VII Jornada EN Cáncer DE Mama Hereditario

Sospecha de alteraciones genéticas de origen germinal en secuenciación tumoral

Ana Vega

Fundación Publica Galega Medicina Xenómica

Organizado por:

GEICAM investigación en cáncer de mama
www.geicam.org

SOLTI INNOVATIVE BREAST CANCER RESEARCH
www.gruposolti.org

Sección SEOM Cáncer Familiar y Hereditario
www.seom.org

Disclosure Information

- Employment: Fundación Pública Galega Medicina Xenómica
- Research Funding: ISCIII, GAIN
- Speaking: ESTRO, SEOR, SOG…
- Grant support: European Commission, ISCIII, FMM
- Other:

Sospecha de alteraciones genéticas de origen germinal en secuenciación tumoral

Fundación Pública Galega de Medicina Xenómica

Guión

- Mutaciones germinales vs somáticas
- Alteraciones genómicas tumorales
- Clasificación de variantes genéticas
- Secuenciación de DNA tumoral
    - Aproximación NGS al análisis del tumor
    - Sospecha variante patogénica germinal
    - Genes susceptibilidad al cáncer
- Recomendaciones para informar variantes germinales de estudios tumorales
- Take home messages

Mutación germinal *versus* somática

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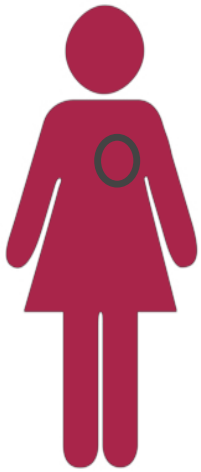
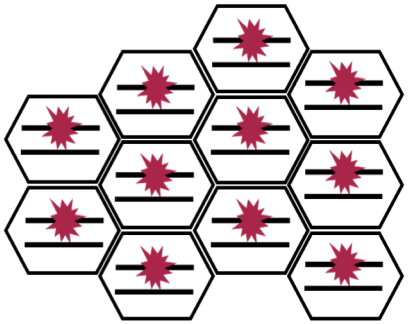
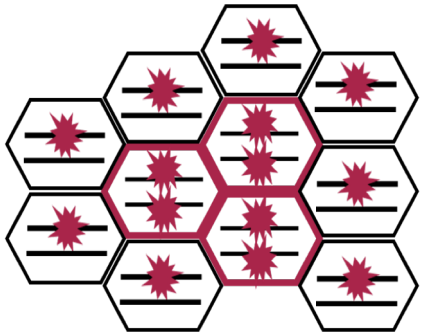
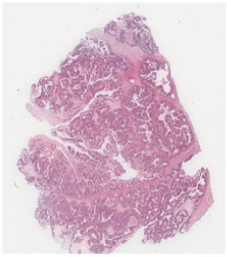
Mutaciones germinales

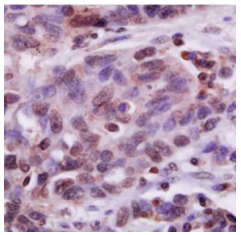




Mutaciones somáticas (tumorales)

