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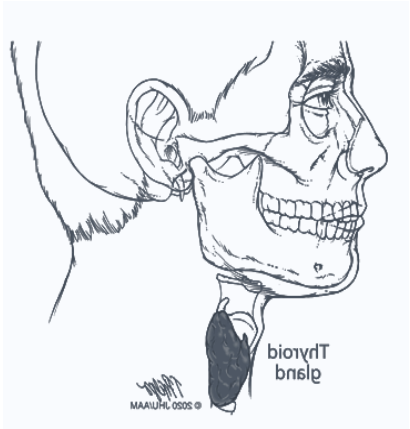
NÚCLEO DE QUITO

1ER SIMPOSIO INTERNACIONAL DE CÁNCER DE TIROIDES Y METABOLISMO

1 y 2 de septiembre de 2023

Rol de la Biología Molecular en el Cáncer Diferenciado de Tiroides y su Importancia Clínica



Dr. Marcos Di Stefano
Jefe del Dpto de Apoyo Diagnóstico

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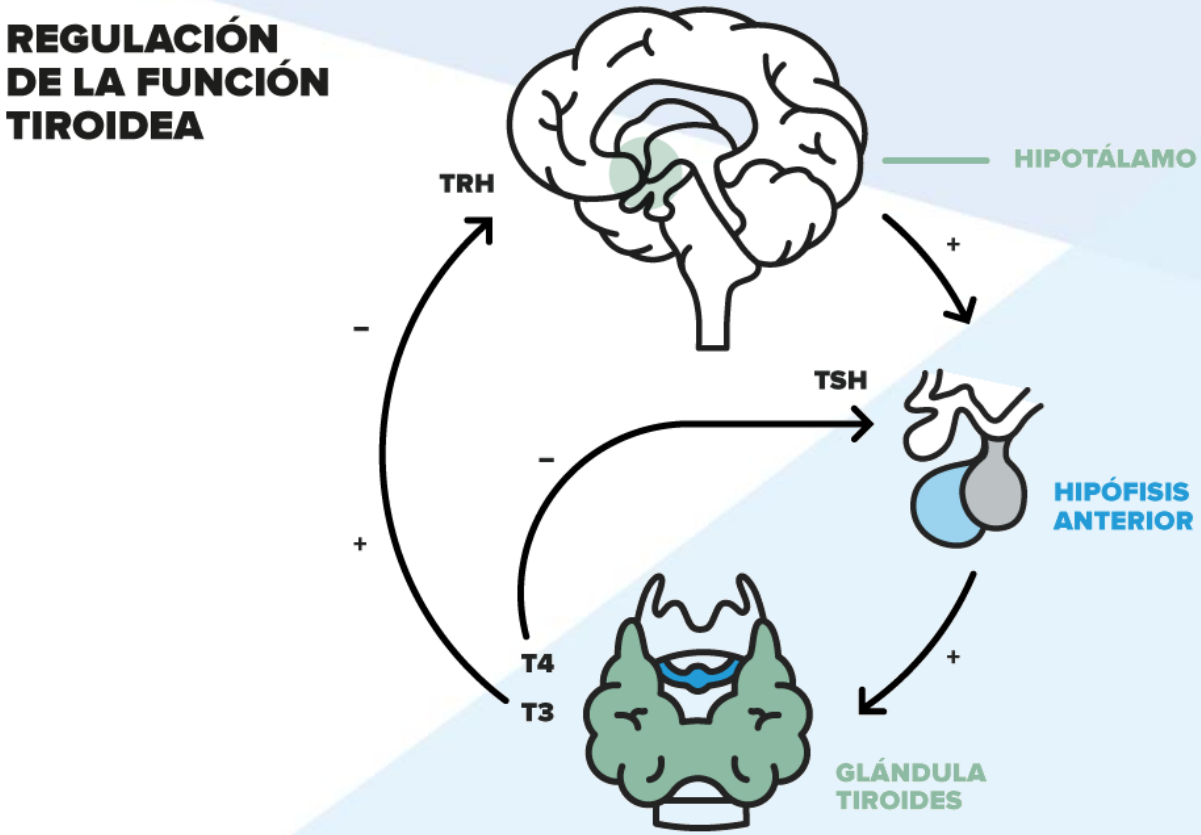
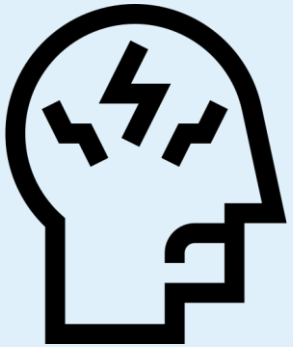
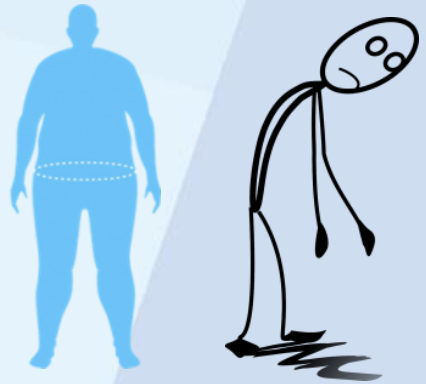
FUNCIÓN TIROIDEA



Metabolismo del cuerpo



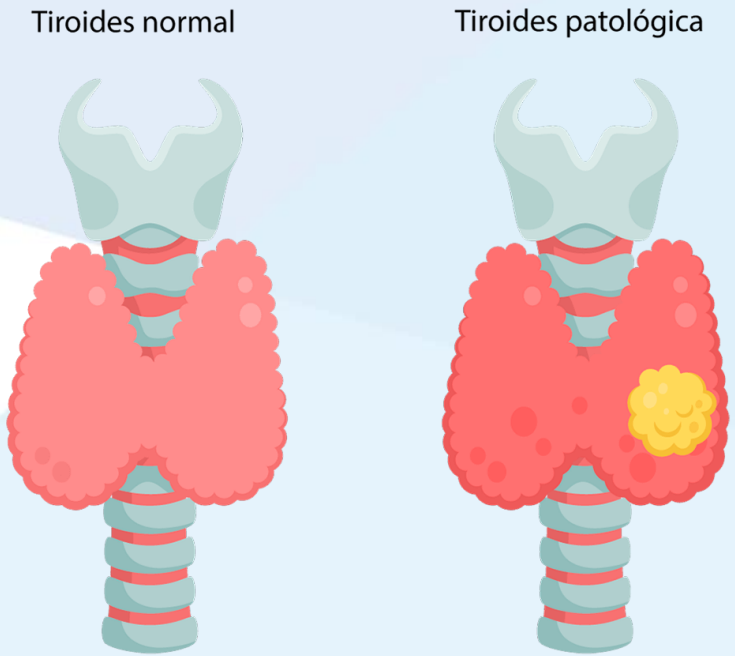


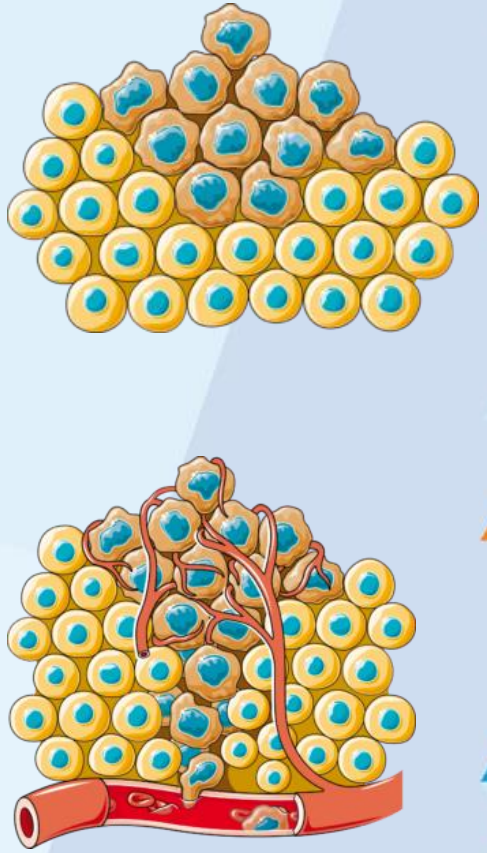
FUENTE: https://www.medigraphic.com/pdfs/medlab/myl-2020/myl202b.pdf

