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7 DÉCADAS
desde 1954
de atención especializada en cáncer

Susceptibilidad Genética al cáncer de mama: recientes avances y aplicación al diagnóstico molecular

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19 de julio de 2024

VHIO VALL D'HEBRON Institut d'Oncologia
Vall d'Hebron Barcelona Hospital Campus

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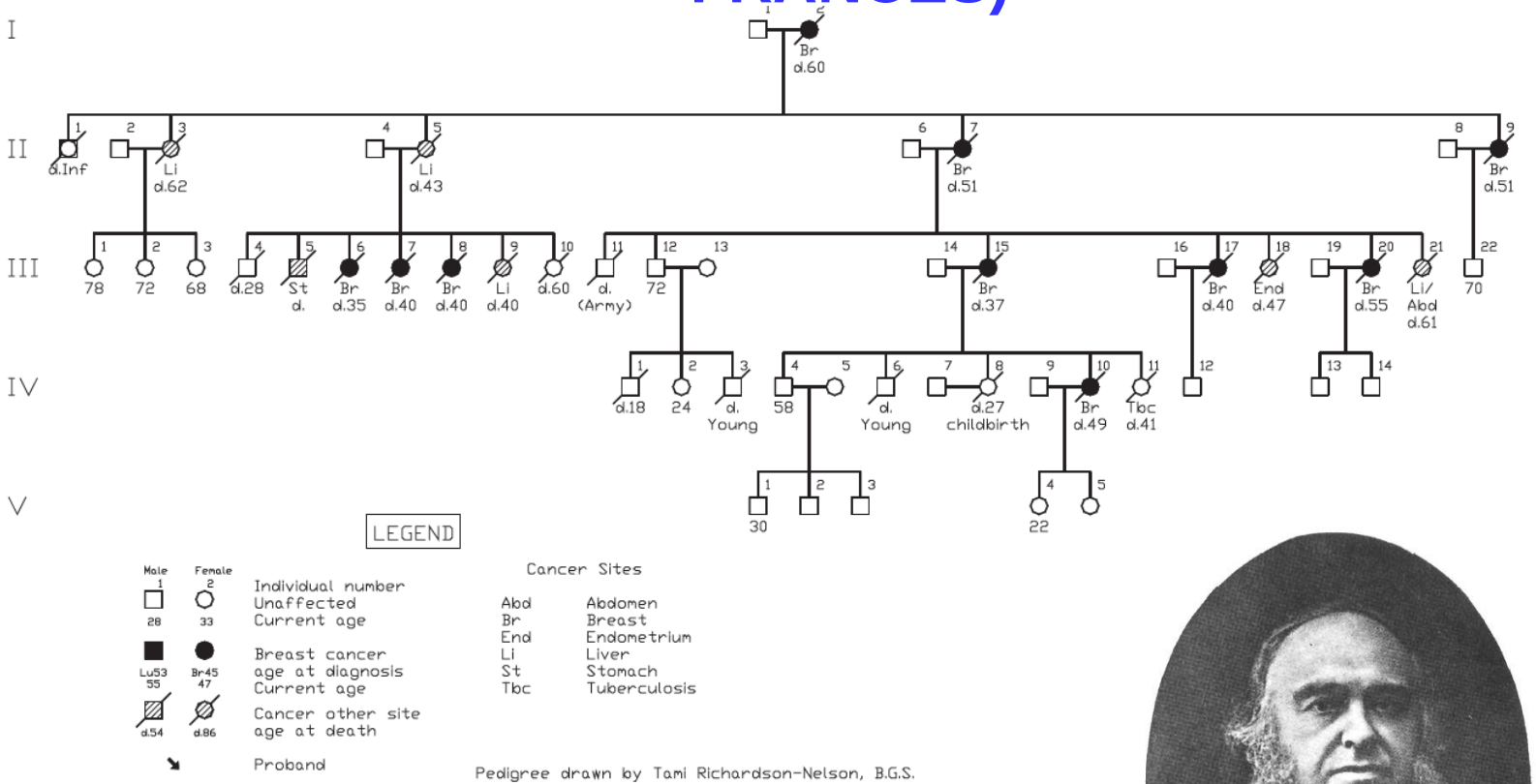
GENES DEL CÁNCER DE MAMA HEREDITARIO

LA PRIMERA HISTORIA FAMILIAR DE CÁNCER FUE DESCRITA EN 1866 POR PAUL BROCA (MÉDICO FRANCÉS)



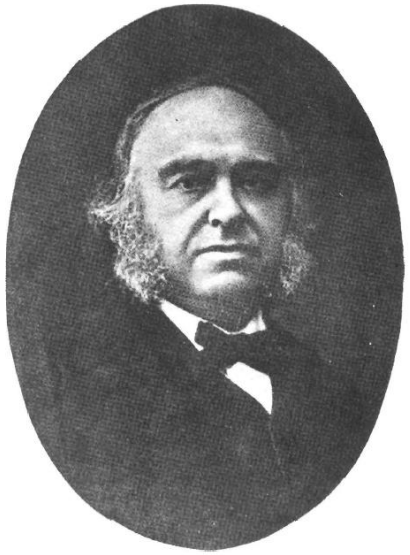


Figure 1. Pierre Paul Broca (1824–80).

Mary-Claire King Identifica en 1990 el sitio en el cromosoma 17 asociado con una historia familiar de cáncer mama/ovario

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En 1994-1995 se describe los genes *BRCA1* y *BRCA2* como responsables de casos de cáncer mama/ovario familiar

BRCA1 (17q21)
5.592 nt

BRCA2 (13q12)
11.385 nt

Genes con función en la reparación del DNA

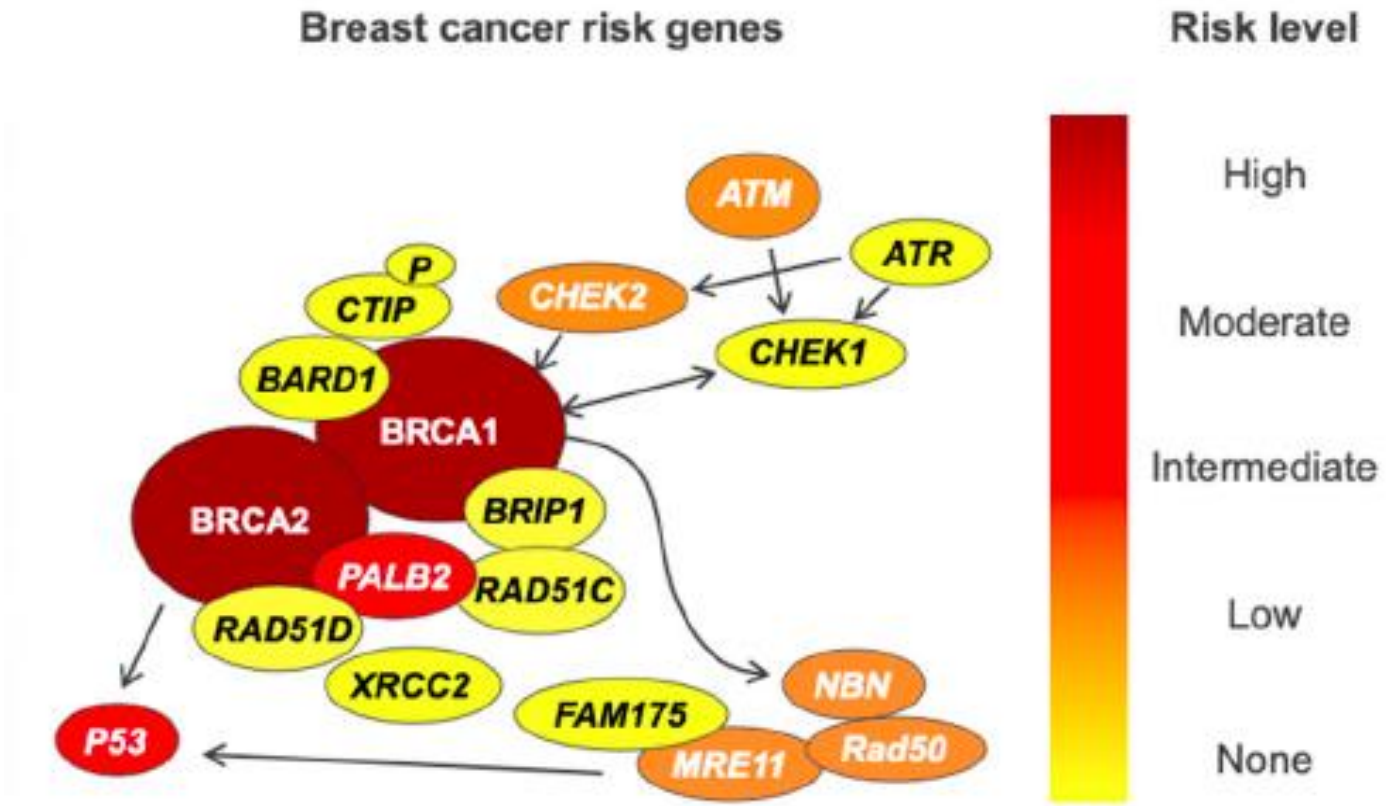

Figure 1. Susceptibility genes present in the double-strand DNA break repair pathway for breast cancer and its different correspondent risks levels in each disease.

Cancers **2020**, *12*, 3046; doi:10.3390/cancers12103046

Pavanello et al

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RIESGO A DESARROLLAR CÁNCER DE MAMA

HEREDITARY BREAST CANCER ASSOCIATED GENES

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Breast Cancer Risk Genes — Association Analysis in More than 113,000 Women

Breast Cancer Association Consortium*

ABSTRACT

BACKGROUND
Genetic testing for breast cancer susceptibility is widely used, but for many genes, evidence of an association with breast cancer is weak, underlying risk estimates are imprecise, and reliable subtype-specific risk estimates are lacking.

METHODS
We used a panel of 34 putative susceptibility genes to perform sequencing on samples from 60,466 women with breast cancer and 53,461 controls. In separate analyses for protein-truncating variants and rare missense variants in these genes, we estimated odds ratios for breast cancer overall and tumor subtypes. We evaluated missense-variant associations according to domain and classification of pathogenicity.

RESULTS
Protein-truncating variants in 5 genes (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*) were associated with a risk of breast cancer overall with a P value of less than 0.0001. Protein-truncating variants in 4 other genes (*BARD1*, *RAD51C*, *RAD51D*, and *TP53*) were associated with a risk of breast cancer overall with a P value of less than 0.05 and a Bayesian false-discovery probability of less than 0.05. For protein-truncating variants in 19 of the remaining 25 genes, the upper limit of the 95% confidence interval of the odds ratio for breast cancer overall was less than 2.0. For protein-truncating variants in *ATM* and *CHEK2*, odds ratios were higher for estrogen receptor (ER)–positive disease than for ER-negative disease; for protein-truncating variants in *BARD1*, *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, and *RAD51D*, odds ratios were higher for ER-negative disease than for ER-positive disease. Rare missense variants (in aggregate) in *ATM*, *CHEK2*, and *TP53* were associated with a risk of breast cancer overall with a P value of less than 0.001. For *BRCA1*, *BRCA2*, and *TP53*, missense variants (in aggregate) that would be classified as pathogenic according to standard criteria were associated with a risk of breast cancer overall, with the risk being similar to that of protein-truncating variants.

CONCLUSIONS
The results of this study define the genes that are most clinically useful for inclusion on panels for the prediction of breast cancer risk, as well as provide estimates of the risks associated with protein-truncating variants, to guide genetic counseling. (Funded by European Union Horizon 2020 programs and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Easton at the University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, United Kingdom, or at dfe20@medschl.cam.ac.uk.

*A complete list of collaborators and investigators is provided in the Supplementary Appendix, available at NEJM.org.

Dr. Dorling, Dr. Carvalho, and Mr. Allen and Drs. Teo, Devilee, and Easton contributed equally to this article.

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DOI: 10.1056/NEJMoa1913948

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Population-Based Study of Genes Previously Implicated in Breast Cancer

C. Hu, S.N. Hart, R. Gnanaolivu, H. Huang, K.Y. Lee, J. Na, C. Gao, J. Lilyquist, S. Yadav, N.J. Boddicker, R. Samara, J. Klebba, C.B. Ambrosone, H. Anton-Culver, P. Auer, E.V. Bandera, L. Bernstein, K.A. Bertrand, E.S. Burnside, B.D. Carter, H. Eliassen, S.M. Gapstur, M. Gaudet, C. Haiman, J.M. Hodge, D.J. Hunter, E.J. Jacobs, E.M. John, C. Kooperberg, A.W. Kurian, L. Le Marchand, S. Lindstroem, T. Lindstrom, H. Ma, S. Neuhausen, P.A. Newcomb, K.M. O'Brien, J.E. Olson, I.M. Ong, T. Pal, J.R. Palmer, A.V. Patel, S. Reid, L. Rosenberg, D.P. Sandler, C. Scott, R. Tamimi, J.A. Taylor, A. Trentham-Dietz, C.M. Vachon, C. Weinberg, S. Yao, A. Ziogas, J.N. Weitzel, D.E. Goldgar, S.M. Domchek, K.L. Nathanson, P. Kraft, E.C. Polley, and F.J. Couch

ABSTRACT

BACKGROUND
Population-based estimates of the risk of breast cancer associated with germline pathogenic variants in cancer-predisposition genes are critically needed for risk assessment and management in women with inherited pathogenic variants.