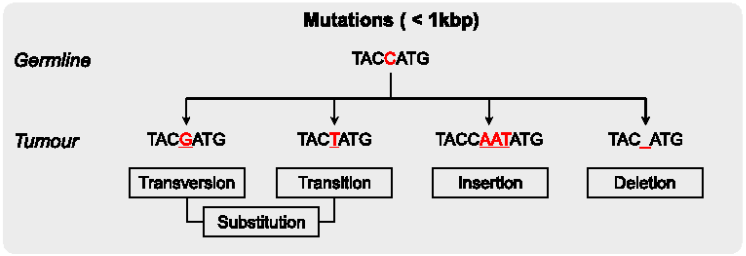


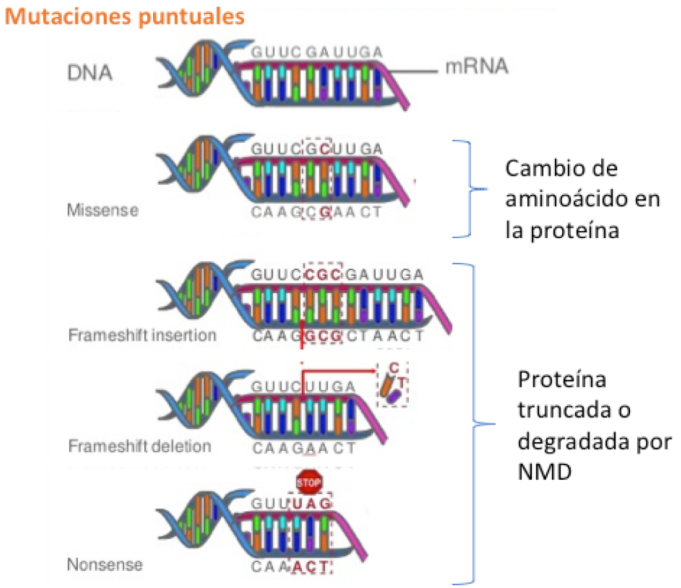




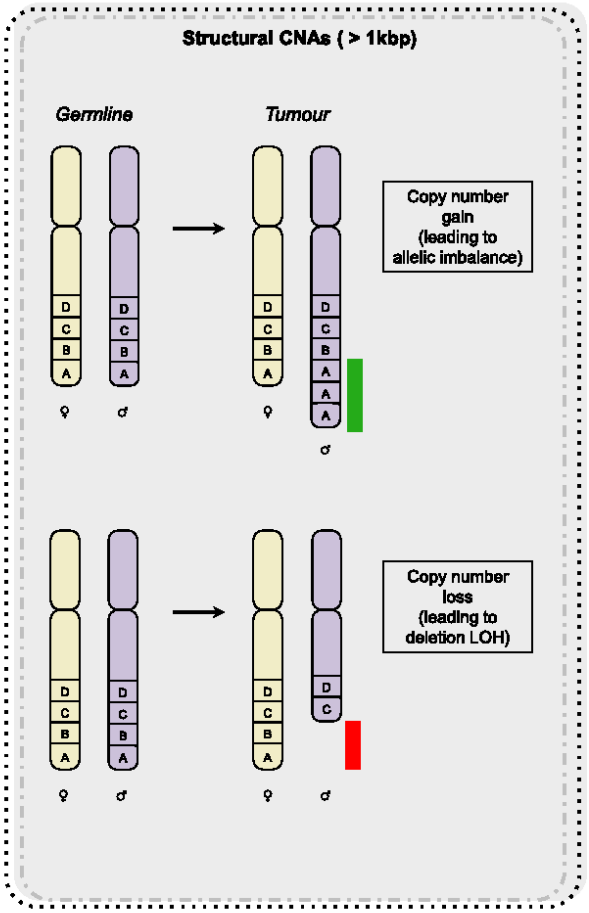
Alteraciones genómicas tumorales

Pequeñas mutaciones puntuales

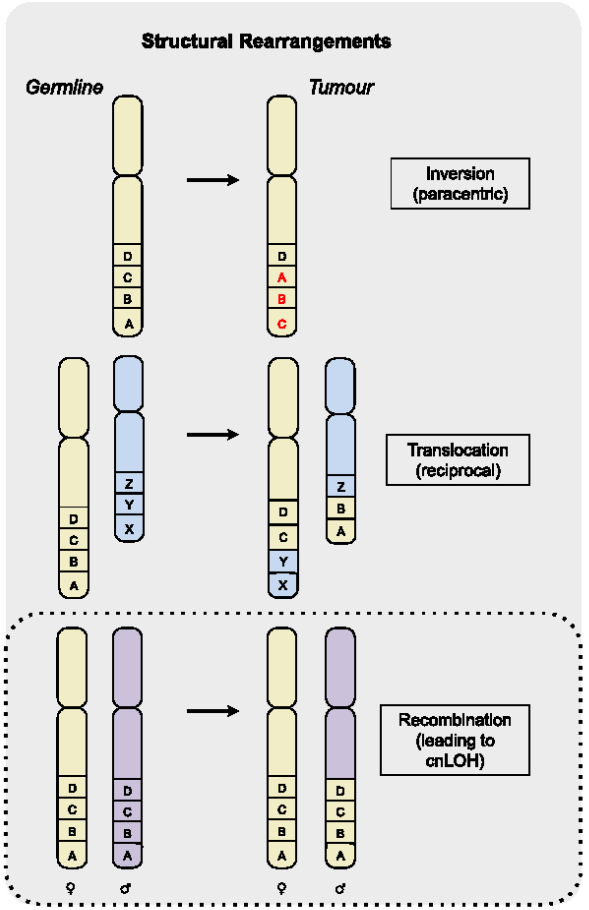




Alteraciones nº copias (CNA)



Reordenamientos estructurales



Clasificación de variantes. Guía ACMG

Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

Pathogenic	(i) 1 Very strong (PVS1) *AND* (a) ≥1 Strong (PS1–PS4) *OR* (b) ≥2 Moderate (PM1–PM6) *OR* (c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) *OR* (d) ≥2 Supporting (PP1–PP5) (ii) ≥2 Strong (PS1–PS4) *OR* (iii) 1 Strong (PS1–PS4) *AND* (a)≥3 Moderate (PM1–PM6) *OR* (b)2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR* (c)1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Likely pathogenic	(i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR* (ii) 1 Strong (PS1–PS4) *AND* 1–2 moderate (PM1–PM6) *OR* (iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR* (iv) ≥3 Moderate (PM1–PM6) *OR* (v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR* (vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Benign	(i) 1 Stand-alone (BA1) *OR* (ii) ≥2 Strong (BS1–BS4)
Likely benign	(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR* (ii) ≥2 Supporting (BP1–BP7)
Uncertain significance	(i) Other criteria shown above are not met OR (ii) the criteria for benign and pathogenic are contradictory

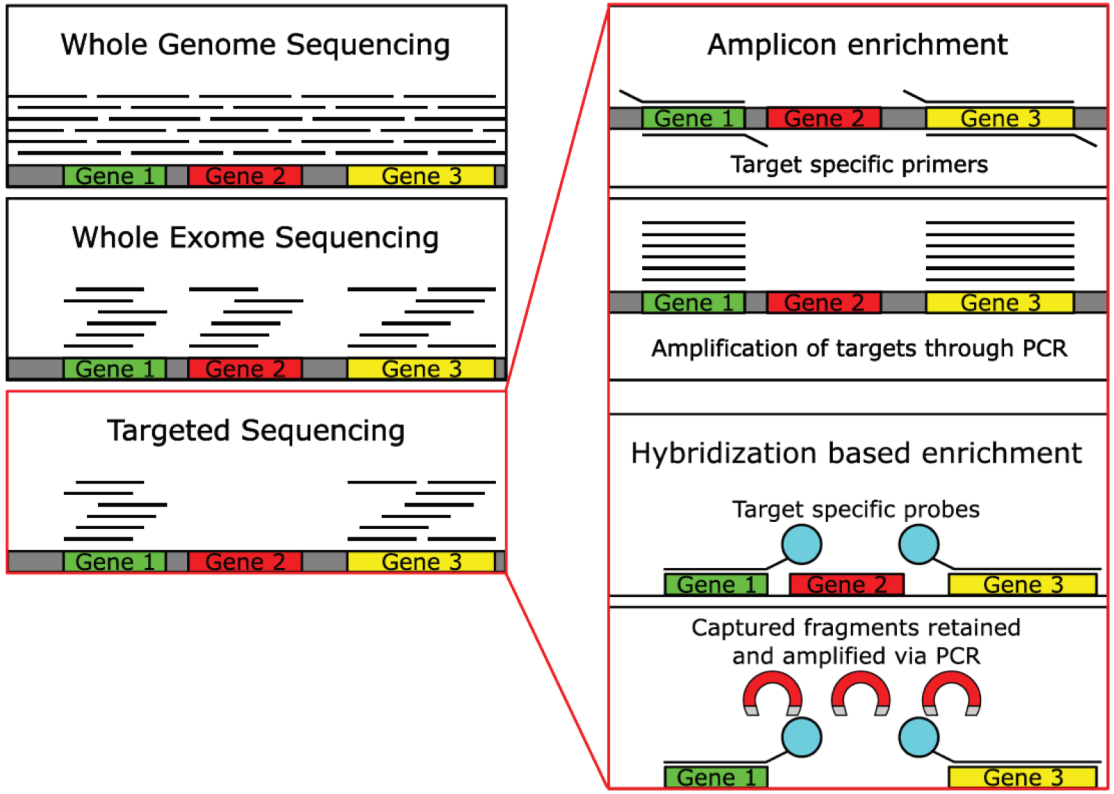
Richards et al. 2015

Secuenciación de ADN tumoral

- Identificación de biomarcadores con implicaciones terapéuticas de predicción, pronóstico, potencial diagnóstico.