CÁNCER DE TIROIDES

FACTORES DE RIESGO

- Déficit de Yodo
- Nódulos tiroideos





Metástasis

FUENTE:https://doi.org/10.1158/1078-0432.CCR-16-0484

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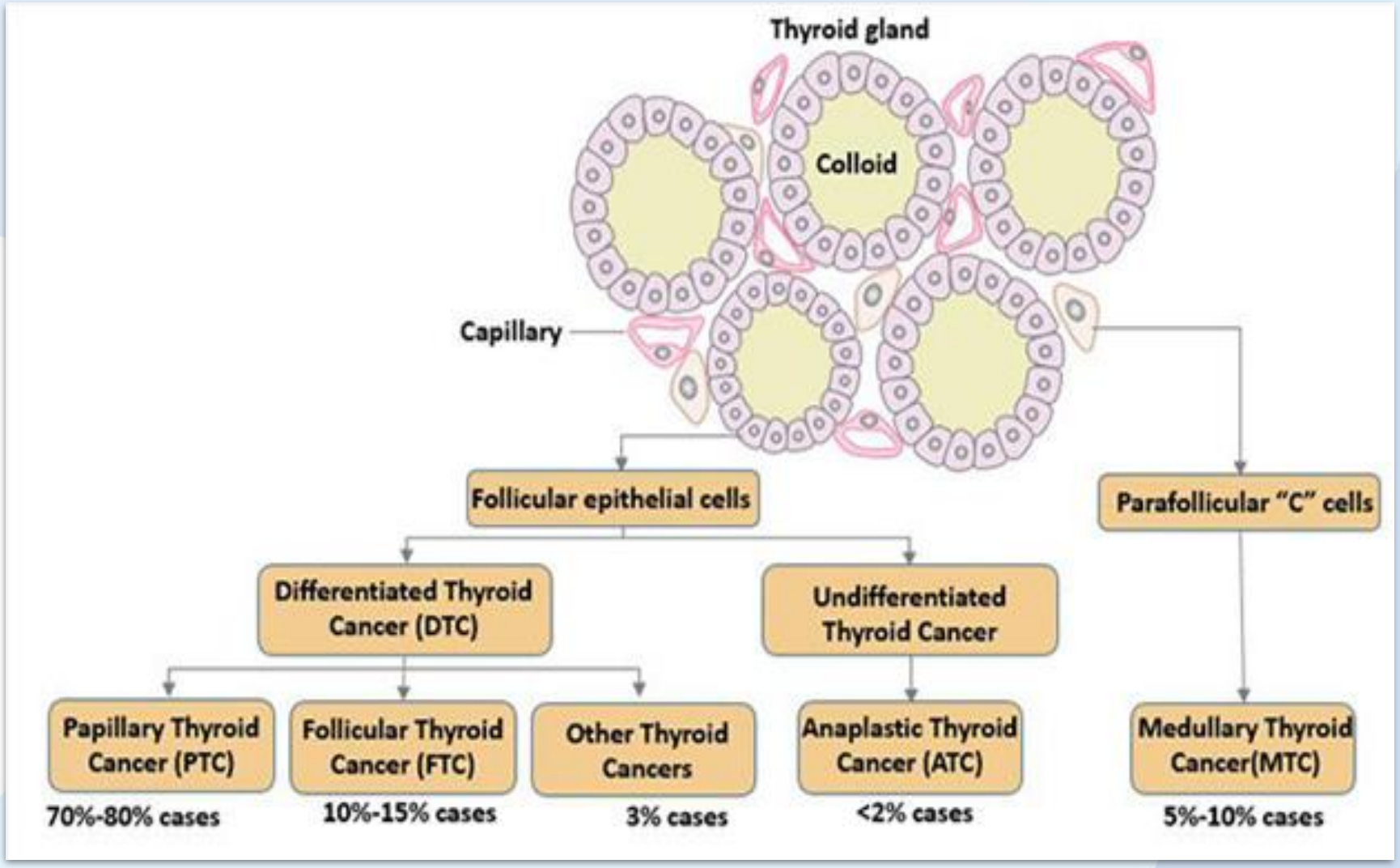
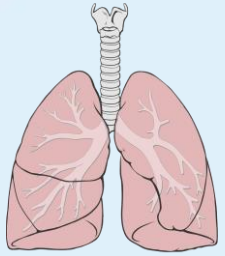
TIPOS DE CÁNCER DE TIROIDES

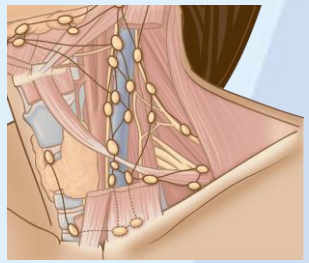


FUENTE:https://www.cusabio.com/c-20962.html
https://academic.oup.com/edrv/article/40/6/1573/5535574

Cáncer Diferenciado De Tiroides (DTC)

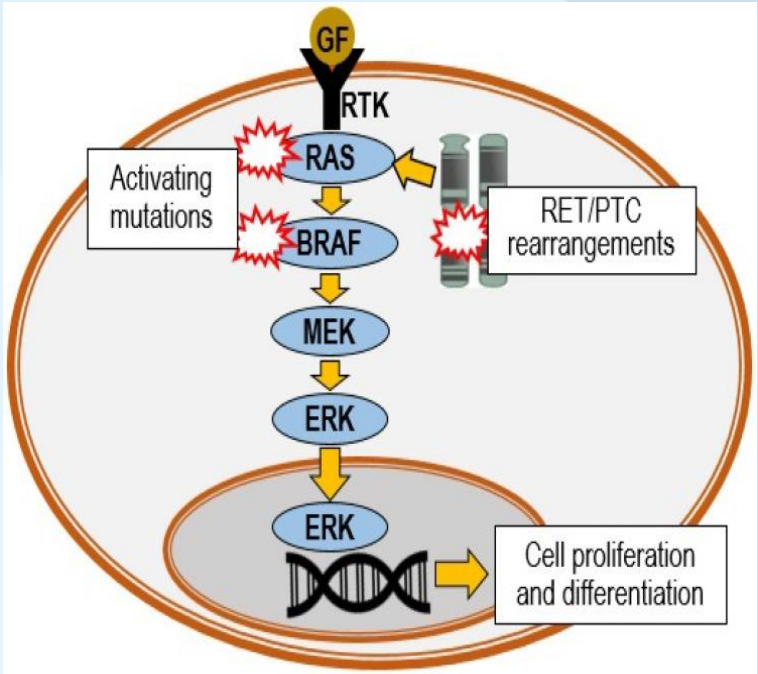
Cáncer Papilar De Tiroides (PTC) : 70- 80%





PTC	*BRAF* (62%), predominantly $BRAF^{V600E}$	*E1F1AX*
	RAS (13%)	*ALK* fusion
	RET-PTC (7%)	*NTRK1* or *NTRK3* fusion
	TERT promoter mutation (9%)	

BRAF V600E mutation in the cancer predicts a faster rate of growth, spread and a higher risk of death. This suggests that all papillary thyroid cancers should be tested for the BRAF V600E mutation. Those patients with cancers that



FUENTE: 10.7150/ijms.29935
https://www.thyroid.org/wp-content/uploads/publications/ctfp/volume6/issue7/ct_patients_v67_8.pdf