METHODS
In a population-based case–control study, we performed sequencing using a custom multigene amplicon-based panel to identify germline pathogenic variants in 28 cancer-predisposition genes among 32,247 women with breast cancer (case patients) and 32,544 unaffected women (controls) from population-based studies in the Cancer Risk Estimates Related to Susceptibility (CARRIERS) consortium. Associations between pathogenic variants in each gene and the risk of breast cancer were assessed.

RESULTS
Pathogenic variants in 12 established breast cancer–predisposition genes were detected in 5.05% of case patients and in 1.63% of controls. Pathogenic variants in *BRCA1* and *BRCA2* were associated with a high risk of breast cancer, with odds ratios of 7.62 (95% confidence interval [CI], 5.33 to 11.27) and 5.23 (95% CI, 4.09 to 6.77), respectively. Pathogenic variants in *PALB2* were associated with a moderate risk (odds ratio, 3.83; 95% CI, 2.68 to 5.63). Pathogenic variants in *BARD1*, *RAD51C*, and *RAD51D* were associated with increased risks of estrogen receptor–negative breast cancer and triple-negative breast cancer, whereas pathogenic variants in *ATM*, *CDH1*, and *CHEK2* were associated with an increased risk of estrogen receptor–positive breast cancer. Pathogenic variants in 16 candidate breast cancer–predisposition genes, including the c.657_661del5 founder pathogenic variant in *NBN*, were not associated with an increased risk of breast cancer.

CONCLUSIONS
This study provides estimates of the prevalence and risk of breast cancer associated with pathogenic variants in known breast cancer–predisposition genes in the U.S. population. These estimates can inform cancer testing and screening and improve clinical management strategies for women in the general population with inherited pathogenic variants in these genes. (Funded by the National Institutes of Health and the Breast Cancer Research Foundation.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Couch at the Department of Laboratory Medicine and Pathology, Mayo Clinic, Stabile 2-42, 200 First St. SW, Rochester, MN 55905, or at couch.fergus@mayo.edu.

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somos esperanza d

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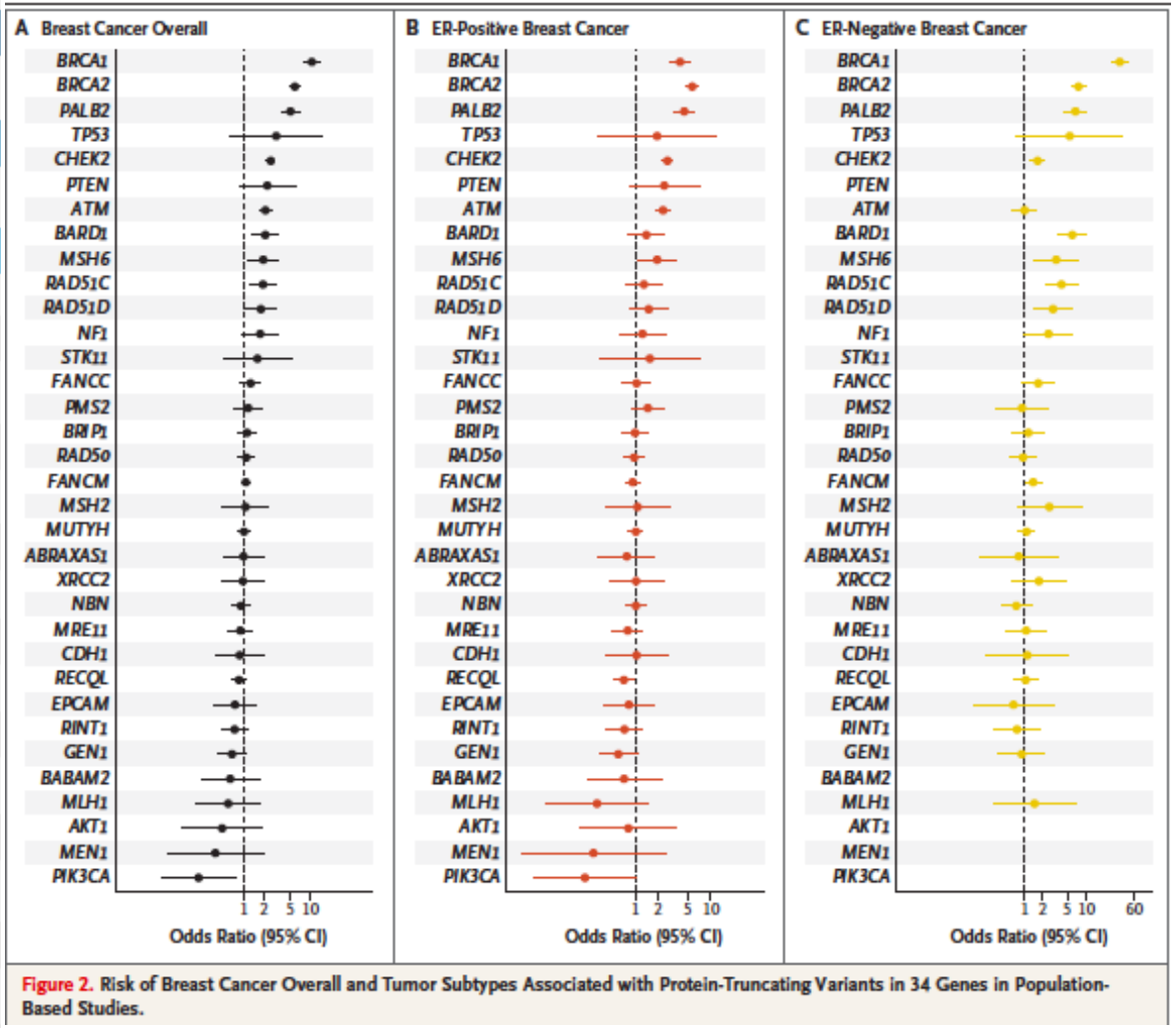
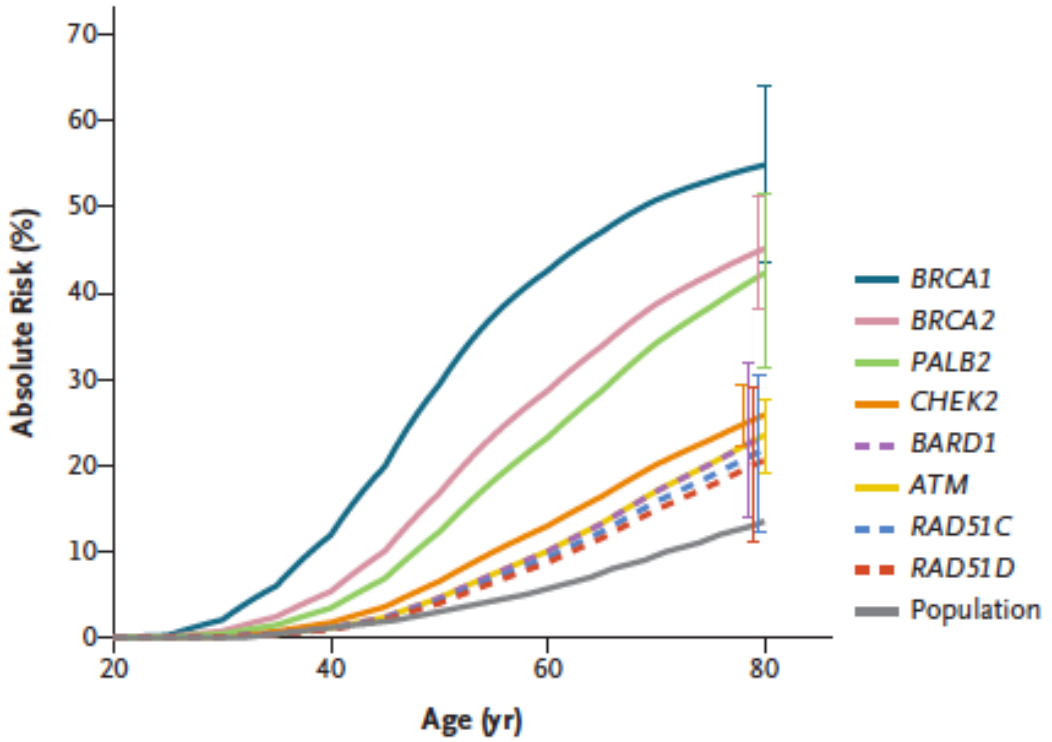


Figure 2. Risk of Breast Cancer Overall and Tumor Subtypes Associated with Protein-Truncating Variants in 34 Genes in Population-Based Studies.



- Approximately **3%** of unselected patients with breast cancer carry a germline *BRCA1/2* pathogenic variant
- This rate increases with:
  - Young age
  - Triple negative phenotype
  - High grade
  - Family history
  - Male breast cancer

BRCA1/BRCA2 GENES QUE EXPLICAN EL MAYOR NÚMERO DE CASOS

Table 2. Associations between Pathogenic Variants in Established Breast Cancer–Predisposition Genes and Risk of Breast Cancer.*

Breast Cancer–Predisposition Gene[1,2,7]	Case Patients (N=32,247)	Controls (N=32,544)	Odds Ratio (95% CI)†	P Value
	no. with pathogenic variant (%)			
ATM	253 (0.78)	134 (0.41)	1.82 (1.46–2.27)	<0.001
BARD1	49 (0.15)	35 (0.11)	1.37 (0.87–2.16)	0.18
BRCA1	275 (0.85)	37 (0.11)	7.62 (5.33–11.27)	<0.001
BRCA2	417 (1.29)	78 (0.24)	5.23 (4.09–6.77)	<0.001
CDH1	17 (0.05)	6 (0.02)	2.50 (1.01–7.07)	0.06
CHEK2	349 (1.08)	138 (0.42)	2.47 (2.02–3.05)	<0.001
NF1‡	19 (0.06)	11 (0.03)	1.93 (0.91–4.31)	0.09
PALB2	148 (0.46)	38 (0.12)	3.83 (2.68–5.63)	<0.001
PTEN	8 (0.02)	3 (0.01)	NA	NA
RAD51C	41 (0.13)	35 (0.11)	1.20 (0.75–1.93)	0.44
RAD51D	26 (0.08)	14 (0.04)	1.72 (0.88–3.51)	0.12
TP53‡	19 (0.06)	2 (0.01)	NA	NA
Total	1621 (5.03)	531 (1.63)	—	—

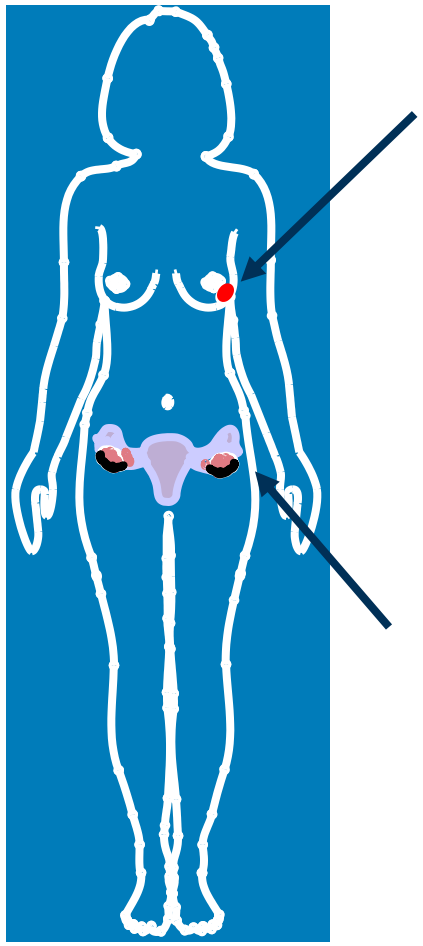
RIESGO DE CÁNCER DE MAMA EN HOMBRES

Table 1. BC risks conferred by PVs in established BC susceptibility genes in both sexes. Estimates may vary according to study population and/or study design.

	Female Breast Cancer			Male Breast Cancer		
Gene	**OR**	**Absolute Risk**	**Study**	**OR**	**Absolute Risk**	**Study**
BRCA1	>10	>50%	[23,24,45,46]	4	0.4%	[34]
BRCA2	>5	>50%	[23,24,45,46]	40	4%	[34]
PALB2	3.4–7.18	40–60%	[23,24,47]	7.3	0.9%	[47]
CHEK2	2.5	20–40%	[23,24]	2.43–3.78	na	[25,31,32]
ATM	2.5–5	20–30%	[33,48–54]	1.78–4.8	na	[31–33]

Valentini V, et al., Gender-Specific Genetic Predisposition to Breast Cancer: *BRCA* Genes and Beyond. *Cancers*. 2024; 16(3):579.