- NGS: Diferentes aproximaciones de secuenciación:

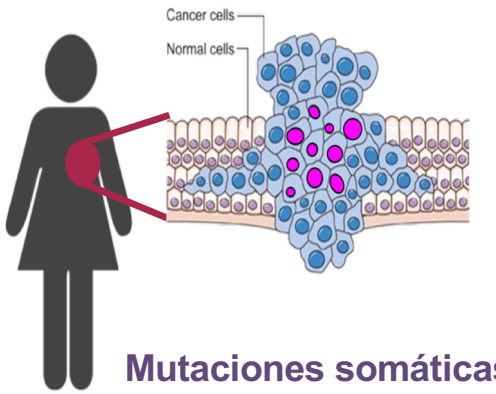
- Secuenciación de genomas (Whole Genome Sequencing)
- Secuenciación de exomas (Whole Exome Sequencing)
- Secuenciación de paneles específicos (Targeted Sequencing)



Bewicke-Copley et al, 2019

Secuenciación de ADN tumoral

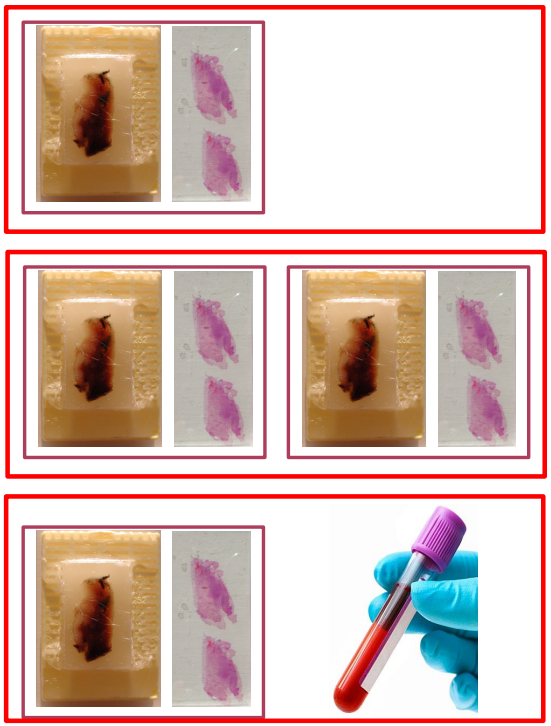
Aproximaciones NGS al análisis del tumor



Mutaciones somáticas

MATERIAL BIOLÓGICO

Tejido tumoral / tejido no tumoral



SECUENCIACIÓN NGS

Ion Proton

Illumina MiSeq

PIPELINE BIOINFORMÁTICO

Secuenciación de ADN tumoral

Aproximaciones NGS al análisis del tumor: identificación variante patogénica posible germinal

	Muestra	PGPV cubiertas?	Necesaria confirmacion germinal?
Sólo tumor	muestra tumoral	pueden inferirse	Si
Pareado tumor-normal con sustracción germinal	muestra tumoral y no tumoral	se enmascaran	NO
Pareado tumor-normal incluyendo análisis de CSG en germinal	muestra tumoral y no tumoral	si (basado en diseño genes)	No, si test germinal está validado

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.- Identificación de síndromes de predisposición al cáncer

- riesgo de cáncer en paciente
- vigilancia y medidas reductoras riesgo paciente y familia.

.- Predecir respuesta a terapias (iPARPs gBRCA1/2, o i-chekpoint inmunes Síndrome de Lynch)

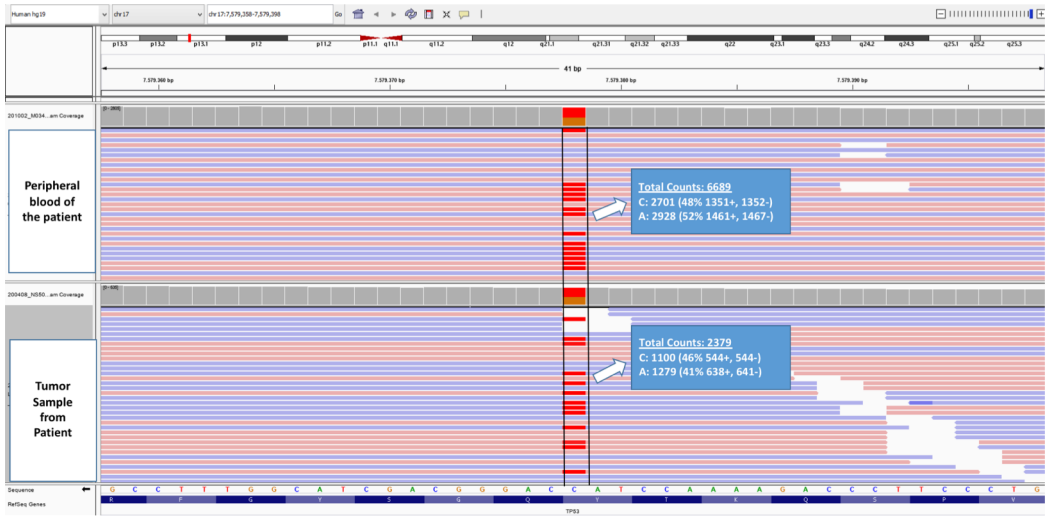
.- Elegibilidad en ensayos clínicos

Secuenciación de ADN tumoral

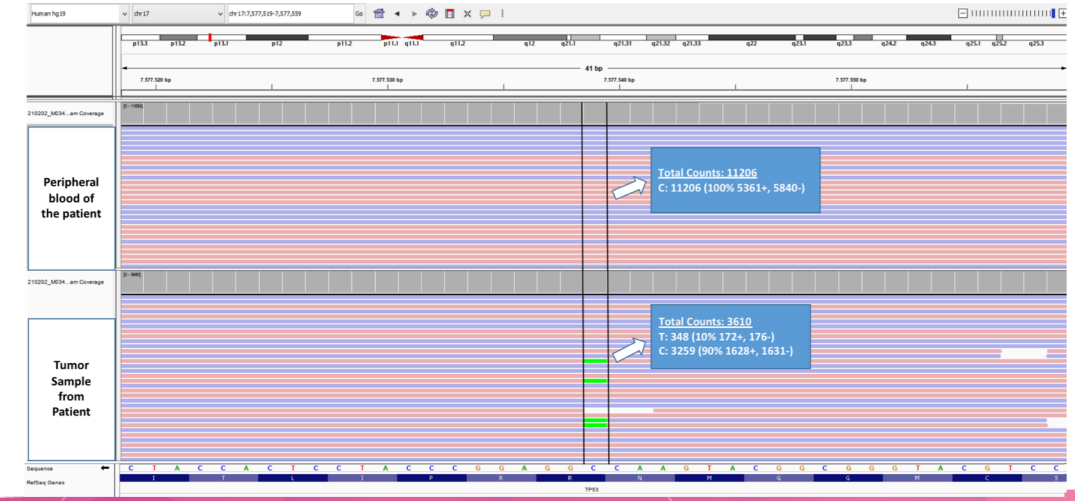
Sospecha variante patogénica germinal

- **Frecuencia alélica de la variante (VAF)**
- Frecuencia variantes germinales/ somáticas en cada gen
- Tipo de variantes: frameshift, missense…
- Mutaciones fundadoras
- Características clínicas del paciente