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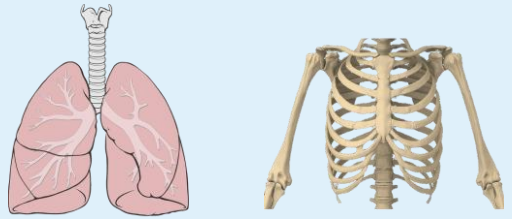
Cáncer Folicular de Tiroides (FTC): 10 – 15%

FTC	*RAS* (49%)	*TSHR* mutations
	PAX8-PPARγ(30–58%)	*BRAF*^{K601E}
	TERT promoter mutation 17%	*E1F1AX*

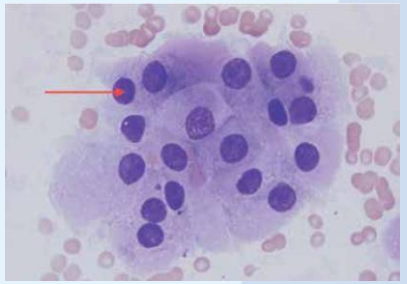


follicular variant of papillary cancer. There is increasing evidence that *RAS* mutation status has significant diagnostic utility when used concurrently with FNAB. This is particularly true for lesions with indeterminate cytology, for which the detection of *RAS* may have a potential impact on initial

Carcinoma de Células de Hurthle(CCH):

Fusión génica PAX8-PPARγ

Aggressive hurthle cell cancer variants are potentially suggested by mutations of the p53 or PI3kinase genes. To date, identifying these



Fuente: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3755930/
DOI: 10.7150/ijms.29935

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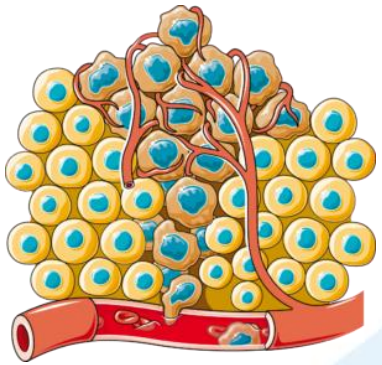
Cáncer Indiferenciado De Tiroides

Cáncer Anaplásico De Tiroides (ATC): < 2%

known to be the most lethal among all thyroid cancers, and the median life expectancy is about 4 months.[1,2] Due to its dismal prognosis, there have been different kinds of treatment modalities to



ATC	*BRAF* 29%
	RAS 23%
	TERT promoter mutation (73%)
	TP53 mutation (59%)

detected in 17% of FTCs, a frequency that is higher than that seen in PTC (9%) [5,30]. *TERT* promoter mutation is generally considered an aggressive molecular signature in thyroid carcinoma, and its significance is further elaborated in a later section.

FUENTE:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6883923/
10.3349/ymj.2012.53.2.352

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Cáncer Parafolicular – Células "C"

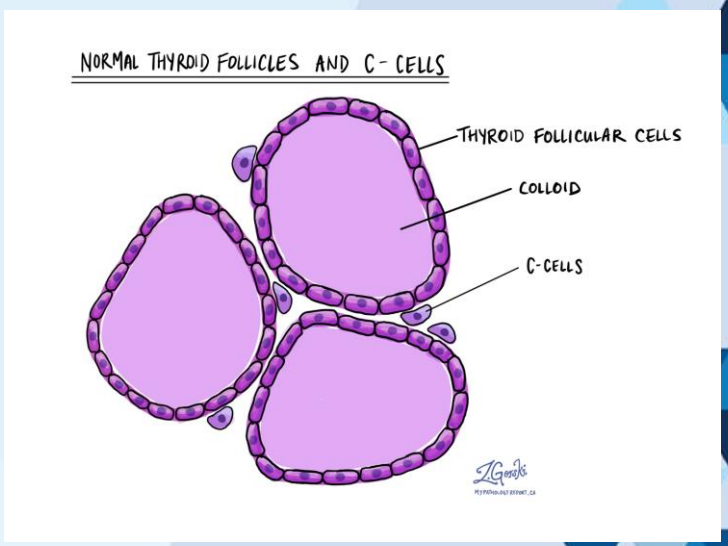
Cáncer Medular De Tiroides (MTC): 5 – 10%

Approximately 75% of MTCs are sporadic while the remaining 25% arise in the setting of multiple endocrine neoplasm (MEN) type 2 with germline gain-of-function mutations in *RET* [5,48]. Three subtypes of MEN2 have been recognized by the WHO: MEN2A, MEN2B, and familial MTC [5]. The

RET point mutation is also the most common driver molecular event in sporadic MTCs, reported in 40–60% of cases [5,48,49]. A small percentage of sporadic MTCs may have a *RAS* mutation [49,50] or *ALK* fusion [49].

MTC	*RET* (40–60%) *RAS* (up to 20%)	*MET* *ALK* fusion

RET point mutation is also the most common driver molecular event in sporadic MTCs, reported in 40–60% of cases [5,48,49]. A small percentage of sporadic MTCs may have a *RAS* mutation [49,50] or *ALK* fusion [49].



Fuente: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6883923/

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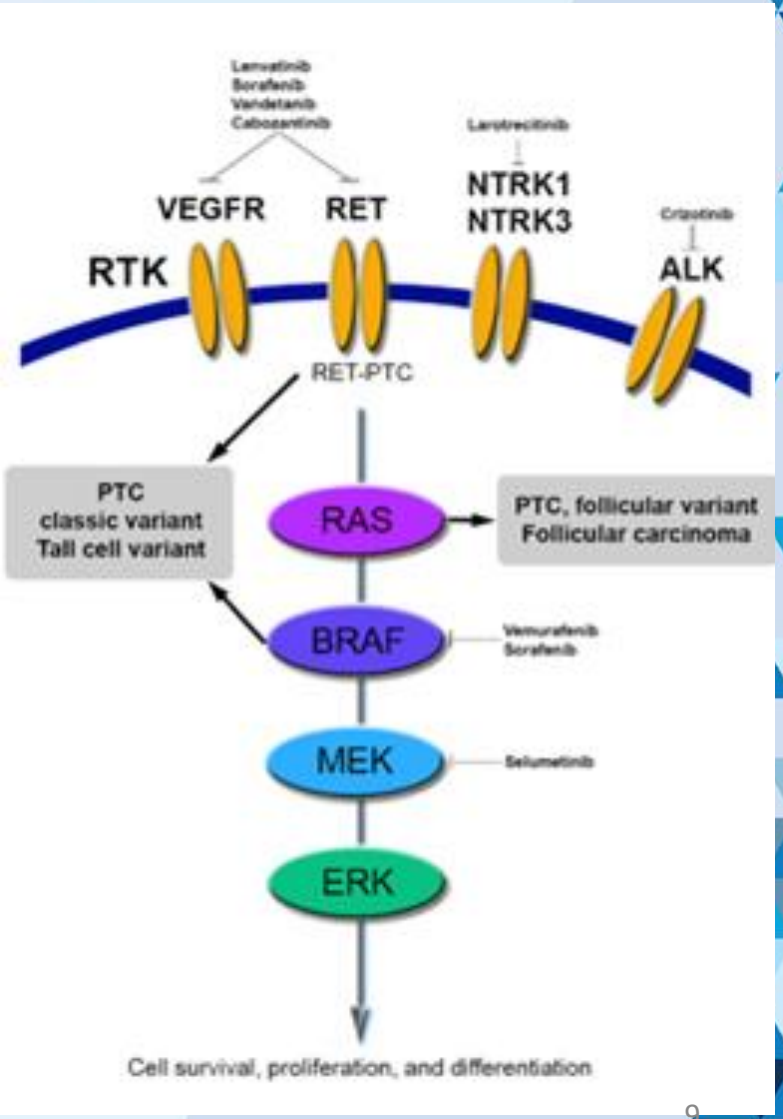
RUTA MOLECULAR

Vía de la proteína quinasa activada por mitógenos (MAPK)

The key molecular alterations in various types of thyroid carcinoma are summarized in Table 1. Constitutive activation of the MAPK signaling pathway plays a central role in the carcinogenesis of thyroid carcinoma. The essential proteins in this pathway are receptor tyrosine kinases (RTKs, which includes VEGFR, RET, ALK, and TRK), RAS, RAF, MEK, and ERK (Figure 1). RAS is a small G-

cohort, alteration of the MAPK pathway is detected in 83% of all PTCs tested [5,9]. The common alterations are *BRAF* mutation (predominantly V600E) in 62%, *RAS* (including *HRAS, NRAS,* and *KRAS)* mutation in 13%, *RET-PTC* rearrangement in 6%, and less frequently *NTRK3* fusion in 1.5%, *NTRK1* fusion in 1.3%, and *ALK* fusion in 0.8%.



