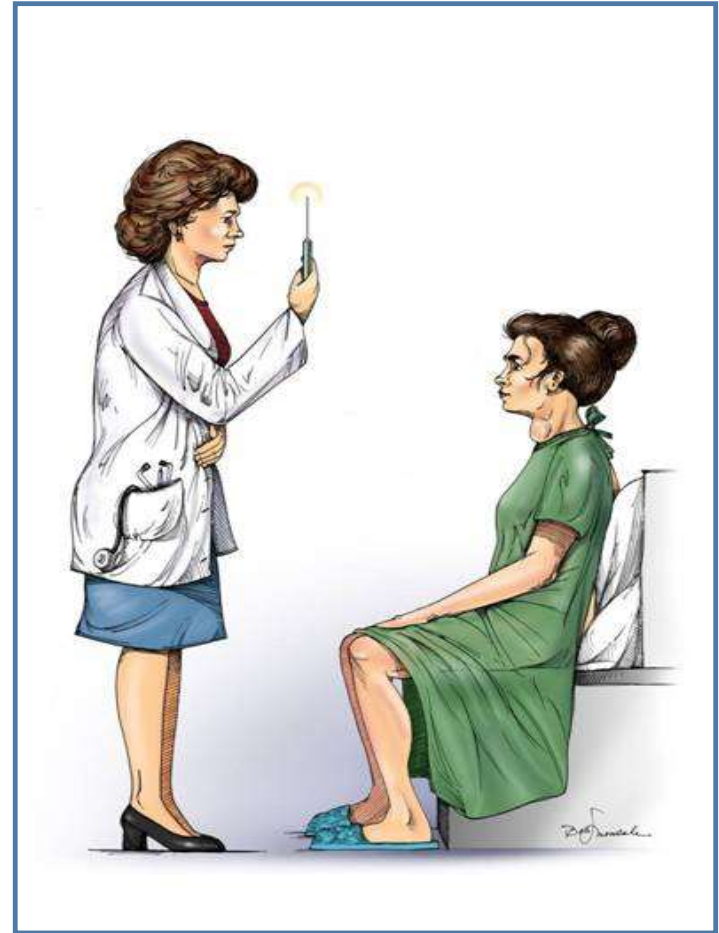
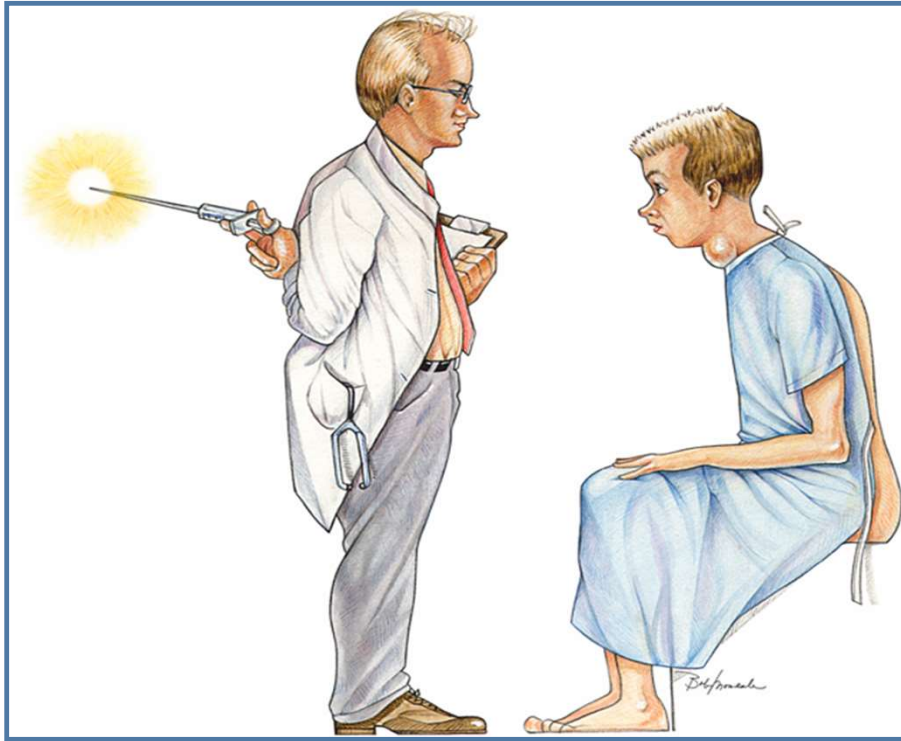
Copy Number Alteration



*National Human Genome
Research Institute. 2007.*

Overview

1. “Some basic molecular biology” ✓
2. “Two clinical problems” →
3. “Molecular diagnostics”
4. “Molecular targets”



Overview

1. “Some basic molecular biology” ✓
2. “Two clinical problems” ✓
3. “Molecular diagnostics” →
4. “Molecular targets”

Benign Call Rate and Molecular Test Result Distribution of ThyroSeq v3

- Retrospective review of 224 cases with Bethesda III/IV cytology
- ThyroSeq v3 test results
- Benign call rate 74%

HOWEVER.....