OVARIAN CANCER TP53:NM_000546.5:exon4:c.309C>A:p.Y103X (Germinal variant)



OVARIAN CANCER TP53 NM_000546.5:c.742C>T,p.Arg248Trp (somatic mutation)



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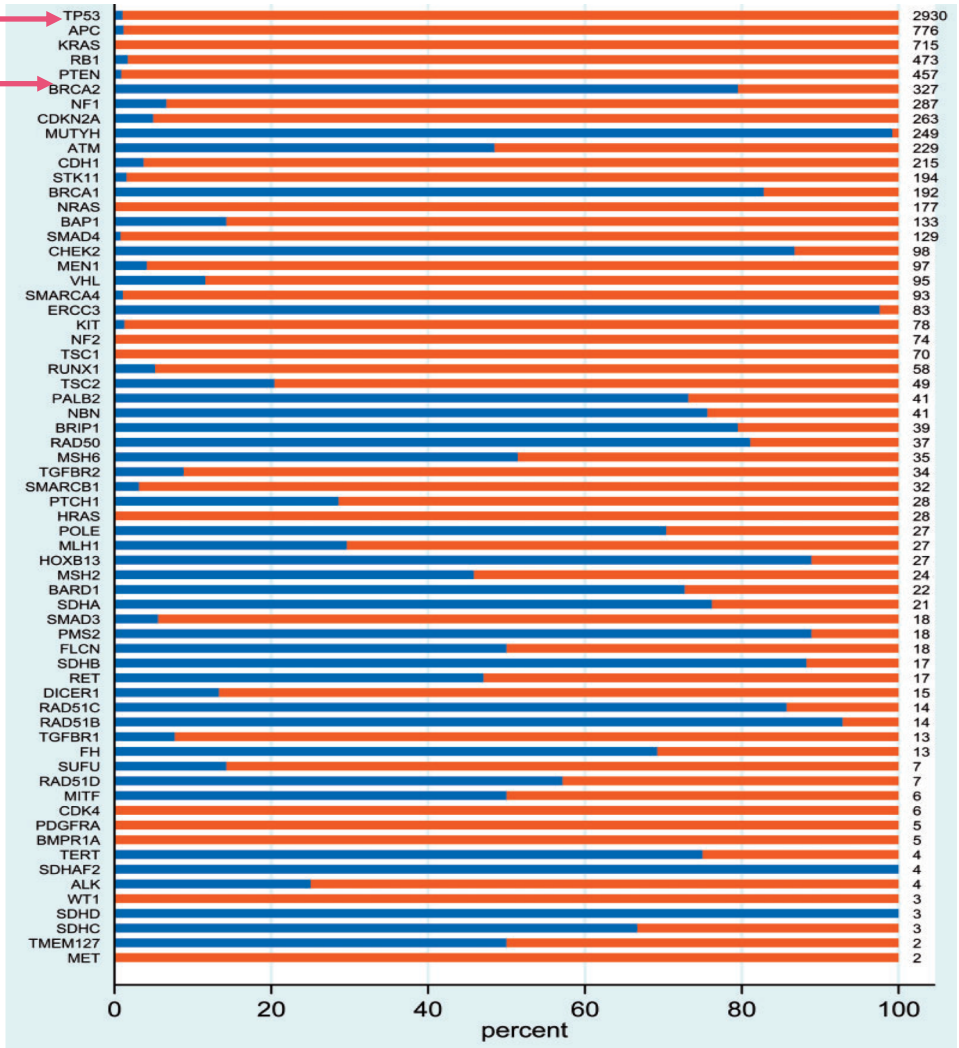

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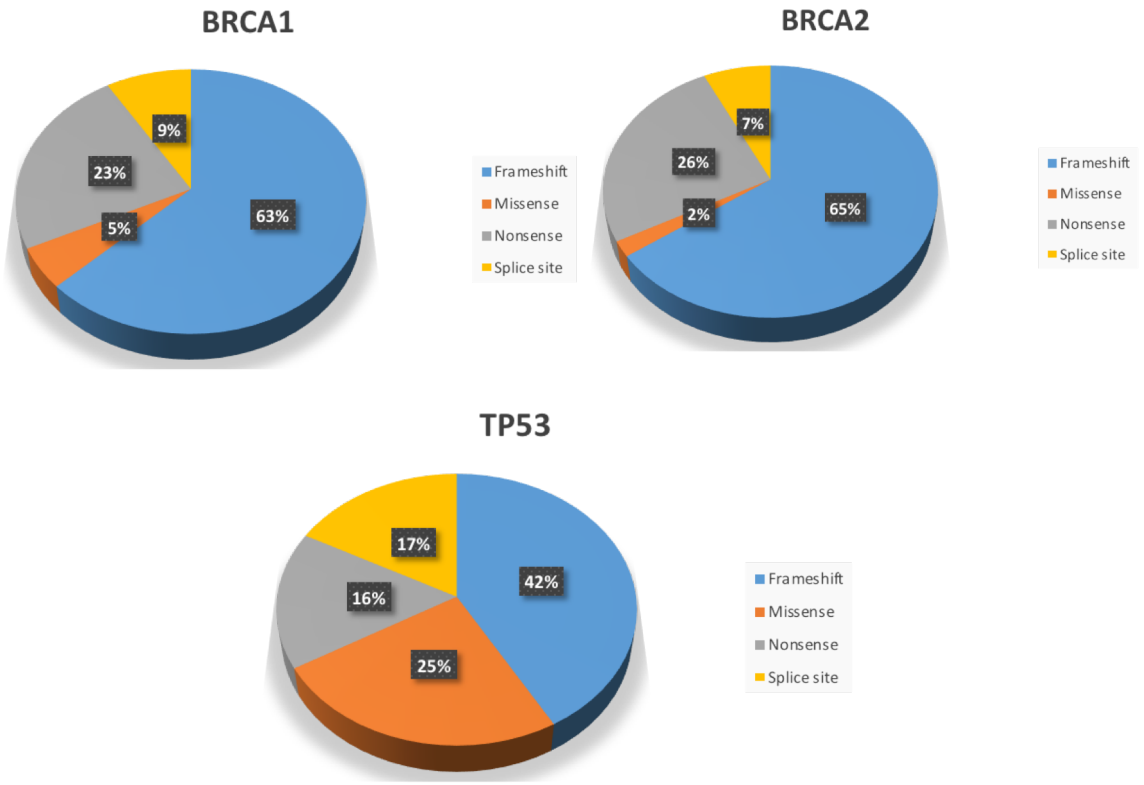