Fuente: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6883923/

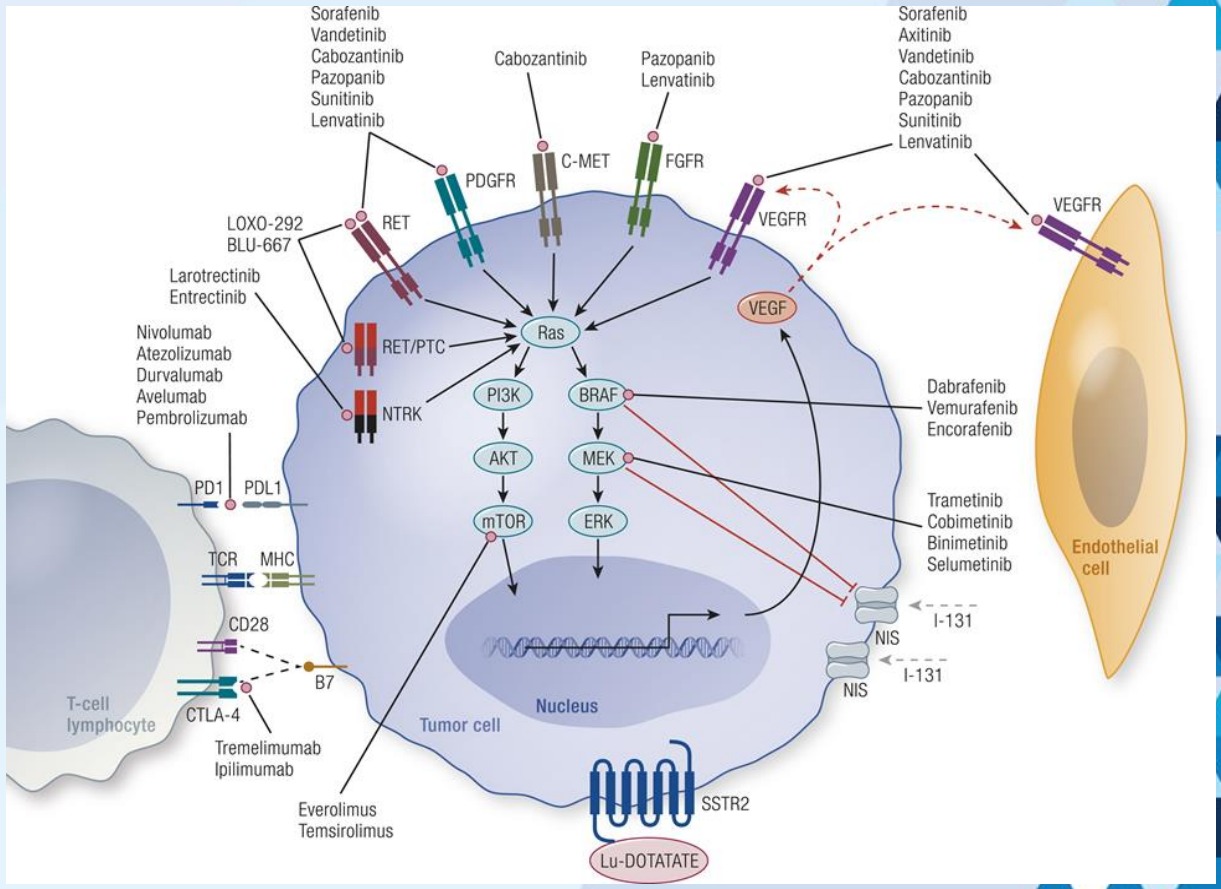
ACCIÓN MOLECULAR EN EL TRATAMIENTO

RESISTENCIA AL YODO RADIACTIVO

the first step for thyroid hormones' synthesis. NIS plays an essential role in the treatment of differentiated thyroid carcinomas (DTC), which usually maintain NIS expression, allowing the recognition and the treatment of recurrences and metastases with radioactive iodine (RAI) (1). Nonetheless, a significant subgroup of DTC

Dabrafenib and trametinib The combination of dabrafenib and trametinib, a selective BRAF and MEK 1/2 inhibitor respectively, was FDA approved in 2018 for the treatment of locally advanced or metastatic *BRAF* V600E-mutant anaplastic thyroid cancer (ATC) and has significantly changed the treatment paradigm of these tumors which were previously viewed as a death sentence

RET mutations occur in approximately 50% of MTC and RET fusions occur rarely in DTC (less than 10%), PDTC, and ATC (approximately 1%). Selpercatinib is a highly selective small molecule RET kinase inhibitor. In May 2020 selpercatinib was approved by the FDA for treatment of *RET*-mutated MTC, RAI-refractory *RET* fusion thyroid cancer and *RET* fusion non-small cell lung cancer. In a phase I-II trial

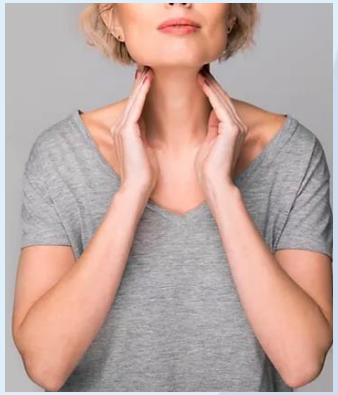


DOI:: 10.1530/EC-17-0302
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10331470/ FUENTE: https://academic.oup.com/edrv/article/40/6/1573/5535574 https://academic.oup.com/edrv/article/40/6/1573/5535574#205360342

CLÍNICA DIAGNÓSTICA

EXAMEN FÍSICO

- Hinchazón de los ganglios linfáticos cercanos.
- Tamaño, número, ubicación y consistencia.



SIGNOS Y SÍNTOMAS

- Aumento repentino del nódulo.
- Ronquera,disnea.
- Disfagia.
- Fatiga, pérdida de peso.

HISTORIA CLÍNICA

- Edad.
- Antecedentes familiares.
- Exposición a radioterapia.