OTROS TUMORES ASOCIADOS A *BRCA1/BRCA2*: OVARIO, PÁNCREAS Y PRÓSTATA

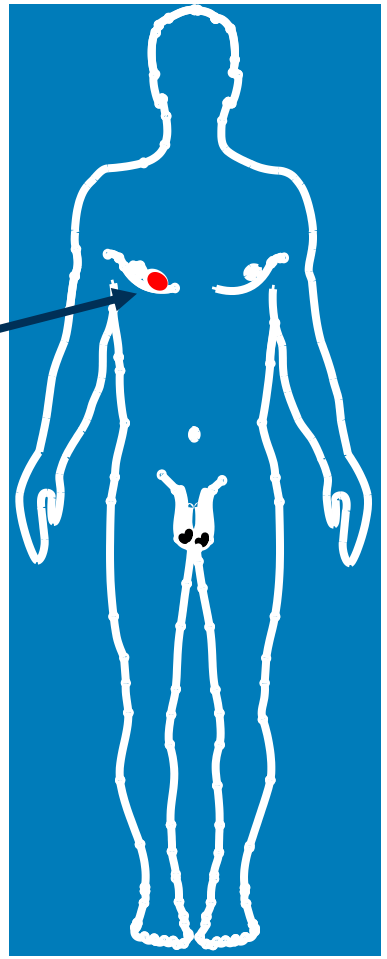


MAMA
50% - 85%

OVARIO
BRCA1: 15% - 45%
BRCA2: 5% - 20%

(páncreas, próstata)

MAMA
BRCA2: 6%



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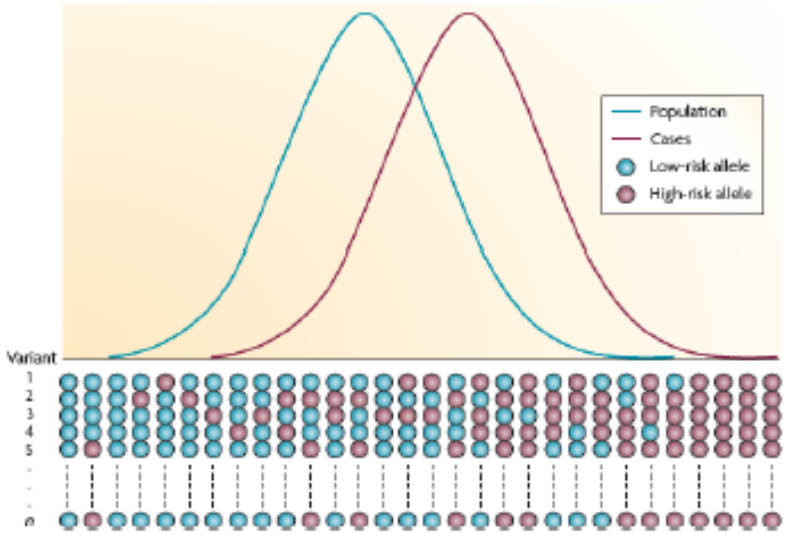
Alelos de baja riesgo

-identificados mediante estudios pangenómicos de asociación (GWAS: genome-wide association studies) de grandes cohortes de pacientes e individuos sanos.
-genes o *loci* de susceptibilidad cuyas variantes son frecuentes en la población y confieren cada una de ellas un RR < 1,5

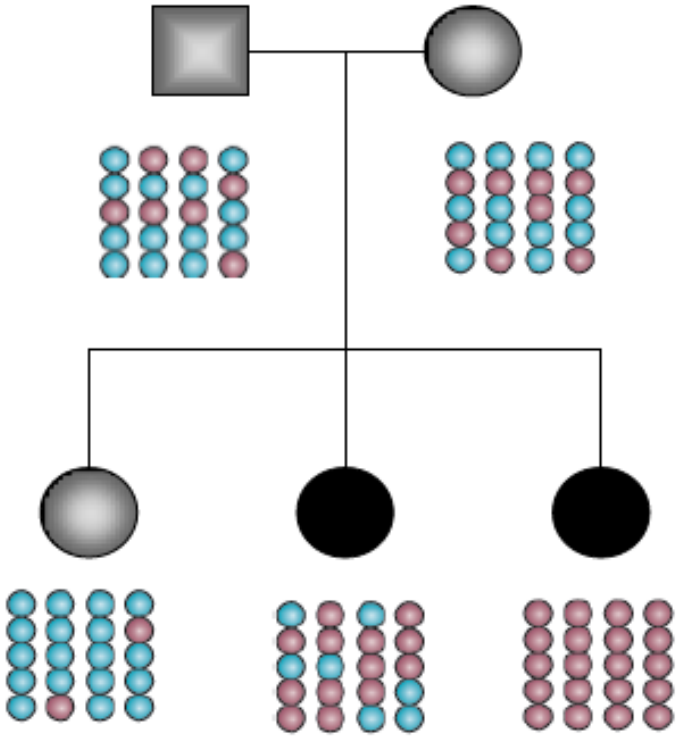
BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors

Andrew Lee, MSci, CASM[1], Nasim Mavaddat, MBBS, PhD[1], Amber N. Wilcox, MPH[2], Alex P. Cunningham, MSc, PhD[1], Tim Carver, PhD[1], Simon Hartley, MSc, PhD[1], Chantal Babb de Villiers, PhD[3], Angel Izquierdo, MD[4], Jacques Simard, PhD[5], Marjanka K. Schmidt, PhD[6], Fiona M. Walter, MD, FRCGP[3], Nilanjan Chatterjee, PhD[7,8], Montserrat Garcia-Closas, MPH, DrPH[2], Marc Tischkowitz, MD, PhD[9], Paul Pharoah, PhD[1,10], Douglas F. Easton, PhD[1,10] and Antonis C. Antoniou, PhD[1]

GENETICS in MEDICINE



Fletcher O, 2010



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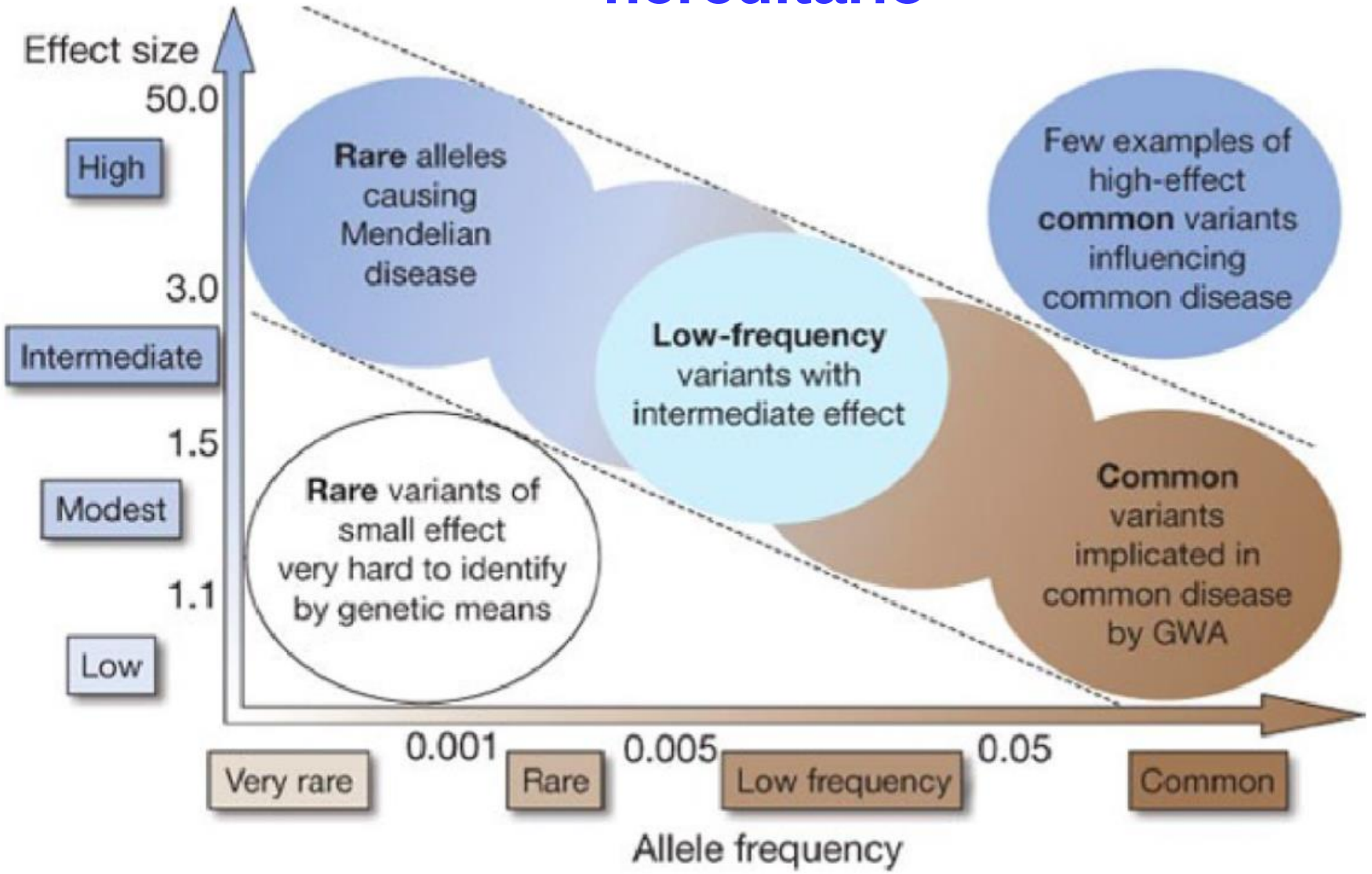
Arquitectura genética del cáncer de mama hereditario



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DIAGNÓSTICO GENÉTICO: GERMINAL

Qué genes evaluar en un panel?

International Journal of Cancer

Opportunistic testing of *BRCA1*, *BRCA2* and mismatch repair genes improves the yield of phenotype driven hereditary cancer gene panels

Lídia Feliubadaló[1,2,3]*, Adrià López-Fernández[4]*, Marta Pineda[1,2,3], Orland Díez[5,6], Jesús del Valle[1,2,3], Sara Gutiérrez-Enríquez[5], Alex Teulé[1,2,3], Sara González[1,2,3], Neda Stjepanovic[4,7], Mónica Salinas[1,2,3], Gabriel Capellá[1,2,3], Joan Brunet[1,8,9], Conxi Lázaro[1,2,3†], and Judith Balmaña[4,7†] on behalf of the Catalan Hereditary Cancer Group[‡]

Table 1. Genes included in each phenotype-based panel

	BC	OC	BOC	HNPCC	Adenomatous polyposis	Li-Fraumeni
BRCA1[1]	***BRCA1***	***BRCA1***	***BRCA1***	***BRCA1***	***BRCA1***	***BRCA1***
BRCA2[1]	***BRCA2***	***BRCA2***	***BRCA2***	***BRCA2***	***BRCA2***	***BRCA2***
PALB2	***PALB2***		***PALB2***			
ATM	***ATM***		***ATM***			
TP53	***TP53***		***TP53***			***TP53***
CHEK2	***CHEK2***		***CHEK2***			***CHEK2***
BRIP1		***BRIP1***	***BRIP1***			
RAD51C		***RAD51C***	***RAD51C***			
RAD51D		***RAD51D***	***RAD51D***			
MLH1[1]	***MLH1***	***MLH1***	***MLH1***	***MLH1***	***MLH1***	***MLH1***
MSH2[1]	***MSH2***	***MSH2***	***MSH2***	***MSH2***	***MSH2***	***MSH2***
MSH6[1]	***MSH6***	***MSH6***	***MSH6***	***MSH6***	***MSH6***	***MSH6***
MUTYH				***MUTYH***	***MUTYH***	
POLD1				***POLD1***	***POLD1***	
POLE				***POLE***	***POLE***	
APC					***APC***	
BMPR1A					***BMPR1A***	
NTHL1					***NTHL1***	
SMAD4					***SMAD4***	

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CONSENSO CATALÁN

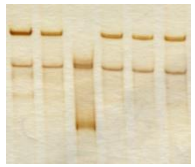
Panel de genes en cáncer de mama y ovario (casos o familias con cáncer de mama o cáncer de mama y cáncer de ovario): **BRCA1, BRCA2, MLH1, MSH2, MSH6, TP53*, BARD1, PALB2, CHEK2, ATM, BRIP1 , RAD51C, RAD51D, PTEN, CDH1****

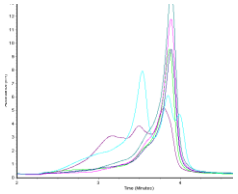
Criterios clínicos:

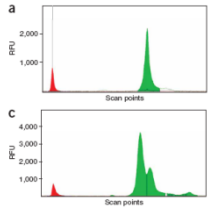
- Cáncer de mama ≤ 40 años.
- Cáncer de mama ≤ 50, si familia no informativa.
- Cáncer de mama triple negativo ≤ 60 años.
- Cáncer de mama en el hombre.
- Tres o más familiares de primer o segundo grado afectados por cáncer de mama (al menos uno en edad ≤ 60 años).
- ≥ 3 casos entre cáncer de mama y páncreas y/O ovario y/o próstata metastática Gleason ≥7.
- Dos casos de cáncer de mama en ≤ 50 años.
- Un caso de cáncer de mama bilateral (el primer diagnosticado ≤ 50 años).
- Un caso de cáncer de mama bilateral y otro de cáncer de mama (uno ≤ 60 años).
- Cáncer de mama HER2- para las que se considere opción de tratamiento con inhibidores de PARP según indicación CatSalut.
- Cáncer de mama e historia familiar de cáncer de ovario
- Cáncer de ovario epitelial invasivo no mucinoso (en los tumores de bajo grado se individualizará en función de edad, historia familiar y posible beneficio a familiares).