Fuente: ClinVar, variantes P/LP germinales

Secuenciación de ADN tumoral

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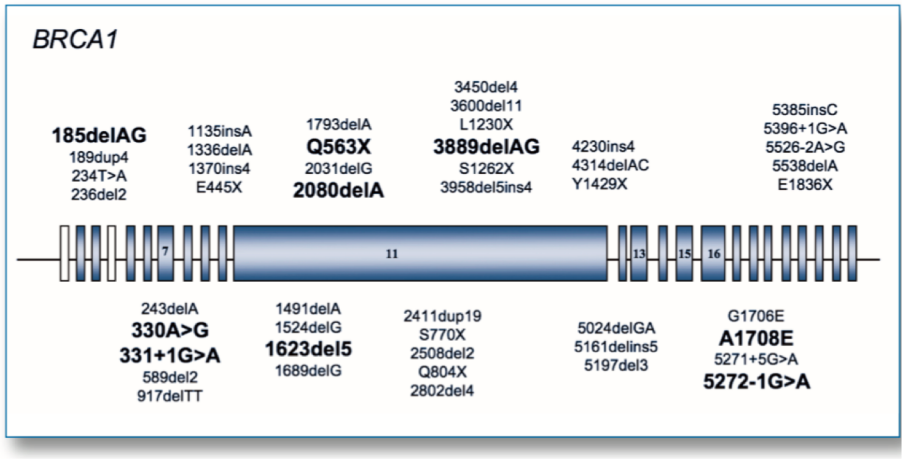

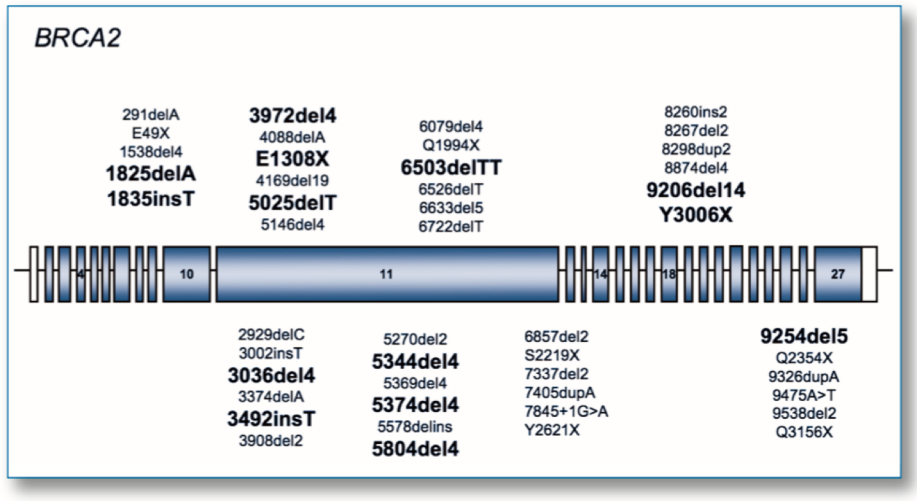

Diez O, Cáncer Hereditario III Ed.SEOM

Secuenciación de ADN tumoral

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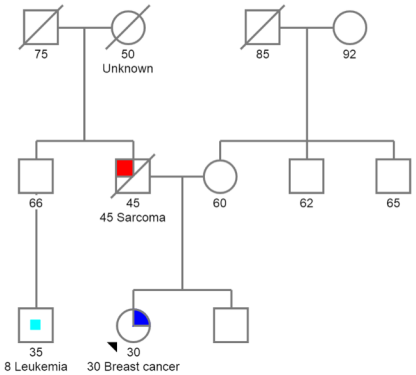

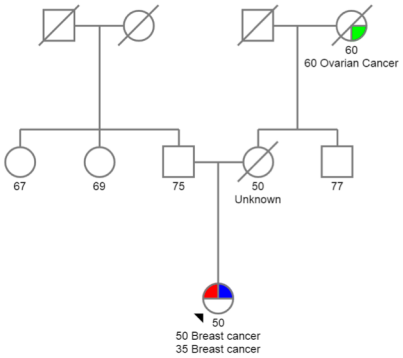

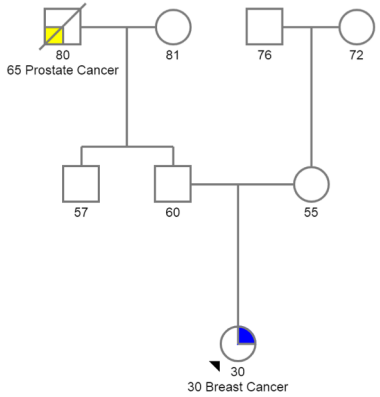

Secuenciación de ADN tumoral

Genes de susceptibilidad al cáncer

Fundación Pública Galega de Medicina Xenómica

ACMG STATEMENT | Genetics inMedicine

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Sarah S. Kalia, ScM[1], Kathy Adelman[2], Sherri J. Bale, PhD[3], Wendy K. Chung, MD, PhD[4,5], Christine Eng, MD[6], James P. Evans, MD, PhD[7], Gail E. Herman, MD, PhD[8], Sophia B. Hufnagel, MD[9], Teri E. Klein, PhD[10], Bruce R. Korf, MD, PhD[11], Kent D. McKelvey, MD[12,13], Kelly E. Ormond, MS[10], C. Sue Richards, PhD[14], Christopher N. Vlangos, PhD[15], Michael Watson, PhD[16], Christa L. Martin, PhD[17], David T. Miller, MD, PhD[18]; on behalf of the ACMG Secondary Findings Maintenance Working Group

Table 1 ACMG SF v2.0 genes and associated phenotypes recommended for return of secondary findings in clinical sequencing