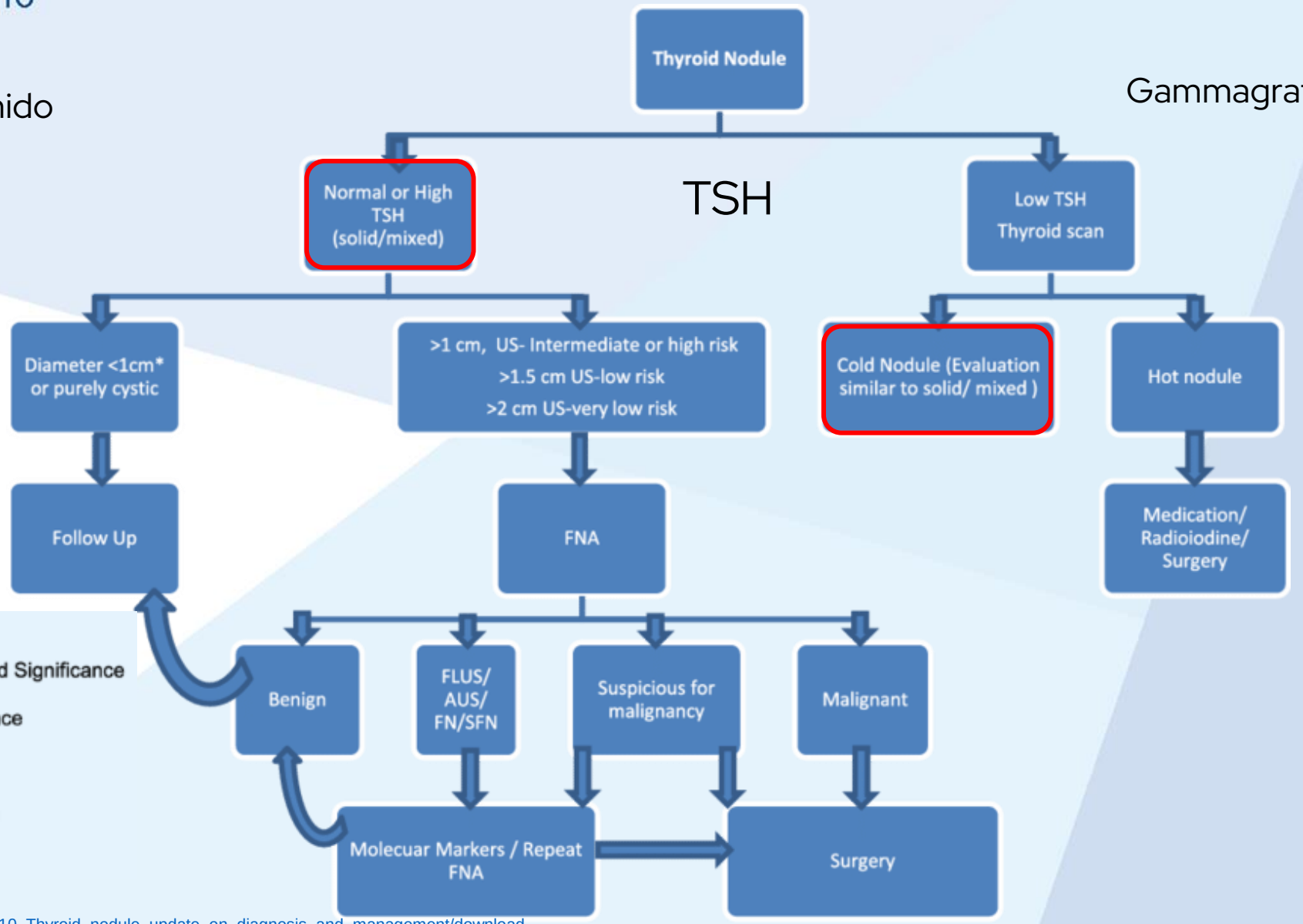
Fuente:https://www.ncbi.nlm.nih.gov/books/NBK459299 /
https://www.ncbi.nlm.nih.gov/books/NBK536943/

ALGORITMO DIAGNÓSTICO

Ultrasonido

Gammagrafía

TSH



US- Ultrasound

FLUS- Follicular Lesion of Undetermined Significance

AUS- Atypia of Undetermined Significance

FN- Follicular Neoplasm

SFN- Suspicious of Follicular Neoplasm

* Some nodules <1 cm may need FNA

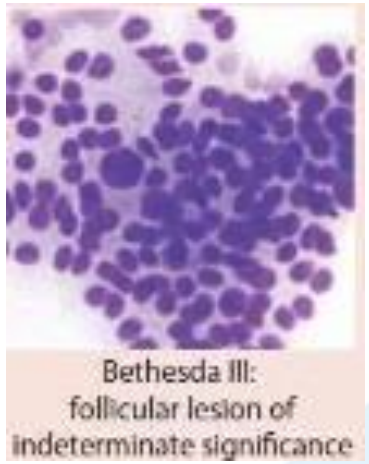
FUENTE:
https://www.researchgate.net/publication/308831010_Thyroid_nodule_update_on_diagnosis_and_management/download

DIANA MOLECULAR

Molecular markers

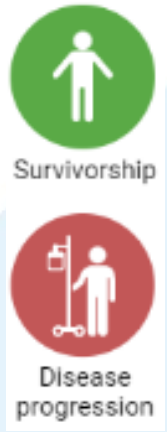
The use of molecular markers in thyroid nodules has been suggested for diagnostic purpose in case of indeterminate cytological diagnosis, to assist with decision making about management option (surgical treatment).

back for a follow up. In the current settings, molecular testing should only be used to supplement cytopathologic evaluation or clinical and imaging assessment [81]. Patients should be counselled regarding the current clinical utility and limitations of these tests. The AACE

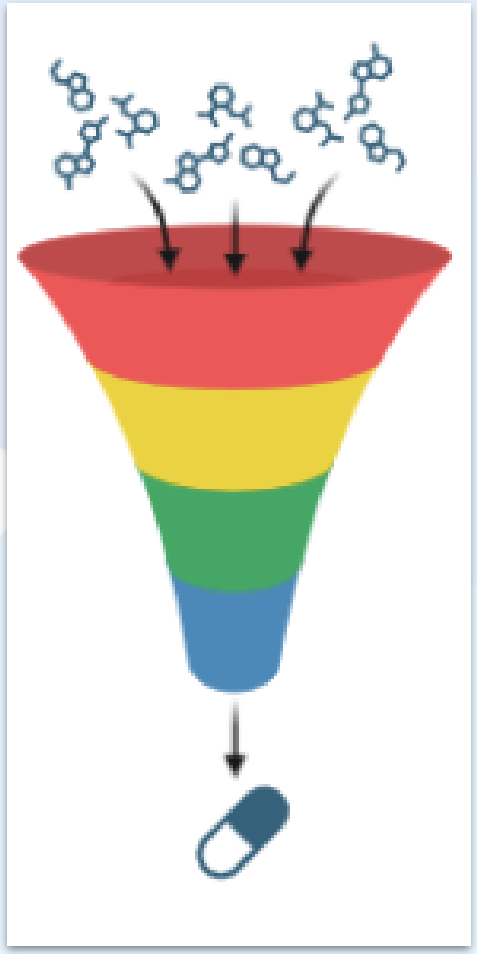


Bethesda III:
follicular lesion of
indeterminate significance

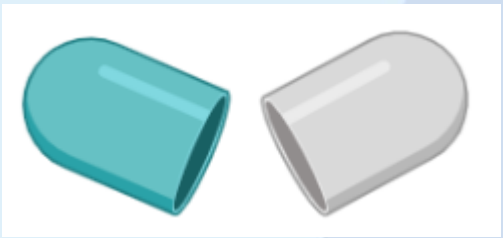
Citología Indeterminada



Evolución clínica



an established practice. With the molecular testing being available, it can be used to supplement the malignancy risk assessment again after considering the clinical and US risk factors and patient preference [68, 103]. If the molecular testing is not available/performed or inconclusive, diagnostic surgical excision can be considered.



strategies in this category. The clinical risk factors, US characteristics (Elastography in addition can be considered in these cases), patient preference and availability/feasibility of the molecular tests should be considered in the decision making process. Some scores such as Mcgill thyroid

FUENTE:
https://www.researchgate.net/publication/308831010_Thyroid_nodule_update_on_diagnosis_and_management/download

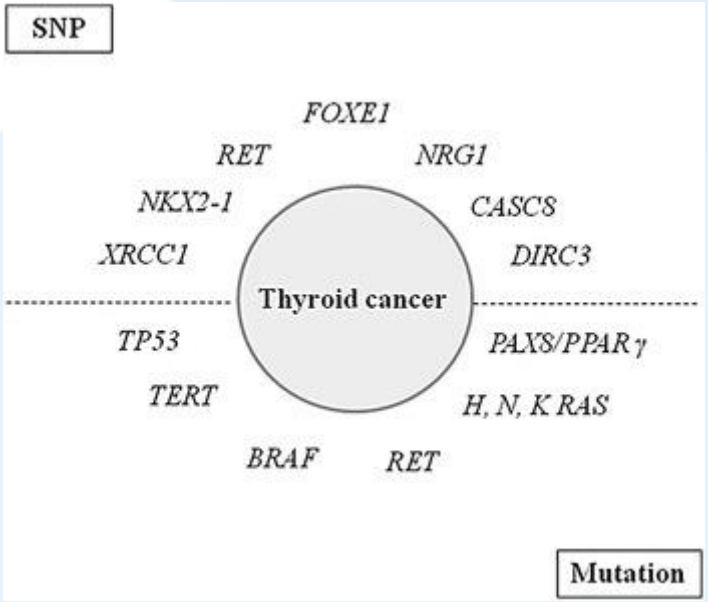
Importancia del perfil molecular

Pruebas moleculares

- Detección temprana.
- Monitoreo al tratamiento.
- Tratamiento personalizado.
- Pronóstico y seguimiento.