Diagnóstico genético (localización de variantes patogénicas en el gen): Evolución de las técnicas

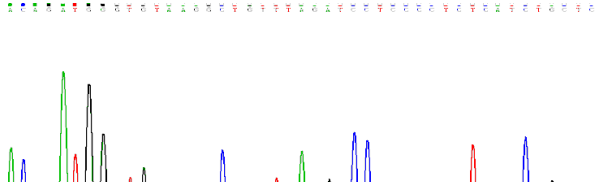
Década de los 90 a los 1eros años de la década de los 2000

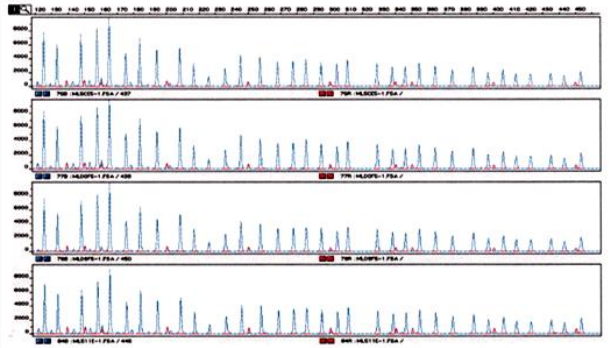




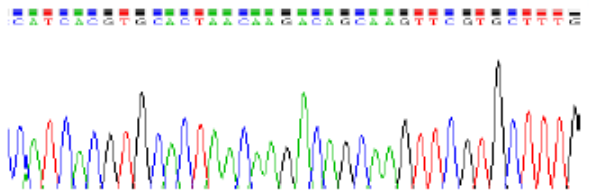


Década de los 2000





Década de los 2010

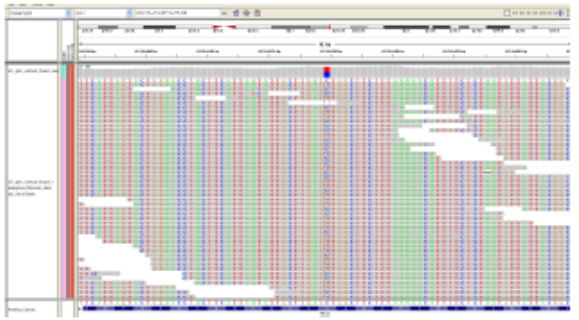


- genes individuales
- secuenciación capilar

↓

- múltiples genes
- secuenciación masiva

HiSeq2500 (Illumina)



• Cómo se hace actualmente el diagnóstico genético germinal

Personal/familial history → **Genetic testing HBOC genes** → **Variant classification** → **Benefits: Clinical management**

- BC<35
- Bilateral BC
- TNBC<50
- Male breast cancer

Germline
Coding regions
Multi-gene testing

Clinical guidelines for Variant Interpretation

Class-5	Pathogenic
Class-4	Likely Pathogenic
Class-3	Uncertain
Class-2	Likely Benign
Class-1	Benign

- Genetic counseling
- Early detection
- Therapeutic strategies

1. Pathogenic variant (loss of function)

2. Absence of pathogenic variant

3. Variant of Unknown Clinical Significance (VUS) → Challenge for genetic laboratories, oncologists and genetic counselors

Listas de variantes obtenidas después de secuenciación masiva de un panel de genes

T...	Gene	Coding consequence	c.DNA	Depth	VF%	ref	alt
SNP	PALB2	nonsense	c.3256C>T	2282	47.1	G	A
SNP	ATM	intronic	c.6348-54T>C	442	49.5	T	C
SNP	ATM	intronic	c.4237-54T>C	924	50.4	T	C
SNP	FAM175A	missense	c.1042G>A	5557	50.1	C	T
SNP	ATM	intronic	c.3403-15T>A	2089	24.2	T	A
INDEL	ATM	intronic	c.72+37_72+38...	5154	99.3	TAA	T
SNP	ATM	intronic	c.8787-55C>T	2162	99.6	C	T
INDEL	ATM	intronic	c.6006+191_60...	3360	99.3	ACT	A
SNP	ATM	intronic	c.8850+60A>G	2095	99.8	A	G
SNP	ATM	intronic	c.2377-56A>G	1622	99.8	A	G
SNP	ATM	missense	c.5948A>G	3322	99.8	A	G
INDEL	ATM	intronic	c.3403-13dupA	2108	65.4	TAA	TAAA
SNP	BARD1	5'UTR	c.-30G>C	1535	54.9	C	G
SNP	BARD1	intronic	c.1811-77A>G	697	51.5	T	C
SNP	BARD1	intronic	c.1811-69T>C	695	51.1	A	G
SNP	BARD1	intronic	c.1315-19G>A	918	52.4	C	T
SNP	BARD1	missense	c.1518_1519de...	1268	51.0	CA	TG
SNP	BARD1	intronic	c.1568+14C>T	1257	51.2	G	A
SNP	BARD1	missense	c.70C>T	1568	54.7	G	A
SNP	BARD1	missense	c.1134G>C	4735	100.0	C	G
SNP	BARD1	intronic	c.158+46A>C	1568	54.2	T	G
INDEL	BLM	intronic	c.3210+44delT	796	51.6	ATTTT...	ATTTTTTT
INDEL	BLM	intronic	c.4077-59_407...	1843	96.7	G	GGAA

Consecuencia clínica de la clasificación de variantes genéticas en genes asociados a cáncer hereditario

Virchows Arch

Table 4 IARC five-tier classification, adapted from [49]. *Based on the recommendations from the EMQN (European Molecular Genetics Quality Network)

Class	Probability (quantitative)	Description (qualitative)	Report?	Predictive testing?	Management of carriers	Research testing
5	>0.99	Definitely pathogenic	Yes	Yes	Full high-risk guidelines	No
4	0.95–0.99	Likely pathogenic	Yes	Yes	Full high-risk guidelines	May be helpful
3	0.05–0.949	Uncertain	Yes*	No	Variant irrelevant to risk assesment (Manage risk based on family history)	May be helpful
2	0.001–0.049	Likely not pathogenic	No*	No	Variant irrelevant to risk assesment (Manage risk based on family history)	May be helpful
1	<0.001	not Pathogenic	No*	No	Variant irrelevant to risk assesment (Manage risk based on family history)	No

Palacios et al., Virchows Arch. 2019 Dec 3

SOLCA
NÚCLEO DE QUITO

GESTIÓN CLÍNICA DE PACIENTES CON UN DIAGNÓSTICO POSITIVO

Consecuencias del diagnóstico genético de un cáncer de mama hereditario

IMPLICACIONES DIAGNÓSTICO GENÉTICO EN CÁNCER HEREDITARIO

Porqué es importante diagnosticar este trastorno genético

- Beneficio terapéutico específico para portadores de alteraciones en *BRCA1/2*: **tratamiento con inhibidores de PARP y con cisplatino**
- Prevención de **segundos tumores primarios** en **pacientes afectas**: mastectomía contralateral y/o cirugía profiláctica
- En **portadores sanos**, medidas de prevención y/o detección precoz: mamografías más resonancia magnética, cirugías profilácticas
- Diagnóstico preimplantacional

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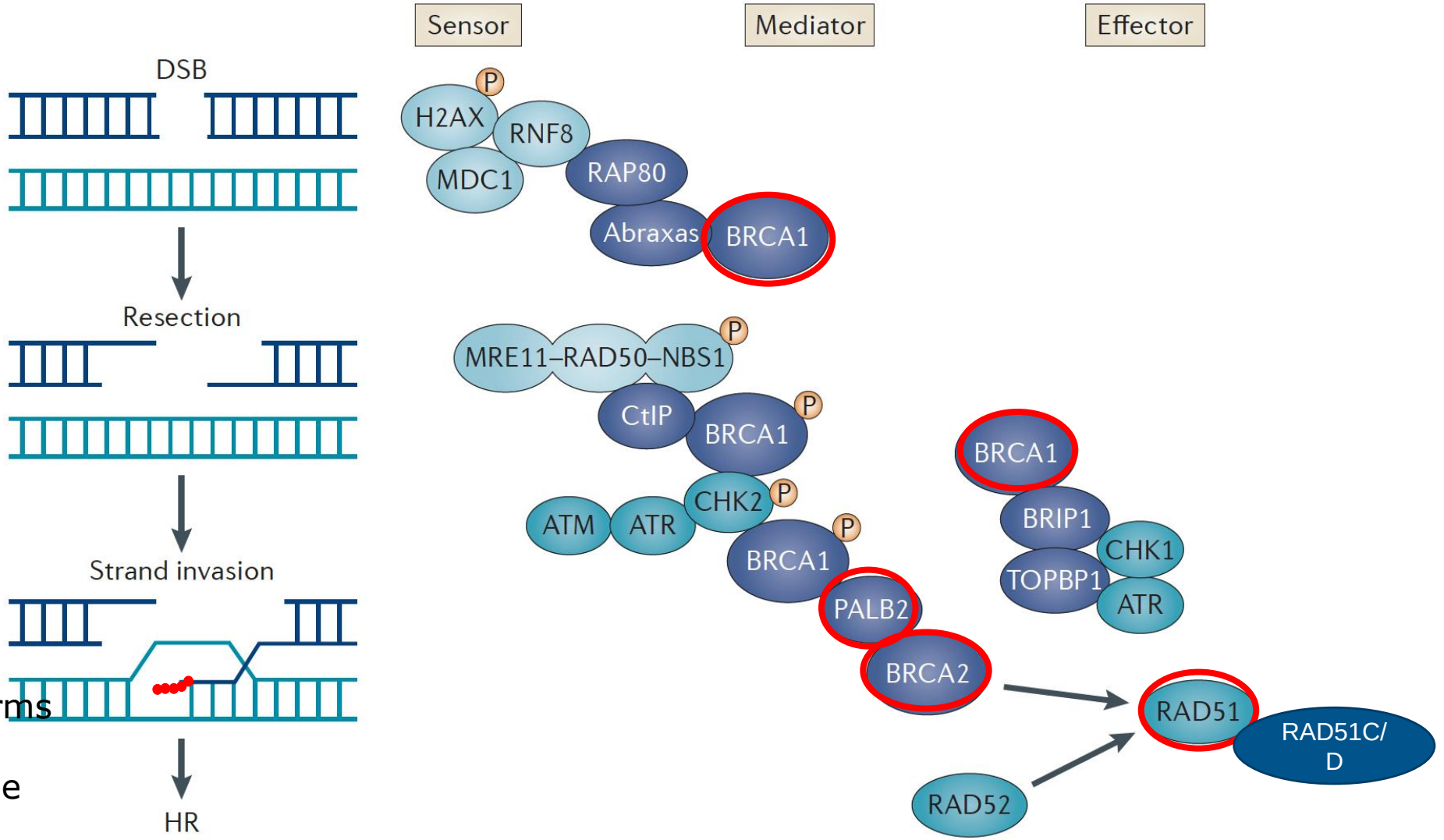
NÚCLEO DE QUITO