Phenotype	MIM disorder	PMID Gene Reviews entry	Typical age of onset	Gene	MIM gene	Inheritance[a]	Variants to report[b]
Hereditary breast and ovarian cancer	604370 612555	20301425	Adult	*BRCA1* *BRCA2*	113705 600185	AD	KP and EP
Li-Fraumeni syndrome	151623	20301488	Child/adult	*TP53*	191170	AD	KP and EP
Peutz-Jeghers syndrome	175200	20301443	Child/adult	*STK11*	602216	AD	KP and EP
Lynch syndrome	120435	20301390	Adult	*MLH1* *MSH2* *MSH6* *PMS2*	120436 609309 600678 600259	AD	KP and EP
Familial adenomatous polyposis	175100	20301519	Child/adult	*APC*	611731	AD	KP and EP
MYH-associated polyposis; adenomas, multiple colorectal, *FAP* type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	608456 132600	23035301	Adult	*MUTYH*	604933	AR[c]	KP and EP
Juvenile polyposis	174900	20301642	Child/adult	*BMPR1A* *SMAD4*	601299 600993	AD	KP and EP
Von Hippel–Lindau syndrome	193300	20301636	Child/adult	*VHL*	608537	AD	KP and EP
Multiple endocrine neoplasia type 1	131100	20301710	Child/adult	*MEN1*	613733	AD	KP and EP
Multiple endocrine neoplasia type 2	171400 162300	20301434	Child/adult	*RET*	164761	AD	KP
Familial medullary thyroid cancer[a]	1552401	20301434	Child/adult	*RET*	164761	AD	KP
PTEN hamartoma tumor syndrome	153480	20301661	Child/adult	*PTEN*	601728	AD	KP and EP
Retinoblastoma	180200	20301625	Child	*RB1*	614041	AD	KP and EP
Hereditary paraganglioma-pheochromocytoma syndrome	168000 (PGL1) 601650 (PGL2) 605373 (PGL3) 115310 (PGL4)	20301715	Child/adult	*SDHD* *SDHAF2* *SDHC* *SDHB*	602690 613019 602413 185470	AD	KP and EP KP KP and EP
Tuberous sclerosis complex	191100 613254	20301399	Child	*TSC1* *TSC2*	605284 191092	AD	KP and EP
WT1-related Wilms tumor	194070	20301471	Child	*WT1*	607102	AD	KP and EP
Neurofibromatosis type 2	101100	20301380	Child/adult	*NF2*	607379	AD	KP and EP
Ehlers-Danlos syndrome, vascular type	130050	20301667	Child/adult	*COL3A1*	120180	AD	KP and EP
Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	154700 609192 608967 610168 610380 613795 611788	20301510 20301312 20301299	Child/adult	*FBN1* *TGFBR1* *TGFBR2* *SMAD3* *ACTA2* *MYH11*	134797 190181 190182 603109 102620 160745	AD	KP and EP
Hypertrophic cardiomyopathy, dilated cardiomyopathy	115197 192600 601494 613690 115196 608751 612098 600858 301500 608758 115200	20301725	Child/adult	*MYBPC3* *MYH7* *TNNT2* *TNNI3* *TPM1* *MYL3* *ACTC1* *PRKAG2* *GLA* *MYL2* *LMNA*	600958 160760 191045 191044 191010 160790 102540 602743 300644 160781 150330	AD XL AD	KP and EP KP KP and EP KP KP and EP (hemi, het, hom) KP KP and EP
Catecholaminergic polymorphic ventricular tachycardia	604772			*RYR2*	180902	AD	KP

Table 1. Continued on next page

Secuenciación de ADN tumoral

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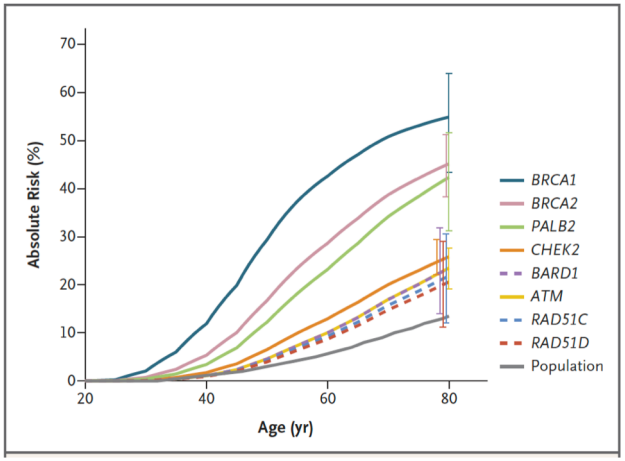
Breast cancer genes



Dorling et al. New England J Cancer 2021

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WT1-related Wilms tumor	194070	20301471	Child	*WT1*	607102	AD	KP and EP
Neurofibromatosis type 2	101100	20301380	Child/adult	*NF2*	607379	AD	KP and EP
Ehlers-Danlos syndrome, vascular type	130050	20301667	Child/adult	*COL3A1*	120180	AD	KP and EP
Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	154700 609192 608967 610168 610380 613795 611788	20301510 20301312 20301299	Child/adult	*FBN1* *TGFBR1* *TGFBR2* *SMAD3* *ACTA2* *MYH11*	134797 190181 190182 603109 102620 160745	AD	KP and EP
Hypertrophic cardiomyopathy, dilated cardiomyopathy	115197 192600 601494 613690 115196 608751 612098 600858 301500 608758 115200	20301725	Child/adult	*MYBPC3* *MYH7* *TNNT2* *TNNI3* *TPM1* *MYL3* *ACTC1* *PRKAG2* *GLA* *MYL2* *LMNA*	600958 160760 191045 191044 191010 160790 102540 602743 300644 160781 150330	AD XL AD	KP and EP KP KP and EP KP KP and EP (hemi, het, hom) KP KP and EP
Catecholaminergic polymorphic ventricular tachycardia	604772			*RYR2*	180902	AD	KP

Table 1. Continued on next page

Secuenciación de ADN tumoral

Genes de cáncer hereditario en paneles comerciales

Fundación Pública Galega de Medicina Xenómica

The Oncomine Comprehensive Assay v3 is available for use on the Ion GeneStudio S5 Systems with Ion Chef Instrument or for use on the Genexus System

Hotspot genes			
AKT1	ESR1	KIT	PDGFRB
AKT2	EZH2	KNSTRN	PIK3CB
AKT3	FGFR1	KRAS	PIK3CA
ALK	FGFR2	MAGOH	PPP2R1A
AR	FGFR3	MAP2K1	PTPN11
ARAF	FGFR4	MAP2K2	RAC1
AXL	FLT3	MAP2K4	RAF1
BRAF	FOXL2	MAPK1	RET
BTK	GATA2	MAX	RHEB
CBL	GNA11	MDM4	RHOA
CCND1	GNAQ	MED12	ROS1
CDK4	GNAS	MET	SF3B1
CDK6	H3F3A	MTOR	SMAD4
CHEK2	HIST1H3B	MYC	SMO
CSF1R	HNF1A	MYCN	SPOP
CTNNB1	HRAS	MYD88	SRC
DDR2	IDH1	NFE2L2	STAT3
EGFR	IDH2	NRAS	TERT
ERBB2	JAK1	NTRK1	TOP1
ERBB3	JAK2	NTRK2	U2AF1
ERBB4	JAK3	NTRK3	XPO1
ERCC2	KDR	PDGFRA	

Full-length genes		
ARID1A	FBXW7	PTEN
ATM	MLH1	RAD50
ATR	MRE11	RAD51
ATRX	MSH6	RAD51B
BAP1	MSH2	RAD51C
BRCA1	NBN	RAD51D
BRCA2	NF1	RNF43
CDK12	NF2	RB1
CDKN1B	NOTCH1	SETD2
CDKN2A	NOTCH2	SLX4
CDKN2B	NOTCH3	SMARCA4
CHEK1	PALB2	SMARCB1
CREBBP	PIK3R1	STK11
FANCA	PMS2	TP53
FANCD2	POLE	TSC1
FANCI	PTCH1	TSC2