Since standard RAI therapy for DTC is not effective in 5–22% of patients, and surgical treatment is not curative in patients with MTC presenting with metastatic disease, small molecules have been developed that target aberrant signaling pathways specifically found in thyroid cancer [3]. Therefore, understanding of the molecular landscape of thyroid cancer is crucial to provide individualized targeted therapies.

Mutación RET implicado en RAI (terapia con yodo radiactivo)



Fuente: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7463725/

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TRATAMIENTO

Aprobados por la FDA

Tirosina Quinasa

- Sorafenib
- Lenvatinib
- Cabozantinib

PTC
FTC

- Vandetanib
- Cabozantinib

MTC

RET

- Selpercatinib
- Pralsetinib

PTC
FTC
MTC

- Selpercatinib

ATC

TRK

(Gen- NTRK)

- Larotrectinib
- Entrectinib

ATC
PTC

BRAF y MEK

- Dabrafenib
- Trametinib

ATC

BRAF (Resistencia- RAI)

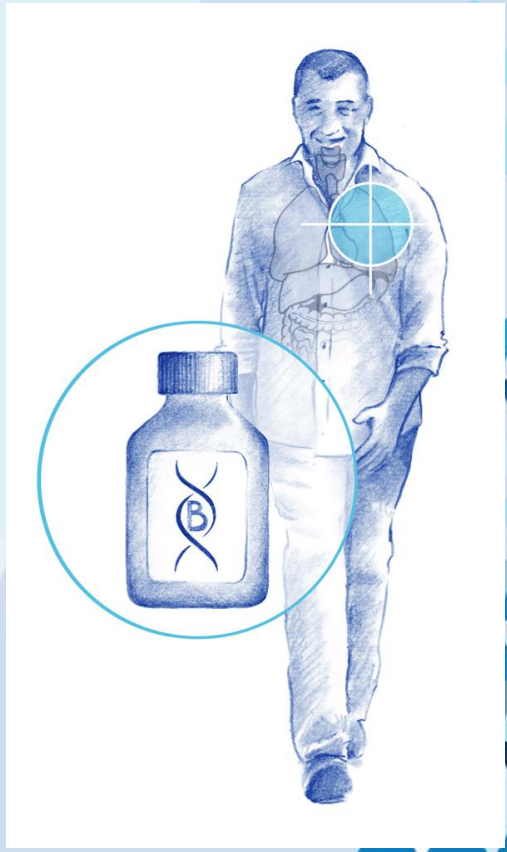
- Vemurafenib

Proteína mTOR

- everolimus

Angiogénesis

- bevacizumab

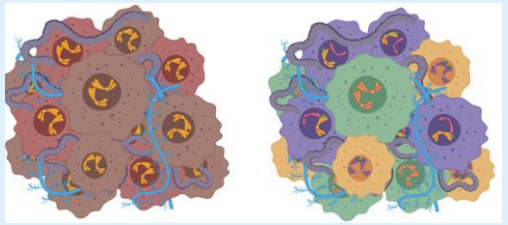


FUENTE:https://www.cancer.gov/about-cancer/treatment/drugs/thyroid https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6883923/ https://www.cancer.org/cancer/types/thyroid-cancer/treating/targeted-therapy.html0

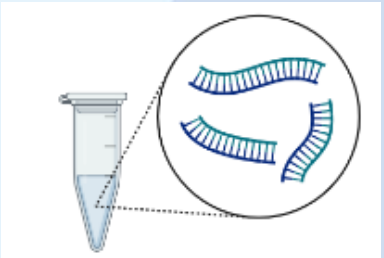
Punción aspiración con aguja fina (PAAF) en marcadores moleculares

- Ultrasonido
- Gammagrafía
- Biopsia - PAAF
- Análisis de sangre

Test moleculares

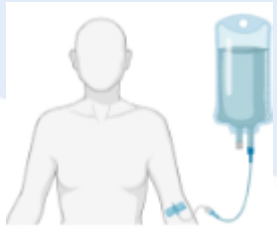


%
Célular tumorales



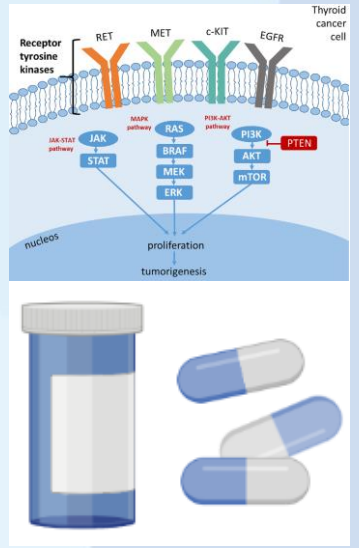
TIPOS DE TRATAMIENTO

Quimioterapia

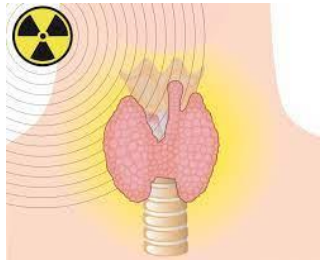


Supresión de hormona tiroidea

Terapia dirigida



RAI



CIRUGÍA

FUENTE: https://www.cancer.gov/espanol/tipos/tiroides/paciente/tratamiento-tiroides-pdq
https://doi.org/10.3389/fendo.2022.860671

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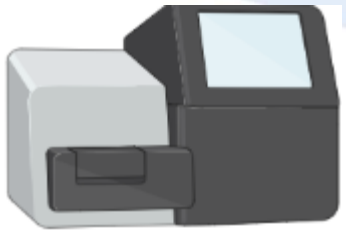
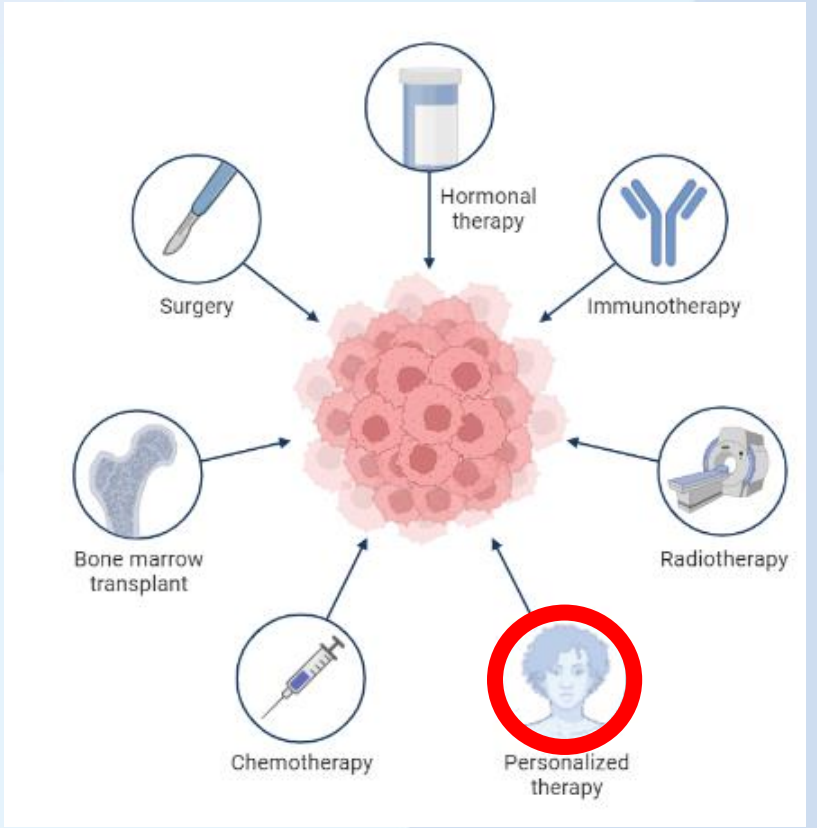
Secuenciación de próxima generación (NGS) en el cáncer de tiroides