TRATAMIENTO ESPECÍFICO DE LOS TUMORES *BRCA1/BRCA2*

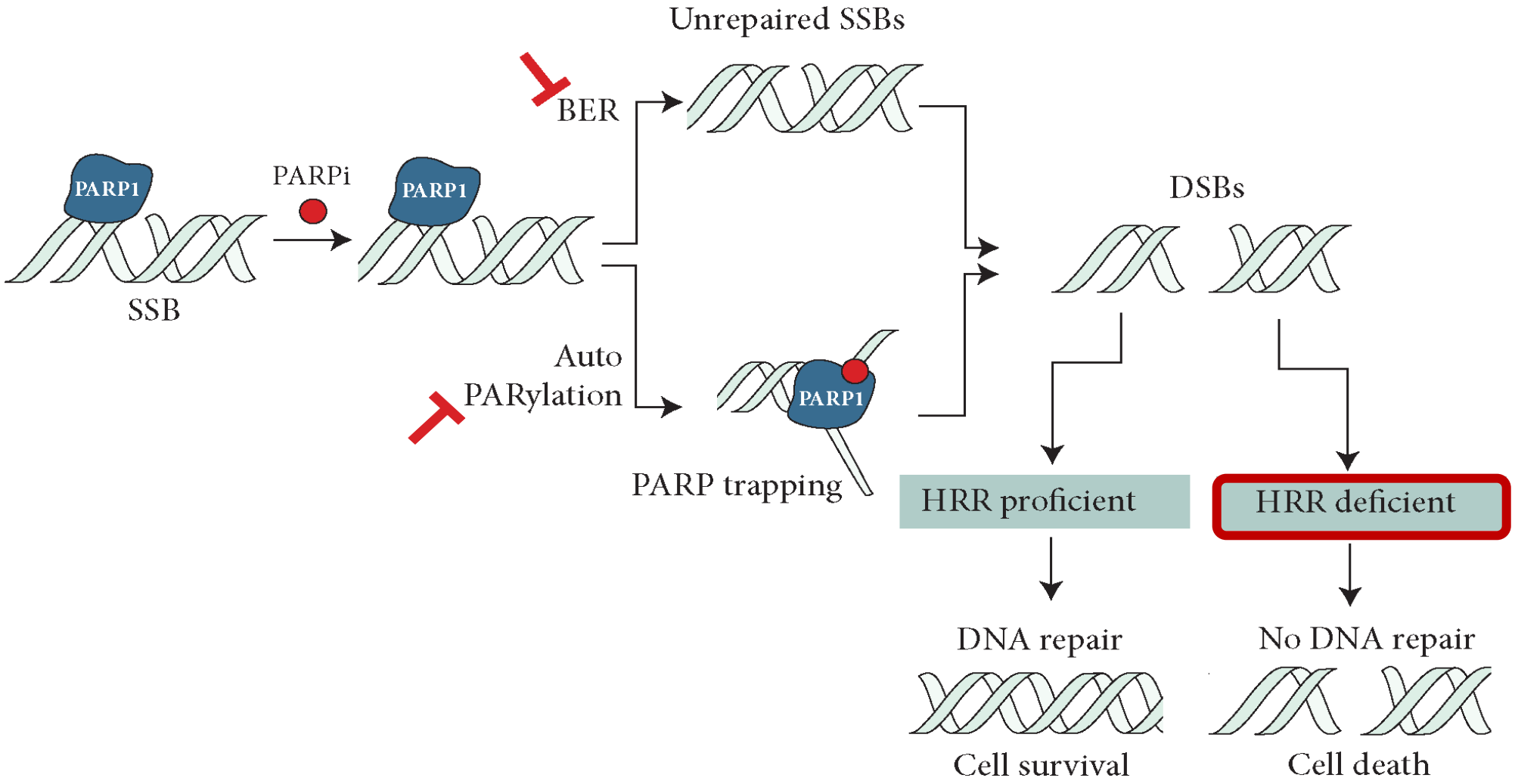
Double strand DNA repair by homologous recombination



RAD51 recombinase forms nucleoprotein filaments that are essential for the homology search and strand exchange

Roy et al NCR 2012

Homologous recombination deficiency as therapeutic target: Mechanism of action of PARPi



Mateo et al Annals of Onc 2019

PARPi in the Adjuvant setting

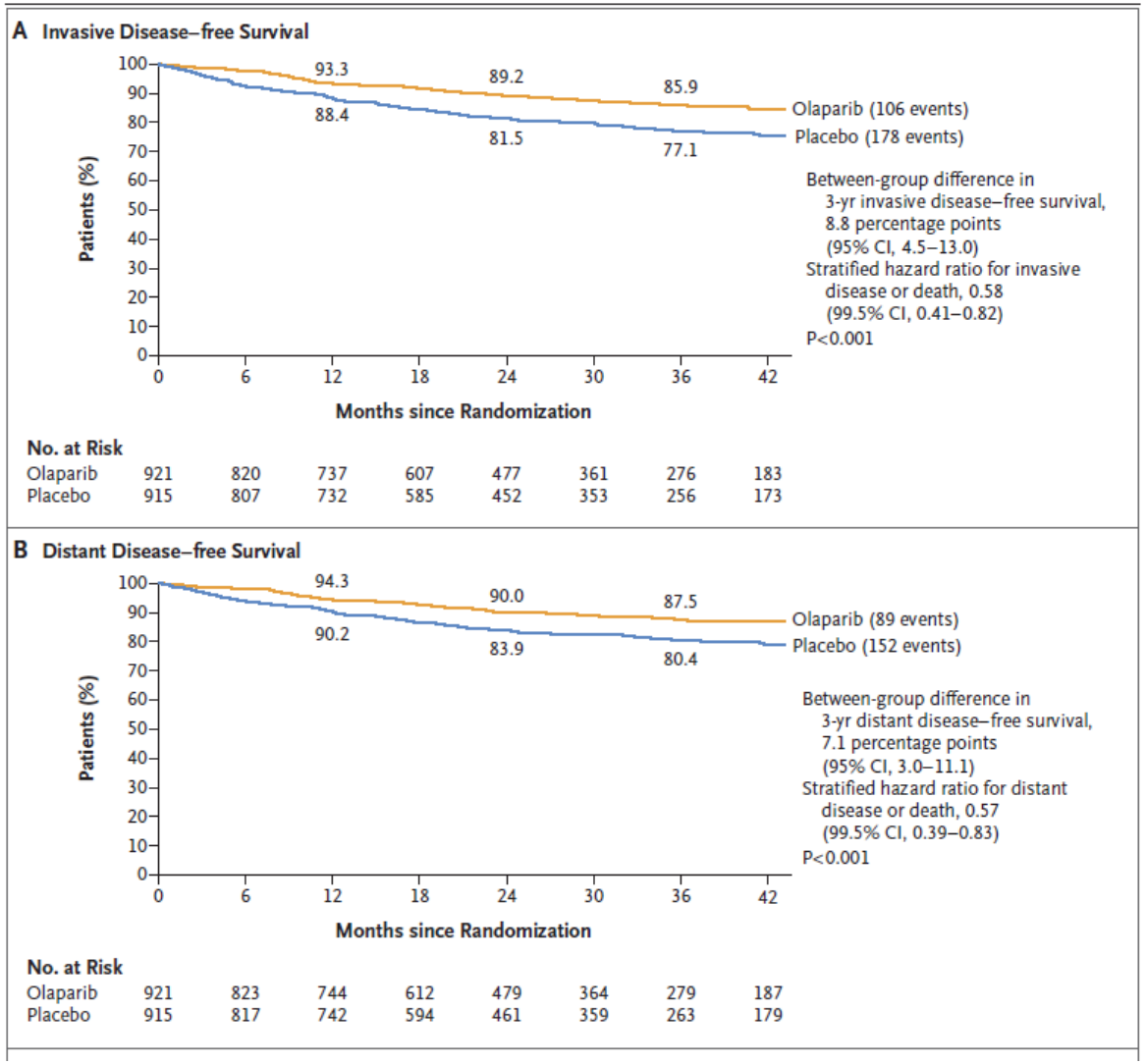
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

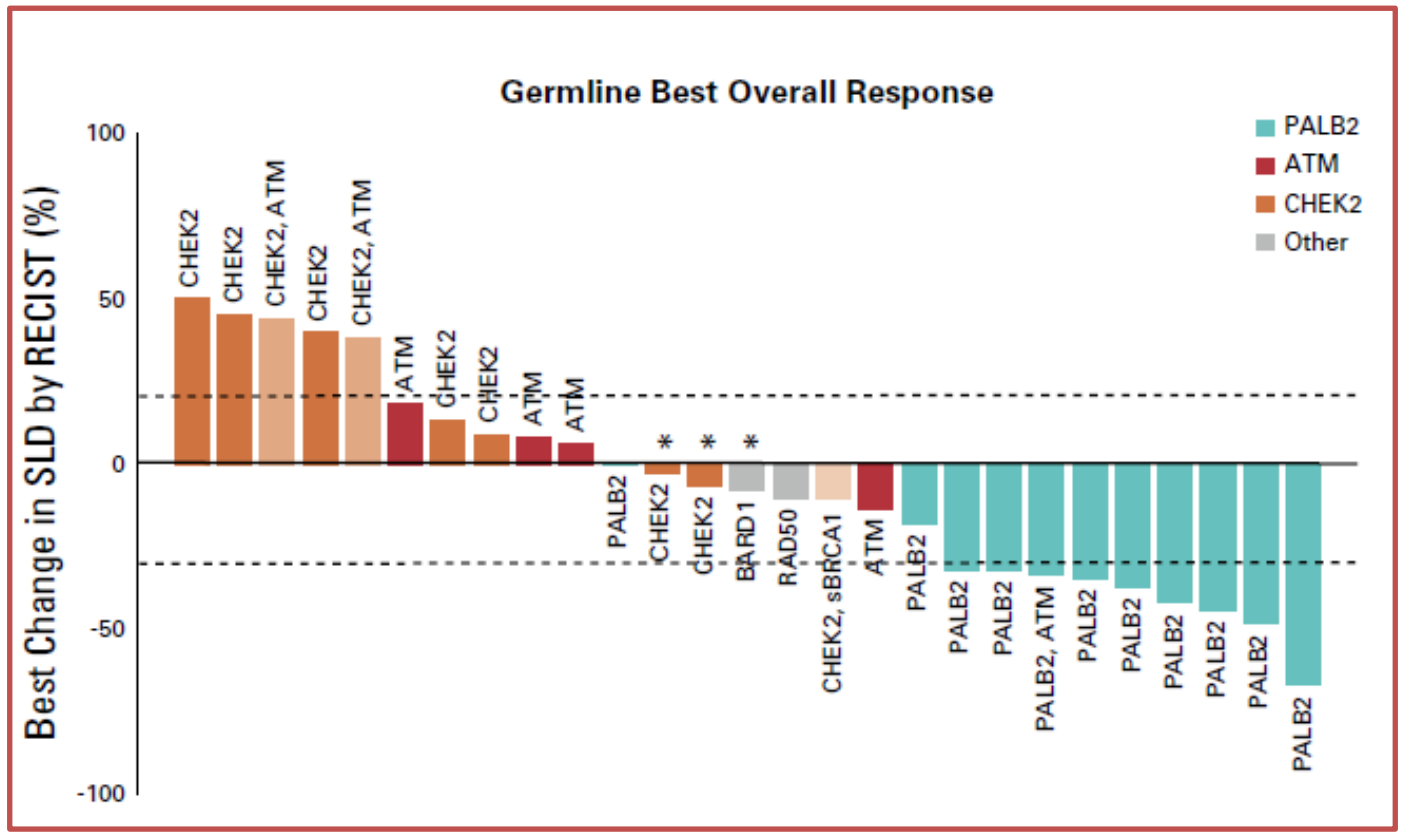
Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

A.N.J. Tutt, J.E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi, R.D. Gelber, E. de Azambuja, A. Fielding, J. Balmaña, S.M. Domchek, K.A. Gelmon, S.J. Hollingsworth, L.A. Korde, B. Linderholm, H. Bandos, E. Senkus, J.M. Suga, Z. Shao, A.W. Pippas, Z. Nowecki, T. Huzarski, P.A. Ganz, P.C. Lucas, N. Baker, S. Loibl, R. McConnell, M. Piccart, R. Schmutzler, G.G. Steger, J.P. Costantino, A. Arahmani, N. Wolmark, E. McFadden, V. Karantza, S.R. Lakhani, G. Yothers, C. Campbell, and C.E. Geyer, Jr., for the OlympiA Clinical Trial Steering Committee and Investigators*

N Engl J Med 2021;384:2394-405.
DOI: 10.1056/NEJMoa2105215



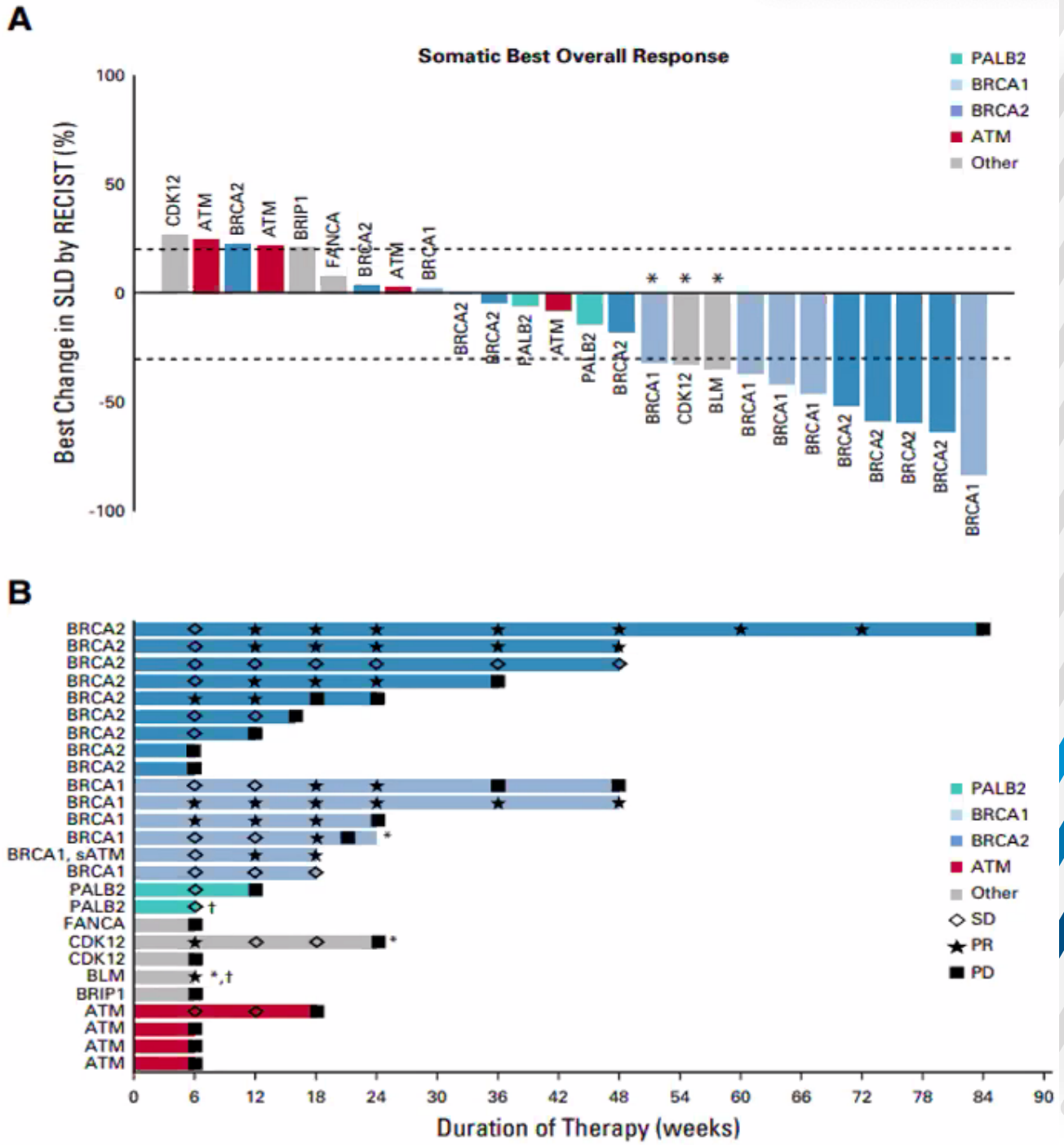
Patients with a germline *PALB2* pathogenic variant respon as good to olaparib as *BRCA*