Thyrosec v3, Afirma GSC: A Systematic Review and Meta-Analysis

- 603 TNs Thyrosec v3 negative 54%
- 635 ITNs Afirma negative 72%
- **HOWEVER.....**

Is Molecular Testing Indicated?

Thyroid lobectomy indicated already?

- Growing 3 cm nodule with history of 3 FNAs
- Symptomatic 4 cm nodule
- How is the molecular test helpful?

Is Molecular Testing Indicated?

Regarding extent of resection and whether total thyroidectomy indicated already?

- Moderate-sized or substernal goiter
- Suspicious cervical lymph node
- Small multinodular goiter and hypothyroidism

Molecular Profiling of 50,734 Bethesda III-IV Thyroid Nodules by ThyroSeq v3

- Retrospective review of 17,205 cases with Bethesda III/IV cytology
- ThyroSeq v3 tests 34% suspicious molecular test

HOWEVER.....

Is Molecular Testing Indicated?

Regarding extent of resection and whether total thyroidectomy or lymphadenectomy indicated already?

- 2 cm TIRADS 4 thyroid nodule with no lymphadenopathy
- Suspicious cervical lymph node...biopsy!
- Multinodular goiter and hypothyroidism

Challenges to Efficacy of Molecular Testing

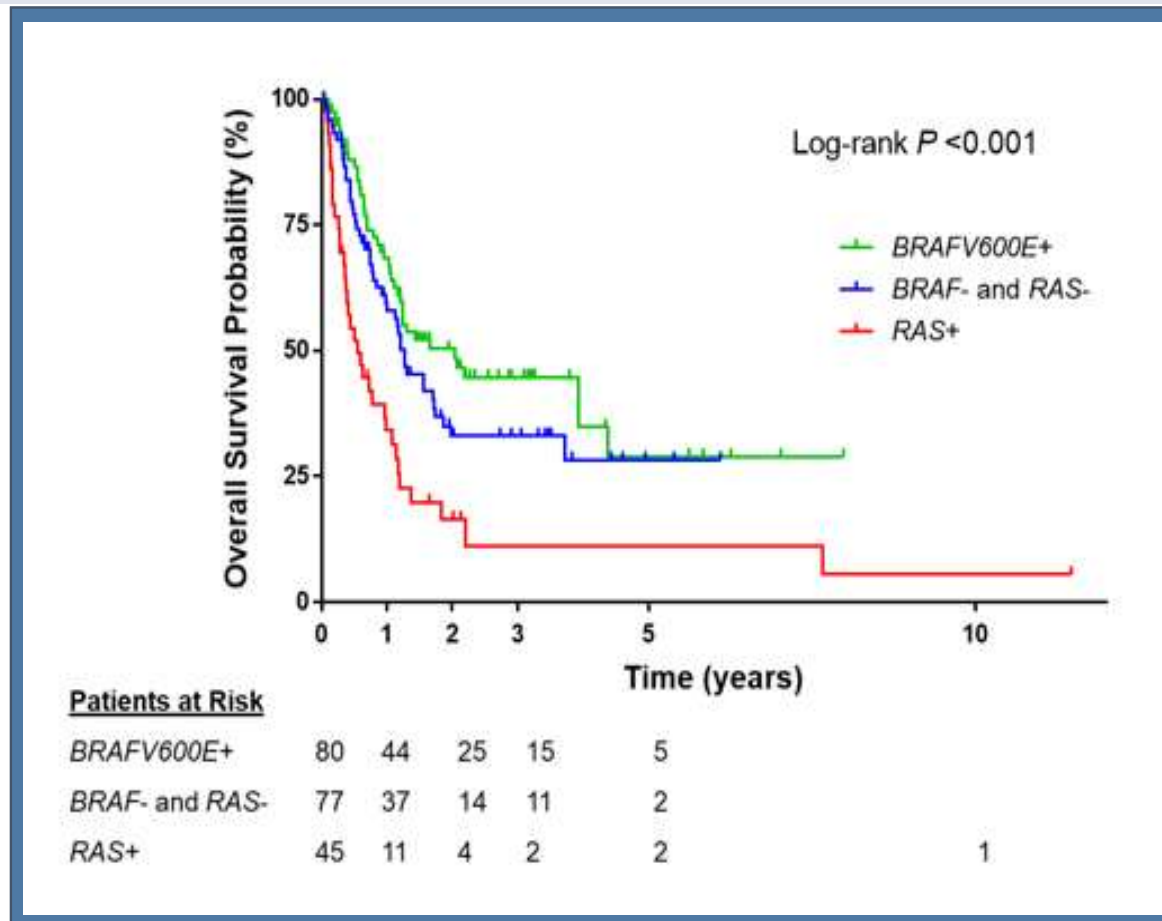
- 773 consecutive patients with introduction of ThyroSec v2
- Cytology shift toward more indeterminate results
- No change in rate of surgery, % overtreatment, or rate of malignancy