Copy number genes		
AKT1	FGFR4	NUTM1
AKT2	FLT3	PDGFRA
AKT3	IGF1R	PDGFRB
ALK	KIT	PIK3CA
AR	KRAS	PRKACA
AXL	MDM2	PRKACB
BRAF	MDM4	PTEN
CCND1	MET	PPARG
CCND2	MYC	RAD51B
CCND3	MYCL	RAF1
CCNE1	MYCN	RB1
CDK2	NTRK1	RELA
CDK4	NTRK2	RET
CDK6	NTRK3	ROS1
EGFR	PDGFRA	RSPO2
ERBB2	PDGFRB	RSPO3
ESR1	PIK3CB	TERT
FGF19	PIK3CA	
FGF3	PPARG	
FGFR1	RICTOR	
FGFR2	TERT	
FGFR3		

Gene fusions (inter- and intragenic)		
AKT2	FGFR2	NUTM1
ALK	FGFR3	PDGFRA
AR	FGR	PDGFRB
AXL	FLT3	PIK3CA
BRCA1	JAK2	PRKACA
BRCA2	KRAS	PRKACB
BRAF	MDM4	PTEN
CDKN2A	MET	PPARG
EGFR	MYB	RAD51B
ERBB2	MYBL1	RAF1
ERBB4	NF1	RB1
ERG	NOTCH1	RELA
ESR1	NOTCH4	RET
ETV1	NRG1	ROS1
ETV4	NTRK1	RSPO2
ETV5	NTRK2	RSPO3
FGFR1	NTRK3	TERT

List of gene targets in the Oncomine Comprehensive Assay v3.

FOUNDATIONONE®CDx

Current Gene List[2]

Genes with full coding exonic regions included in FoundationOne®CDx for the detection of substitutions, insertion-deletions (indels), and copy-number alterations (CNAs).

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B)	APC
AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2
BTK	C11orf30 (EMSY)	CALR	CARD11	CASP8	CBFB	CBL	CCND1	CCND2
CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73	CDH1
CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C
CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R	CTCF
CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1	DDR2
DIS3	DNMT3A	DOT1L	EED	EGFR	EP300	EPHA3	EPHB1	EPHB4
ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRFI1	ESR1	EZH2	FAM46C
FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14
FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4
FH	FLCN	FLT1	FLT3	FOXL2	FUBP1	GABRA6	GATA3	GATA4
GATA6	GID4 (C17orf39)	GNA11	GNA13	GNAQ	GNAS	GRM3	GSK3B	H3F3A
HDAC1	HGF	HNF1A	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKNK1	MLH1	MPL	MRE11A	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	NT5C2	NTRK1	NTRK2	NTRK3	P2RY8	PALB2	PARK2
PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-1)	PDCD1LG2 (PD-L2)		PDGFRA
PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1	PMS2
POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A	PRKCI	PTCH1
PTEN	PTPN11	PTPRO	QKI	RAC1	RAD21	RAD51	RAD51B	RAD51C
RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10	REL	RET
RICTOR	RNF43	ROS1	RPTOR	SDHA	SDHB	SDHC	SDHD	SETD2
SF3B1	SGK1	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO	SNCAIP	SOCS1
SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3	STK11	SUFU
SYK	TBX3	TEK	TET2	TGFBR2	TIPARP	TNFAIP3	TNFRSF14	TP53
TSC1	TSC2	TYRO3	U2AF1	VEGFA	VHL	WHSC1 (MMSET)	WHSC1L1	WT1
XPO1	XRCC2	ZNF217	ZNF703					

Recomendaciones para informar variantes germinales de estudios tumorales

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1221–1231, 2019
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Published online 3 May 2019

SPECIAL ARTICLE

Germline-focussed analysis of tumour-only sequencing: recommendations from the ESMO Precision Medicine Working Group

D. Mandelker[1*], M. Donoghue[2], S. Talukdar[3], C. Bandlamudi[2], P. Srinivasan[2], M. Vivek[4,5], S. Jezdic[6], H. Hanson[3], K. Snape[3], A. Kulkarni[7], L. Hawkes[8], J.-Y. Douillard[6], S. E. Wallace[9], E. Rial-Sebbag[10], F. Meric-Bersntam[11], A. George[12,13], D. Chubb[13], C. Loveday[13], M. Ladanyi[1,4], M. F. Berger[1,2], B. S. Taylor[2,3,5] & C. Turnbull[7,13,14,15*]

Genetics inMedicine | ACMG STATEMENT

Points to consider for reporting of germline variation in patients undergoing tumor testing: a statement of the American College of Medical Genetics and Genomics (ACMG)

Marilyn M. Li, MD[1], Elizabeth Chao, MD, PhD[2], Edward D. Esplin, MD, PhD[3], David T. Miller, MD, PhD[4], Katherine L. Nathanson, MD[5], Sharon E. Plon, MD, PhD[6,7], Maren T. Scheuner, MD, MPH[8,9] and Douglas R. Stewart, MD[10]; ACMG Professional Practice and Guidelines Committee[11]

Review > J Oncol Pract. 2019 Sep;15(9):465-473. doi: 10.1200/JOP.19.00201.

When Should Tumor Genomic Profiling Prompt Consideration of Germline Testing?

Kim DeLeonardis [1], Lauren Hogan [1], Stephen A Cannistra [1], Deepa Rangachari [1], Nadine Tung [1]

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Affiliation

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Recomendaciones para informar variantes germinales de estudios tumorales

SPECIAL ARTICLE

Germline-focussed analysis of tumour-only sequencing: recommendations from the ESMO Precision Medicine Working Group

Case series: 17152 tumor normal sequencing MSK. 65 CSG

- **Asociaciones "On-tumour"-"Off-tumour" de genes con el tipo tumoral**
- **Accionabilidad clínica**

High-A-CSGs: 25 CSG de ACMG + 5 (PALB2, RAD51C, RAD51D, BRIP1, SDHA)