PALB2 N=13	s*BRCA1/2* N=17^	*ATM & CHEK2*** N=17
Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr Somatic: 0/2 – both SD* (limited assessments)	8/16 PR (50%)	0/13 germline 0/4 somatic

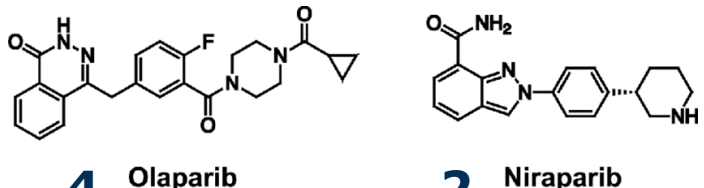
Tung, JCO 2020

And for somatic HRD related genes?



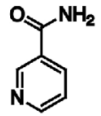
PARP inhibitors in the clinics

Approved PARPi

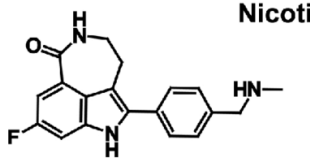


4 Olaparib
AstraZeneca
Approved: 2014

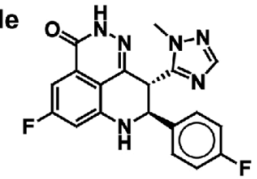
2 Niraparib
Tesaro
Approved: 2018



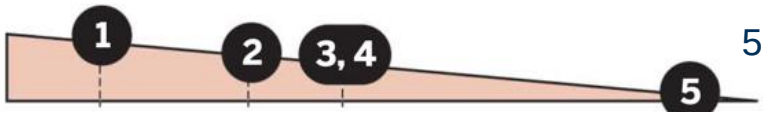
Nicotinamide



3 Rucaparib
Clovis
Approved: 2017

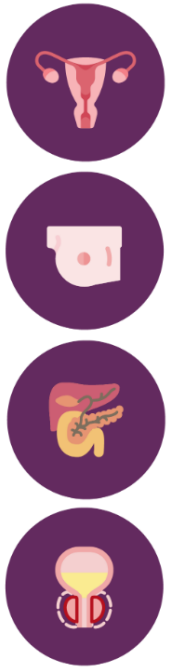


1 Talazoparib
Pfizer
Approved: 2018



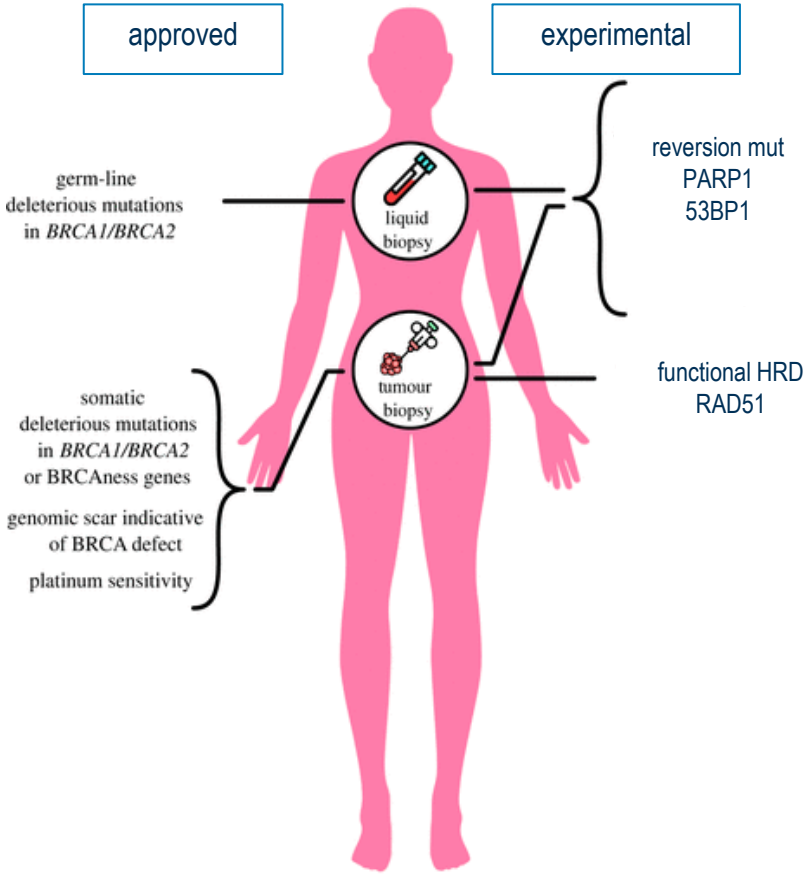
5 Veliparib

Cancer types



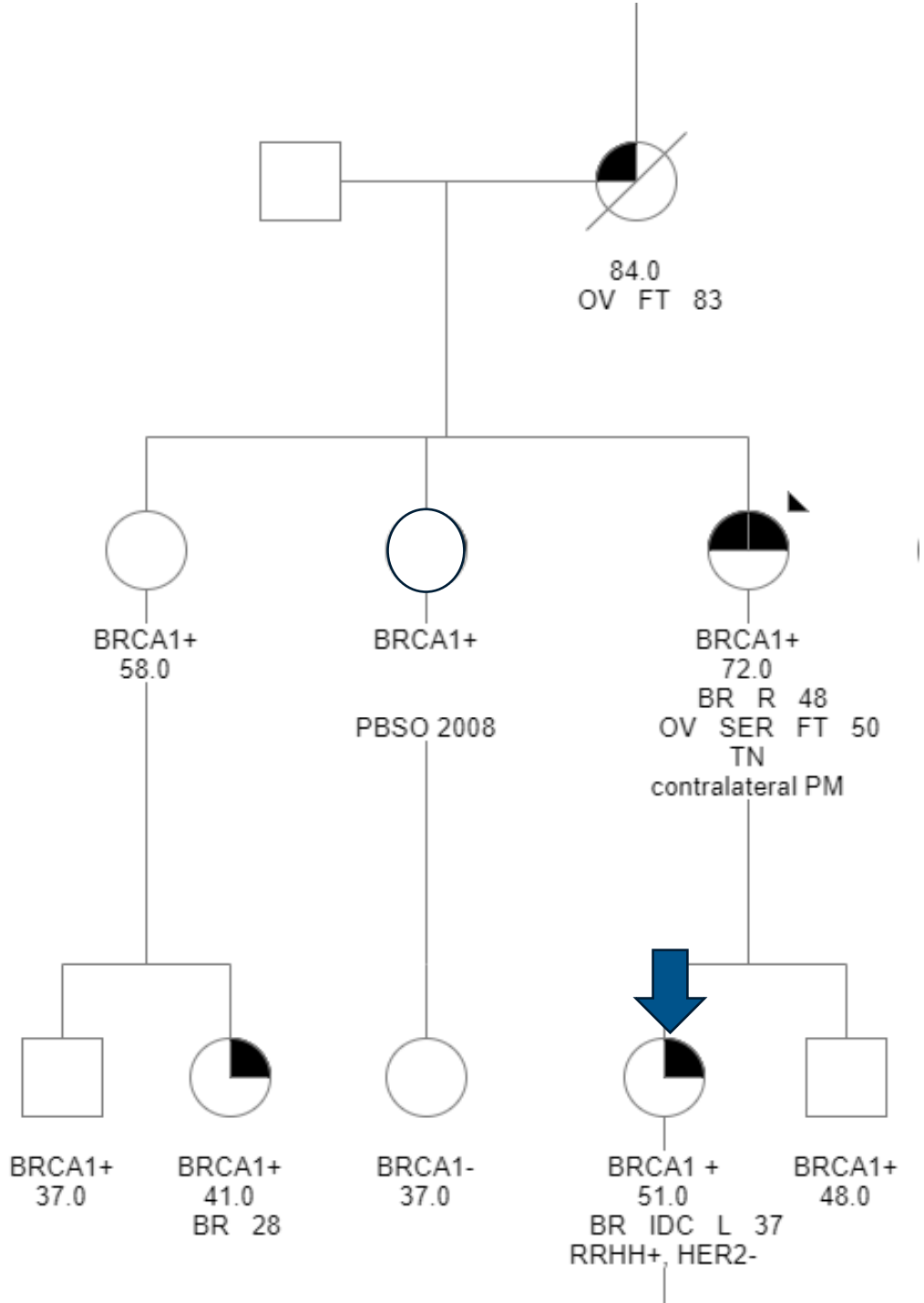
Monotherapy
Maintenance

Biomarkers for PARPi



Spiegel et al, DNA Repair. 2021
Adapted from Lord & Ashworth, Science 2017
Adapted from Wicks et al, Open Biol. 2022

gBRCA1/2, germline BRCA1/2; tBRCA1/2, tumor BRCA1/2; HRR, homologous recombination repair; HRD, homologous recombination deficiency



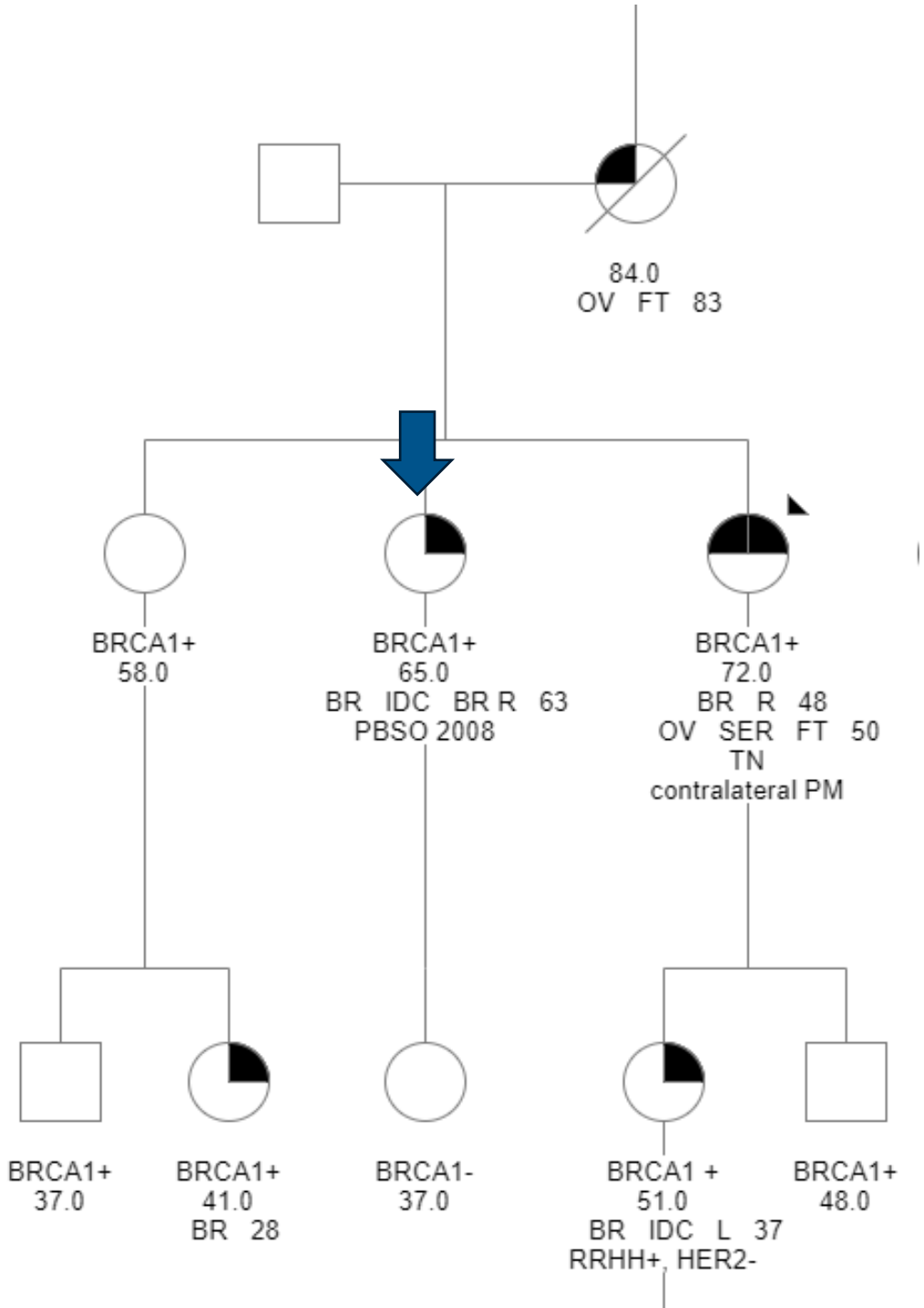
2010: 37 year old, left invasive breast cancer cT2N0M0