Challenges to Efficacy of Molecular Testing

Costs

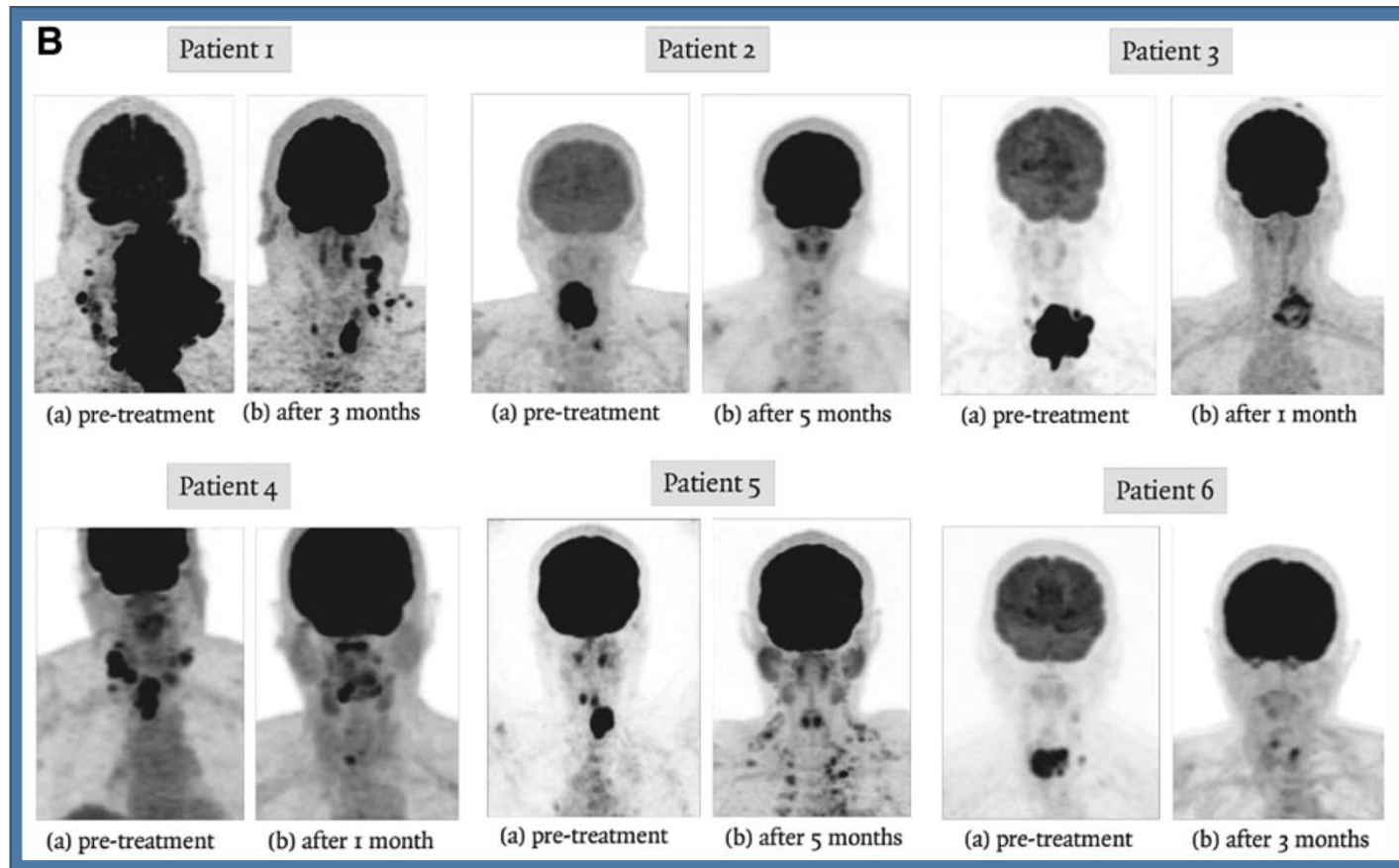
- Thyroid lobectomy or total thyroidectomy \$600-\$1200
- Afirma Genomic Sequencing Classifier \$3,600
- Afirma Xpression Atlas \$2900
- ThyroSec v3 \$3,600
- ThyGeNext (\$1266) & ThyraMiR v2 (\$3000)