Standard-A-CSGs: 27 high penetrance, on tumor

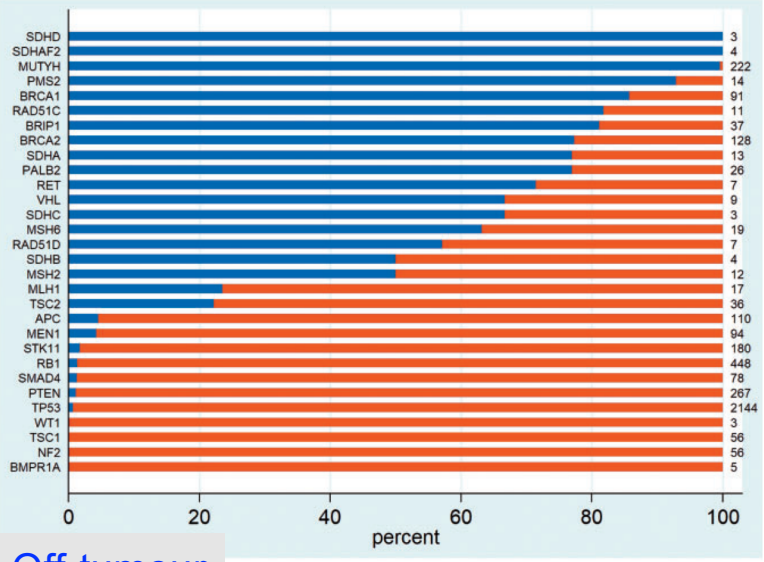
- **Tasa conversión germinal (Germline convertion rate):**

Nº variantes patogénicas germinales / número total de variantes identificadas en el tumor *100

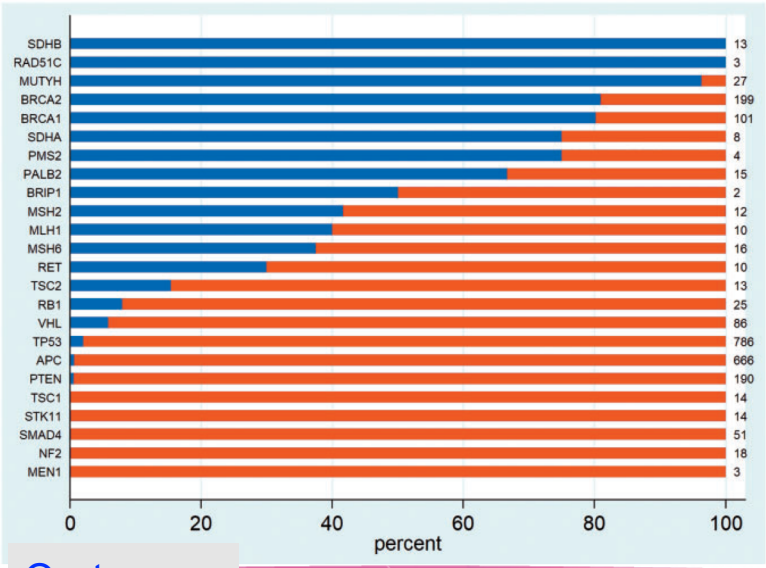
30 high-A CSG

germinales

tumorales



Off-tumour



On-tumour

Recomendaciones para informar variantes germinales de estudios tumorales

ESMO
SPECIAL ARTICLE

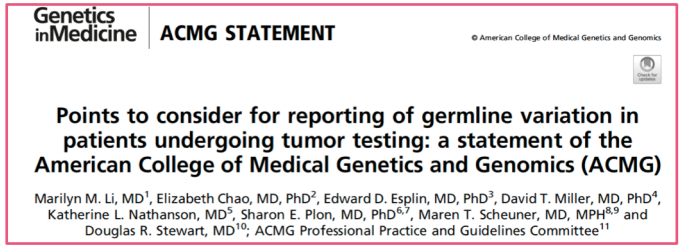
Box 1. Recommendations for genes to be included for germline-focussed analysis and triggering of germline sample laboratory confirmation

	Any tumour type		Associated tumour type only
Tumour arising any age	*BRCA1*	*RAD51C*	*FLCN*
	BRCA2	*RAD51D*	*FH*
	BRIP1	*RET*	*BAP1*
	MLH1	*SDHA*	*POLE*
	MSH2	*SDHAF2*	
	MSH6	*SDHB*	
	PALB2	*SDHC*	
	PMS2	*SDHD*	
	VHL[a]	*TSC2*	
		MUTYH[b]	
Tumour arising age <30 only	*RB1*		*TP53*[c]
	APC		*NF1*

[a]Renal tumours to be excluded.
[b]*MUTYH* should be included for germline-focussed tumour analysis but reporting and germline follow-up testing should only be performed on detection of two pathogenic variants.
[c]Brain tumours to be excluded.

Recomendaciones para informar variantes germinales de estudios tumorales

ACMG STATMENT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Consideraciones para profesionales clínicos

- Informar al paciente que se haga una prueba tumoral la posibilidad de identificar variante germinal. Si hay sospecha de síndrome de predisposición al cáncer se debe valorar prueba específica germinal.
- La elección y autonomía del paciente deben ser respetados.
- Si se utilizan compañías/plataformas, debe existir disponibilidad de especialistas con formación en genética del cáncer para responder cuestiones especificas
- Informar al paciente que el descubrimiento de una PGPV impulsaría la derivación para una consulta genética y la posibilidad de pruebas de línea germinal confirmatorias.
- La prueba confirmatoria de la línea germinal debe realizarse en un laboratorio que cuente con los recursos adecuados y experiencia en la realización de pruebas e interpretación de la línea germinal.
- Los resultados positivos de la prueba de línea germinal deben ser comunicados por personal cualificados y con experiencia (por ejemplo, oncólogos con expertos en genética, genetistas y asesores genéticos).

Take home messages

Aproximación NGS estudio de tumor

- Existen distintos tipos de test
- El test pareado tumor-normal no sustituye al germinal

Genes a considerar

- Genes altamente accionables (High-CSGs): “on tumour” + “off-tomur”
- Genes accionabilidad estándar (St-CSGs): “on tumour” (solo alta penetrancia?)
- Tasa conversión germinal >10%. Excepciones dx <30 años. TP53, NF1 on tumour

Variantes patogénicas posiblemente germinales

- Frecuencia alélica de la variante (VAF) puede verse afectada por biología del tumor
- Una variante fundadora conocida en un GSC es probablemente germinal, pero NECESITA confirmación ortogonal.
- Datos clínicos del paciente y tumor
- Antes de solicitar una confirmación germinal de una variante, debe revisarse por especialista en genética. Sólo variantes patogénicas/posiblemente patogéncias (clase 4/5).
- Antes de solicitar la confirmación germinal de una variante el paciente debe estar informado de las implicaciones del estudio y tiene que dar su consentimiento informado. Si se identifica variante germinal derivar al paciente a CG para seguimiento personal y familiar.


grazie
dakujem
merci
thanks
gracias
ありがとう
спасибо
hvala
obrigado
gràcies
spas
díky
mochchakkeram
bedankt
danke
bakka bèr
شكراً
thank you
gracias
ačiū
grazas
Arigatō
grazie
감사합니다
Tak
merci
eskerrik asko
gràcies
obrigado
aitäh
asante
dziękuję
ngiyabonga
terima kasih
tack
Salamat
dankon
köszönöm
dank
kiitos
Շնորհակալություն
dankie