Bilateral mastectomy + risk reduction salpyngoophorectomy + breast reconstruction

Adjuvant chemotherapy with anthracyclies and carboplatin + taxane
Aromatase inhibitor x 7 years

Multiple complications: implants, early abrupt menopause, osteoporosis, depression, sensitive neuropathy grade 2, fatigue, thyroid

Discharged in december 2023



4/2023: 63 year old, right breast triple negative breast cancer, cT2N0M0 ki67 85%, TILs>50%

Neoadjuvant therapy within a clinical trial with a PARP inhibitor + immunotherapy

Breast conservative surgery + sentinel lymph node biopsy→ pathological complete response
Adjuvant radiotherapy
Adjuvant PARPi adjuvant x 6 months

No toxicity
No evidence of disease

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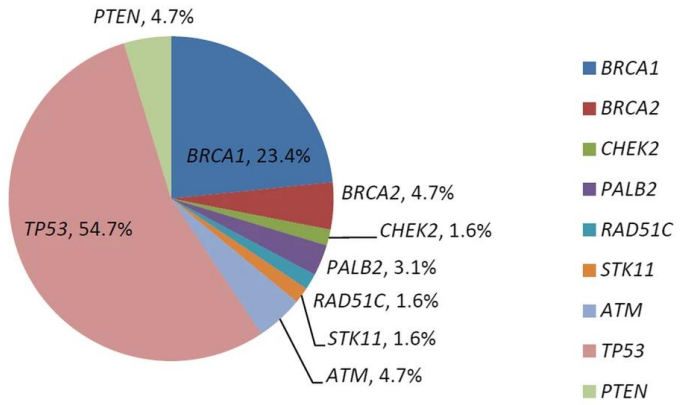
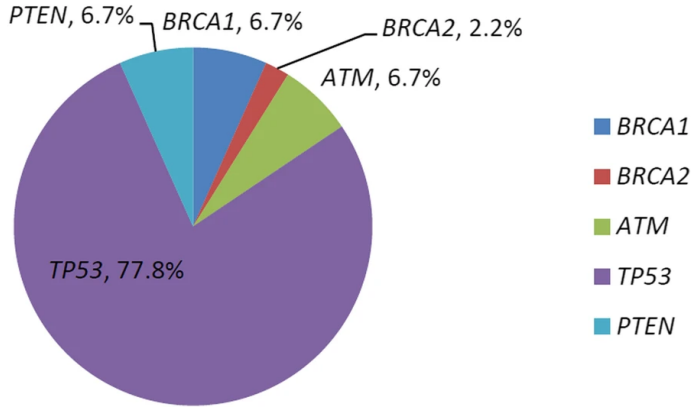
NÚCLEO DE QUITO

DIAGNÓSTICO GENÉTICO: TUMORAL

Somatic *BRCA1/2* mutations, what is the prevalence?



Deleterious mutations germline + somatic
28% BRCA1/2



Somatic mutations

8,9% BRCA1 y BRCA2

Germline and somatic mutations of multi-gene panel in Chinese patients with epithelial ovarian cancer: a prospective cohort study. *Journal of Ovarian Research* **volume 12**, Article number: 80 (2019)

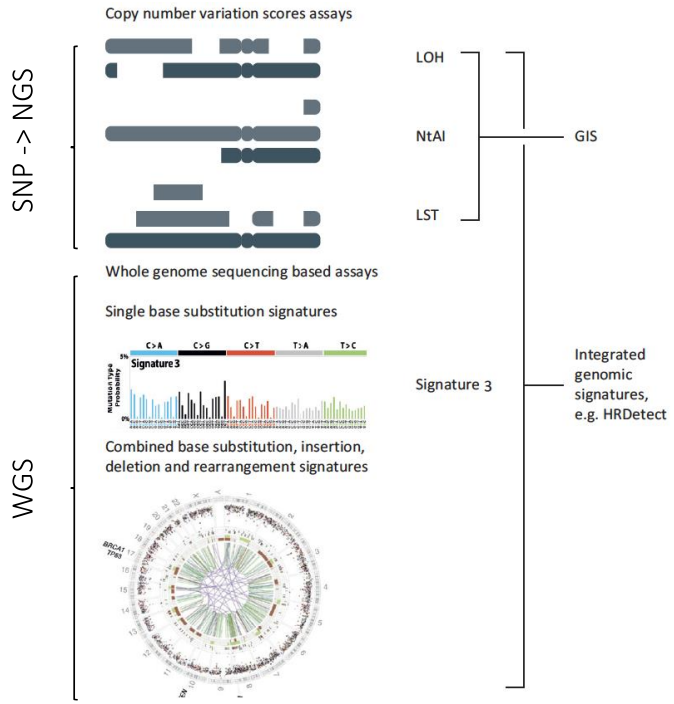
Biomarkers of HRD

Cause of HRD
HRR-gene alterations

BRCA1	*FANCL*
BRCA2	*FANCN/PALB2*
ATM	*BARD1*
RAD51B	*CHEK1*
RAD51C	*CHEK2*
RAD51D	*CDK12*
RAD54L	*PPP2R2A*
FANCJ/BRIP1	

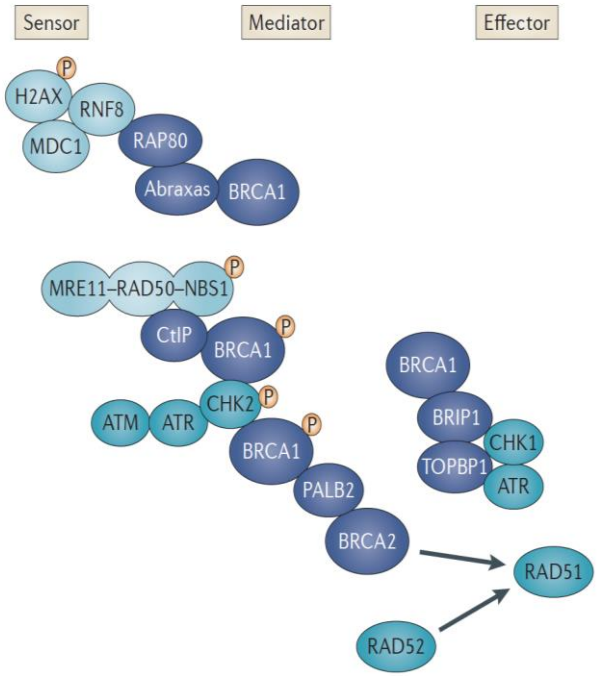
HRR, homologous recombination repair;
SNP (arrays), single nucleotide polymorphism (array);
NGS, next generation sequencing;
WGS, whole genome sequencing

Consequence of HRD
Genomic scars



Static

Current status of HRD
Functional tests



Dynamic

Adapted from Miller et al, Annals of Oncology 2020

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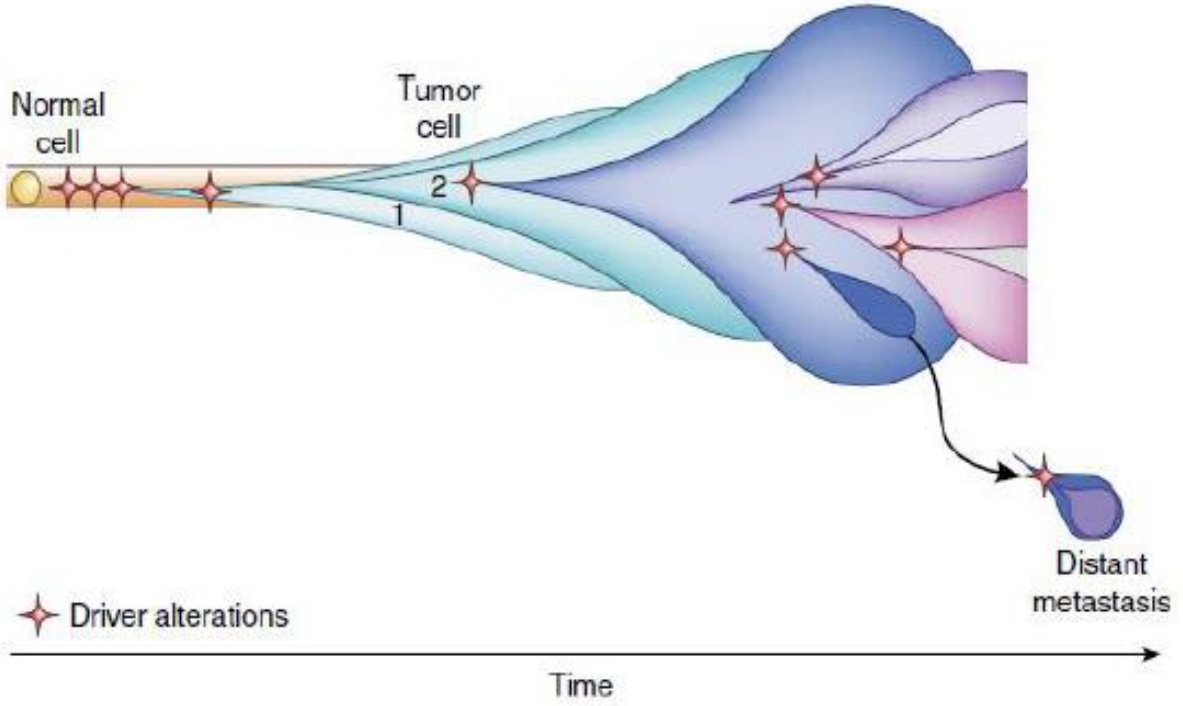
RETOS DEL DIGANÓSTICO GENÉTICO

Análisis de tejido tumoral

-tejido suficiente
-tumor fresco
-DNA fragmentado
-artefactos (C:G>T:A)
-métodos-PCR: amplicones cortos
-pureza celular (microdisección)
-límite de detección
-cobertura, profundidad (500X)
-heterogeneidad intratumoral



Toward understanding and exploiting tumor heterogeneity

VOLUME 21 | NUMBER 8 | AUGUST 2015 NATURE MEDICINE

Ash A Alizadeh[1–3], Victoria Aranda[4], Alberto Bardelli[5,6], Cedric Blanpain[7], Christoph Bock[8,9], Christine Borowski[4], Carlos Caldas[10], Andrea Califano[11–13], Michael Doherty[14], Markus Elsner[15], Manel Esteller[16], Rebecca Fitzgerald[17], Jan O Korbel[18], Peter Lichter[19], Christopher E Mason[20], Nicholas Navin[21,22], Dana Pe'er[11,23], Kornelia Polyak[24], Charles W M Roberts[25], Lillian Siu[26], Alexandra Snyder[27], Hannah Stower[4], Charles Swanton[28–30], Roel G W Verhaak[22,31], Jean C Zenklusen[32], Johannes Zuber[33] & Jessica Zucman-Rossi[34]

Análisis de tejido tumoral

-secuenciación germinal → somática

-variante patogénica identificada = predisposición
" " NO identificada = repetir el estudio tumor

-secuenciación somática → germinal

-variante patogénica identificada = verificar o descartar la variante en línea germinal
" " NO identificada = ausencia de la variante