FUENTE: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8238320/

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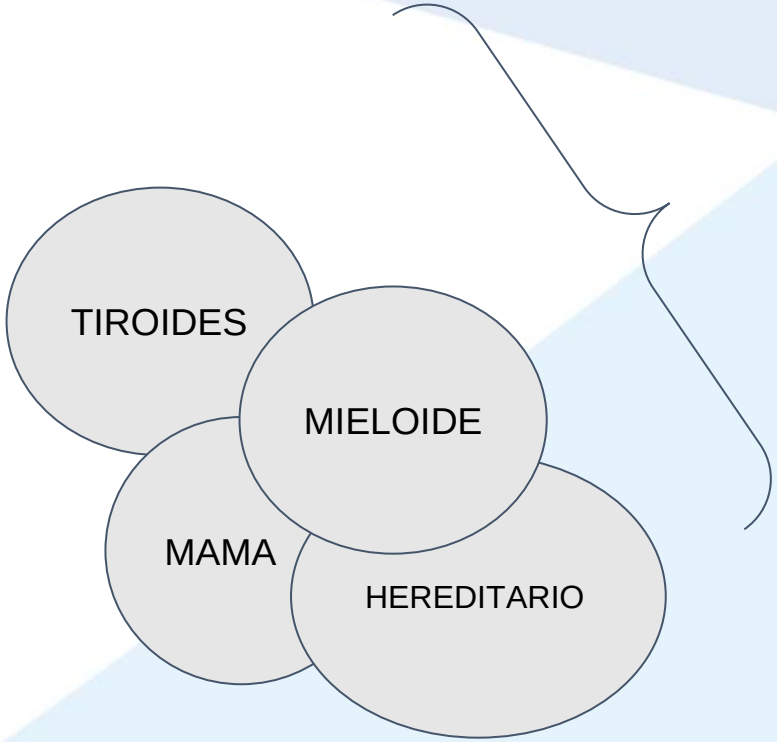
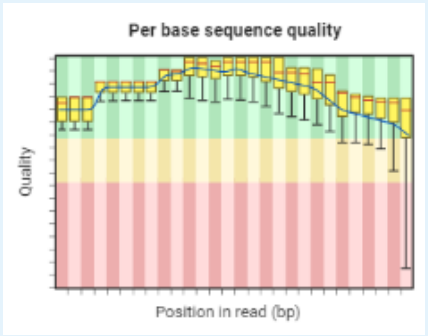
NGS



Importancia en la puntuación de calidad



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NGS - SOLCA QUITO

Estudio de neoplasias hematológicas

VARIANTES DE SIMPLE NUCLEÓTIDO E INDELs			FUSIÓN, EMPALME, O SALTO DE EXÓN			EXPRESIÓN DE GEN			
ABL1	GNAS	SH2B3	ABL1	IKZF3	PTK2B	ABL1	DLEU1	MYBL1	TAL1
AKT3	IDH1	SLC29A1	ABL2	JAK2	RARA	AICDA	DNMT3B	MYC	TLX1
ALK	IDH2	SRSF2	ALK	KAT6A	RBM15	ASB13	DNTT	MYH11	TLX3
ASXL1	IKZF3	STAT3	BCL11B	KLF2	ROS1	BATF3	E2F2	NEK6	TNFRSF13B
BAX	IL7R	STAT5B	BCL2	KMT2A	RUNX1	BCL2	ENTPD1	NFKB1	TNFSF4
BCL2	JAK1	STAT6	BCL6	MALT1	RUNX1T1	BCL2A1	EXOC2	NME1	WT1
BIRC3	JAK2	TYK2	BCR	MECOM	SEMA6A	BCL3	FAM216A	NTRK3	
BRAF	JAK3	U2AF1	BIRC3	MKL1	SETD2	BCL6	FLT3	PAICS	
BTK	KDM6A	WT1	CBFB	MLF1	STIL	BLNK	FOXP1	PDCD1	
CALR	KIT	XPO1	CCND1	MLLT10	TAL1	BMF	FUT8	PDCD1LG2	
CARD11	KRAS		CCND3	MLLT4	TCF3	BMP7	HOXA9	PIM1	
CBL	MPL		CDK6	MYC	TFG	CCDC50	HOXA10	PIM2	
CCND1	MYD88		CHD1	MYH11	TP63	CCND1	ID4	PPAT	
CD79B	NOTCH1		CHIC2	NF1	TYK2	CCND2	IL16	PRKAR2B	
CEBPA	NOTCH2		CIITA	NFKB2	ZCCHC7	CCND3	IRF4	PTPN1	
CREBBP	NPM1		CREBBP	NOTCH1		CD274	IRF8	PYCR1	
CRLF2	NRAS		CRLF2	NTRK3		CD44	ITPKB	RAB29	
CSF3R	NT5C2		CSF1R	NUP214		CDC25A	KIAA0101	RAG1	
DCK	PAX5		DEK	NUP98		CDKN2A	LIMD1	RAG2	
DNM2	PDGFRA		DUSP22	P2RY8		CDKN2B	LMO1	RANBP1	
DNMT3A	PHF6		EBF1	PAG1		CEBPA	LMO2	RARA	