Prognosticating ATC by Genetic Targets



Cabanillas Z *et al.*,
F1000Research. 2018.

Complete Surgical Resection Following Neoadjuvant Dabrafenib Plus Trametinib in BRAFV600E-Mutated Anaplastic Thyroid Carcinoma



Wang, J *et al.*
Thyroid. 2019.

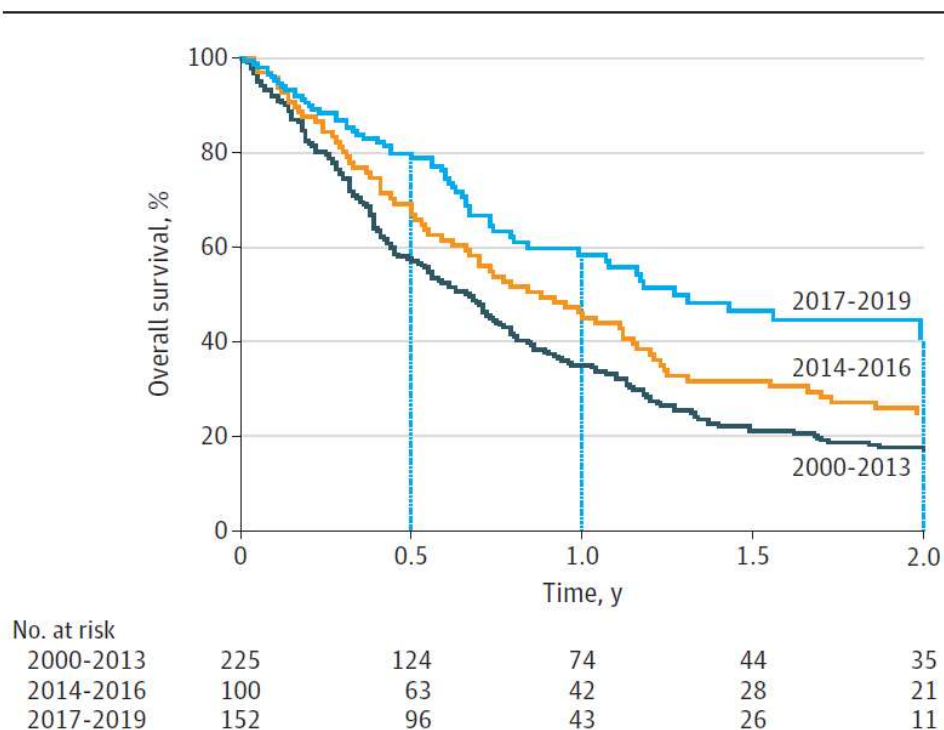
Overall Survival and Progression Free Survival for Patients in Relation to Surgery After BRAF-directed Therapy



Zhao X *et al. Thyroid.* 2023.

Introduction of Immunotherapy and Targeted Therapy

Figure 2. Two-Year Overall Survival (OS) of Patients with Anaplastic Thyroid Carcinoma According to Year of Presentation



Two-Year Overall Survival (OS) of Patients with Anaplastic Thyroid Carcinoma According to Year of Presentation (479 patients)

Group	OS Year 1	OS Year 2
2000-2013	35%	18%
2014-2016	47%	25%
2017-2019	59%	42%

Maniakas A *et al.* JAMA Oncol. 2020.

Moving forward.....

Translation to practice and/or policy?

Intervention studies?

Classi
Epid

Role of environmental disparities?

Community participation?

epidemiology

ar



Disparities in Treatment for Thyroid Cancer

- Lower socioeconomic status, Black, Hispanic or Latino, less education, no insurance or Medicaid experienced increased complications, worse survival
- Less access to high quality hospitals & high-volume surgeons
- Less likely to participate in clinical trials
- ? Access to molecular diagnostics and molecular-targeted therapy

Megwalu & Ma *Ca Invest* 2023
Davis *et al. Thyroid* 2023
Chen *et al. Lancet* 2023

Courtesy of Mark Zafereo