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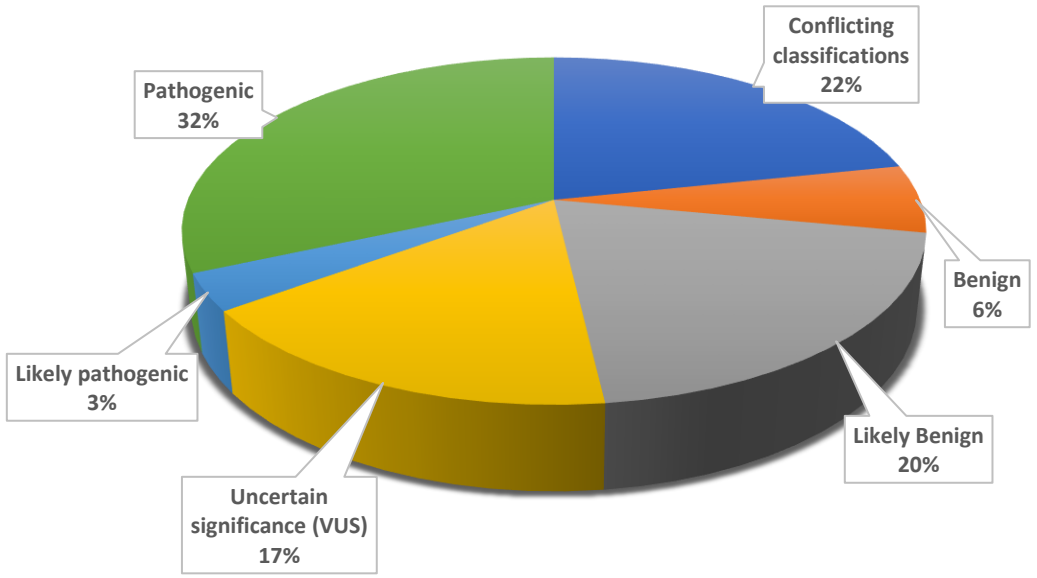
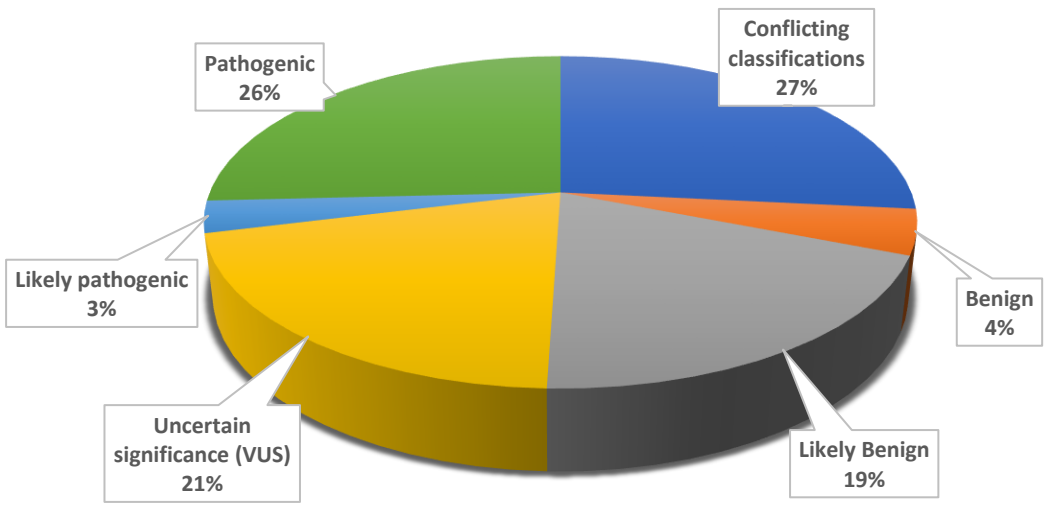
Retos:

VUS variantes con insuficiente información y/o contradictoria

BRCA1



BRCA2



ClinVar (May 12 2024)

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FUTURO DEL DIAGNÓSTICO GENÉTICO

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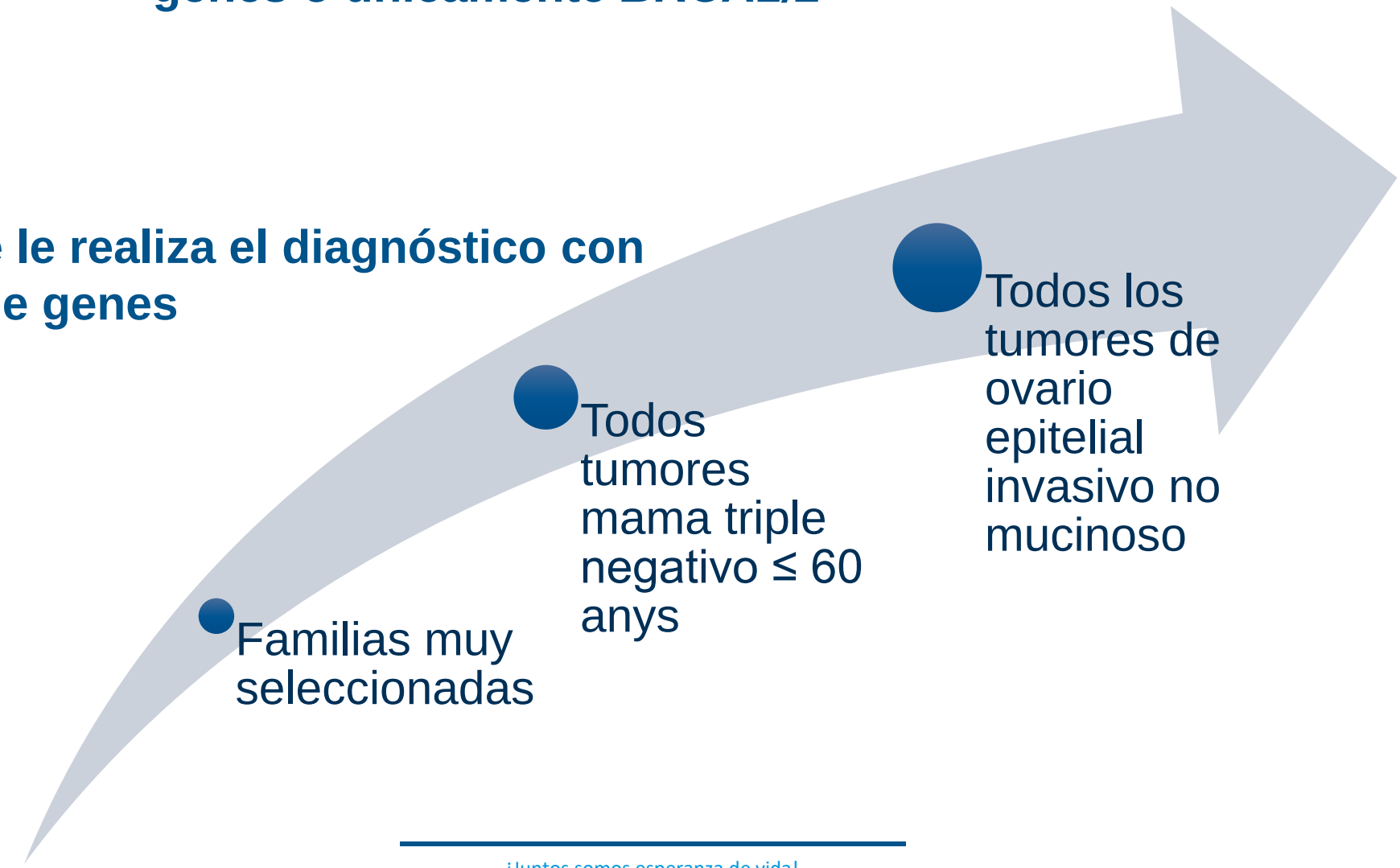
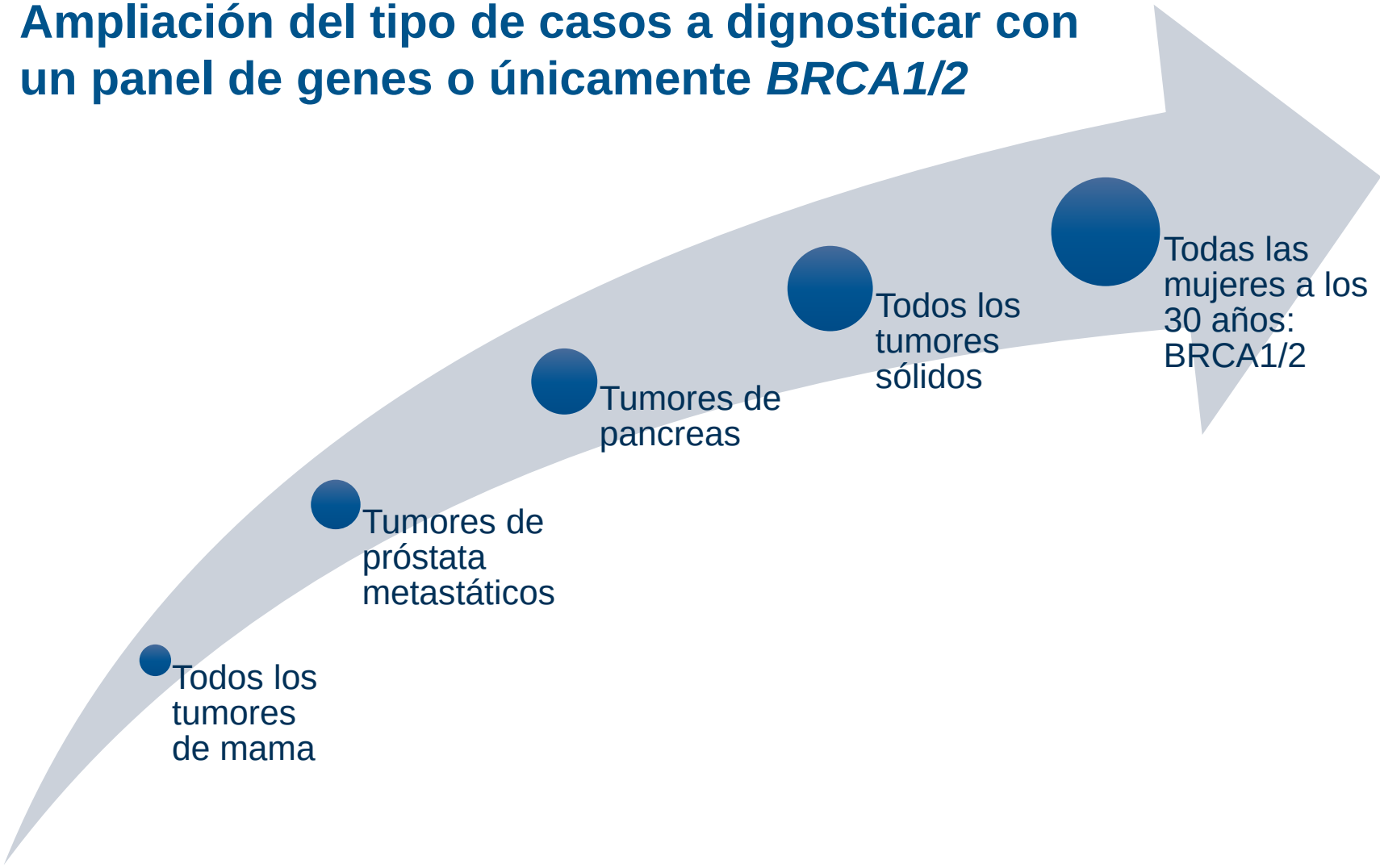
Futuro:
Ampliación del tipo de casos a dignosticar con un panel de genes o únicamente *BRCA1/2*

A quién se le realiza el diagnóstico con un panel de genes



Futuro:
Ampliación del tipo de casos a dignosticar con un panel de genes o únicamente *BRCA1/2*



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NÚCLEO DE QUITO

Futuro

- Evaluación de todas las regiones de los genes, codificantes y no codificantes
- Implementación del diagnóstico genético en DNA y RNA
- Implementación del genotipado en la rutina diagnóstica de los más de 300 alelos para estimación del riesgo poligénico

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NÚCLEO DE QUITO

Conclusiones

- Los genes de alto y moderado riesgo del cáncer de mama hereditario tienen función en reparación de las roturas del DNA
- Combinación de cientos de diferentes cambios genéticos repartidos por el genoma confieren un riesgo bajo de cáncer de mama
- Las variantes de significado incierto no permiten una gestión médica de los portadores
- El descubrimiento de los genes de *BRCA1* y *BRCA2* fue determinante para completar la arquitectura genética del cáncer de mama y el desarrollo de terapia específica para este tipo de tumores

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NÚCLEO DE QUITO

Genetic susceptibility to breast and ovarian cancer

Missing heritability

Genetic diagnosis based on RNA and WGS
Anna Esteve CNAG
Lara Nonell VHIO
Rodrigo Dienstmann VHIO
(ISCIII funding)

New susceptibility genes
Complexo Consortium
Lara Nonell VHIO
(ISCIII funding)

Accurate interpretation and clinical classification of VUS
ENIGMA
Violeta Serra VHIO
Judith Balmaña VHIO
(ISCIII and EraPerMed funding)

Hereditary Cancer Genetics Group
Vall D'Hebron Institute of Oncology, VHIO

Thanks!

Judith Balmaña
Sara Gutiérrez Enríquez
Adrià López
Eduard Pérez
Sara Torres
Adriana Bareas
Estela Carrasco
Mara Cruellas
Maite Torres
Orland Díez
Renan Gomes
Setareh Kompanian
Ester Aguado Flor
Joanna Domènech Vivó
Laia Peralba

Instituto de Salud Carlos III

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