Estudio de cánceres pediátricos

PUNTOS CALIENTES (HOTSPOTS)			COBERTURA EXON COMPLETO		VARIANTES DE NÚMERO DE COPIAS		DRIVERS DE FUSIÓN				EXPRESIÓN DE GEN	
ABL1	FASLG	MYC	APC	RB1	ABL2	GLI1	ABL1	KMT2A	NUTM1	WHSC1	BCL2	MET
ABL2	FBXW7	MYCN	ARID1A	RUNX1	ALK	GLI2	ABL2	KMT2B	NUTM2B	YAP1	BCL6	MYC
ALK	FGFR1	NCOR2	ARID1B	SMARCA4	BRAF	IGF1R	AFF3	KMT2C	PAX3	ZMYND11	FGFR1	MYCN
ACVR1	FGFR2	NOTCH1	ATRX	SMARCB1	CCND1	JAK1	ALK	KMT2D	PAX5	ZNF384	FGFR4	TOP2A
AKT1	FGFR3	NPM1	CDKN2A	SOCS2	CDK4	JAK2	BCL11B	LMO2	PAX7		IGF1R	
ASXL1	FLT3	NRAS	CDKN2B	SUFU	CDK6	JAK3	BCOR	MAML2	PDGFB			
ASXL2	GATA2	NT5C2	CEBPA	SUZ12	EGFR	KIT	BCR	MAN2B1	PDGFRA			
BRAF	GNA11	PAX5	CHD7	TCF3	ERBB2	KRAS	BRAF	MECOM	PDGFRB			
CALR	GNAQ	PDGFRB	CRLF1	TET2	ERBB3	MDM2	CAMTA1	MEF2D	PLAG1			
CBL	H3F3A	PIK3CA	DDX3X	TP53	FGFR1	MDM4	CCND1	MET	RAF1			
CCND1	HDAC9	PIK3R1	DICER1	TSC1	FGFR2	MET	CIC	MKL1	RANBP17			
CCND3	HIST1H3B	PPM1D	EBF1	TSC2	FGFR3	MYC	CREBBP	MLLT10	RARA			
CCR5	HRAS	PTPN11	EED	WHSC1	FGFR4	MYCN	CRLF2	MN1	RECK			
CDK4	IDH1	RAF1	FAS	WT1	GLI1	PDGFRA	CSF1R	MYB	RELA			
CIC	IDH2	RET	GATA1	XIAP	GLI2	PIK3CA	DUSP22	MYBL1	RET			
CREBBP	IL7R	ROHA	GATA3				EGFR	MYH9	ROS1			
CRLF2	JAK1	SETBP1	GNA13				ETV6	MYH11	RUNX1			
CSF1R	JAK2	SETD2	ID3				EWSR1	NCOA2	SS18			
CSF3R	JAK3	SH2B3	IKZF1				FGFR1	NCOR1	SSBP2			
CTNNB1	KDM4C	SH2D1A	KDM6A				FGFR2	NOTCH1	STAG2			
DAXX	KDR	SMO	KMT2D				FGFR3	NOTCH2	STAT6			
DNMT3A	KIT	STAT3	MYOD1				FLT3	NOTCH4	TAL1			
EGFR	KRAS	STAT5B	NF1				FOSB	NPM1	TCF3			
EP300	MAP2K1	TERT	NF2				FUS	NR4A3	TFE3			
ERBB2	MAP2K2	TPMT	PHF6				GLI1	NTRK1	TP63			
ERBB3	MET	USP7	PRPS1				GLIS2	NTRK2	TSLP			
ERBB4	MPL	ZMYM3	PSMB5				HMGA2	NTRK3	TSPAN4			
ESR1	MSH6		PTCH1				JAK2	NUP98	UBTF			
EZH2	MTOR		PTEN				KAT6A	NUP214	USP6			

Estudio de tumores sólidos

PUNTOS CALIENTES (HOTSPOTS)			COBERTURA EXON COMPLETO		VARIANTES DE NÚMERO DE COPIAS		DRIVERS DE FUSIÓN	
AKT1	FOXL2	MYCN	ARID1A	PMS2	AKT1	CCND1	AKT2	NOTCH4
AKT2	GATA2	MYD88	ATM	POLE	AKT2	CCND2	ALK	NRG1
AKT3	GNA11	NFE2L2	ATR	PTCH1	AKT3	CCND3	AR	NTRK1
ALK	GNAQ	NRAS	ATRX	PTEN	ALK	CCNE1	AXL	NTRK2
AR	GNAS	NTRK1	BAP1	RAD50	AR	CDK2	BRAF	NTRK3
ARAF	H3F3A	NTRK2	BRCA1	RAD51	AXL	CDK4	BRCA1	NUTM1
AXL	HIST1H3B	NTRK3	BRCA2	RAD51B	BRAF	CDK6	BRCA2	PDGFRA
BRAF	HNF1A	PDGFRA	CDK12	RAD51C	CCND1	EGFR	CDKN2A	PDGFRB
BTK	HRAS	PDGFRB	CDKN1B	RAD51D	CCND2	ERBB2	EGFR	PIK3CA
CBL	IDH1	PIK3CA	CDKN2A	RB1	CCND3	ESR1	ERBB2	PPARG
CCND1	IDH2	PIK3CB	CDKN2B	RNF43	CCNE1	FGF19	ERBB4	PRKACA
CDK4	JAK1	PPP2R1A	CHEK1	SETD2	CDK2	FGF3	ERG	PRKACB
CDK6	JAK2	PTPN11	CREBBP	SLX4	CDK4	FGFR1	ESR1	PTEN
CHEK2	JAK3	RAC1	FANCA	SMARCA4	CDK6	FGFR2	ETV1	RAD51B
CSF1R	KDR	RAF1	FANCD2	SMARCB1	EGFR	FGFR2	ETV4	RAF1
CTNNB1	KIT	RET	FANCI	STK11	ERBB2		ETV5	RB1
DDR2	KNSTRN	RHEB	FBXW7	TP53	ESR1		FGFR1	RELA
EGFR	KRAS	RHOA	MLH1	TSC1	FGF19		FGFR2	RET
ERBB2	MAGOH	ROS1	MRE11	TSC2	FGF3		FGFR3	ROS1
ERBB3	MAP2K1	SF3B1	MSH2		FGFR1		FGR	RSPO2
ERBB4	MAP2K2	SMAD4	MSH6		FGFR2		FLT3	RSPO3
ERCC2	MAP2K4	SMO	NBN		FGFR2		JAK2	TERT
ESR1	MAPK1	SPOP	NF1		AKT1		KRAS	
EZH2	MAX	SRC	NF2		AKT2		MDM4	
FGFR1	MDM4	STAT3	NOTCH1		AKT3		MET	
FGFR2	MED12	TERT	NOTCH2		ALK		MYB	
FGFR3	MET	TOP1	NOTCH3		AR		MYBL1	
FGFR4	MTOR	U2AF1	PALB2		AXL		NF1	
FLT3	MYC	XPO1	PIK3R1		BRAF		NOTCH1	

Panel de cáncer hereditario

Tabla 3: Contenido genético del panel de cáncer hereditario de TruSight

ACD	DIS3L2	GREM1	PIK3CA	SDHD
AIP	EPCAM	HOXB13	PMS2	SLX4
AKT1	ERCC1	KIF1B	POLD1	SMAD4
APC	ERCC2	KIT	POLE	SMARCA4
ATM	ERCC3	LZTR1	POT1	SMARCB1
BAP1	ERCC4	MAX	PRKAR1A	SMARCE1
BARD1	ERCC5	MEN1	PTCH1	SPINK1
BLM	FAM175A	MET	PTEN	SPRED1
BMPR1A	FANCA	MITF	RAD50	STK11
BRCA1	FANCB	MLH1	RAD51	SUFU
BRCA2	FANCC	MRE11A	RAD51B	TERF2IP
BRIP1	FANCD2	MSH2	RAD51C	TERT
CASR	FANCE	MSH3	RAD51D	TMEM127
CDC73	FANCF	MSH6	RB1	TP53
CDH1	FANCG	MUTYH	RECQL4	TSC1
CDK4	FANCI	NBN	RET	TSC2
CDKN1B	FANCL	NF1	RHBDF2	VHL
CDKN2A	FANCM	NF2	RINT1	WT1
CEBPA	FH	NSD1	RUNX1	XPA
CHEK2	FLCN	NTHL1	SDHA	XPC
CTRC	GALNT12	PALB2	SDHAF2	XRCC2
DDB2	GATA2	PDGFRA	SDHB	
DICER1	GPC3	PHOX2B	SDHC	

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CONCLUSIONES:

- **La activación constitutiva de la vía MAPK** es crucial para la patogenia y la terapia dirigida. Genes como **BRAF, RAS, RET** y otras, que pueden ser indicativos del subtipo de cáncer de tiroides

- **El 85% tiene buen pronóstico,** tomando en cuenta cáncer anaplásico de tiroides y el cáncer medular de tiroides tienen pronóstico adverso.

- La terapia dirigida con la ayuda de la biología molecular, es clave cuando existe **ambigüedad en la caracterización celular del tejido**, específicamente en el cáncer de tiroides

- **Resistencia a la terapia** con inhibidores de **tirosina quinasa (ITK)** en pacientes con carcinoma medular de tiroides (CMT) que presentan mutaciones en el gen **RET**.

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1 y 2 de septiembre de 2023

GRACIAS