Héritas
Medicina de precisión

CIRCULO MEDICO DE ROSARIO 1910

Curso

Biología molecular aplicada al diagnóstico médico

2021

Clase: Diagnóstico Molecular de Cáncer Hereditario

Círculo Médico de Rosario | Fecha: 26/10/21

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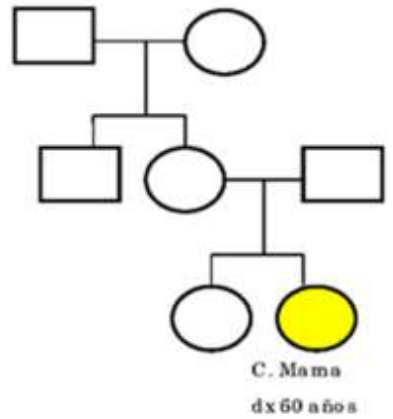
Programa

- **Introducción:**
  - ✓ Cáncer y el genoma
- **Cáncer Hereditario:**
  - ✓ Síndrome de Cáncer Hereditario de Mama y Ovario (SCHMO)
  - ✓ Cáncer Colorrectal (CCR) Hereditario
  - ✓ Asesoramiento Genético
  - ✓ Bioinformática y el análisis de variantes
- **Interpretación y curaduría de variantes germinales en Cáncer:**
  - ✓ Guías utilizadas
  - ✓ El análisis de paneles genéticos
  - ✓ VUS : El elemento sorpresa y la incertidumbre
  - ✓ Ejemplos

Cáncer y el Genoma

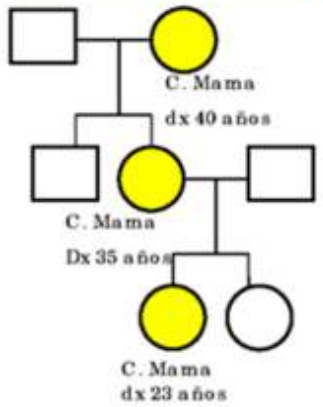
El cáncer es una enfermedad genética pero no específicamente hereditaria

Cáncer esporádico



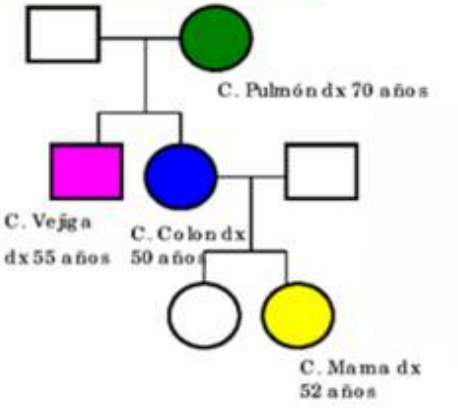
- Único caso en la familia
- Edad de aparición avanzada

Cáncer hereditario



- Múltiples casos del mismo tipo de cáncer
- Herencia vertical: autosómica dominante

Cáncer Familiar



- Varios miembros afectados con múltiples neoplasias en diferentes generaciones

https://www.cancer.org/es/cancer/causas-del-cancer/genetica/sindromes-de-cancer-familiar.html / https://www.cancer.gov/

Cáncer y el Genoma

Genes supresores de tumores

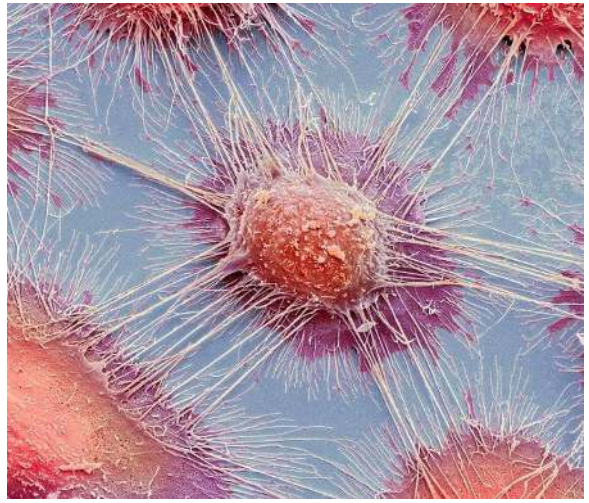
Inactivación, ambos alelos afectados, perdida de función de una proteína

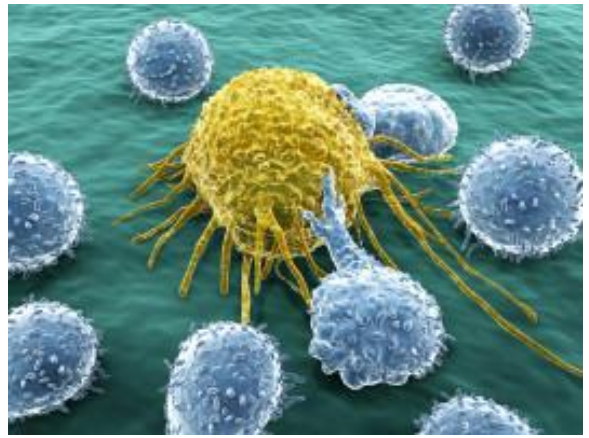
Genes involucrados en la reparación del ADN

Alteración con pérdida de función, aumenta la tasa mutacional

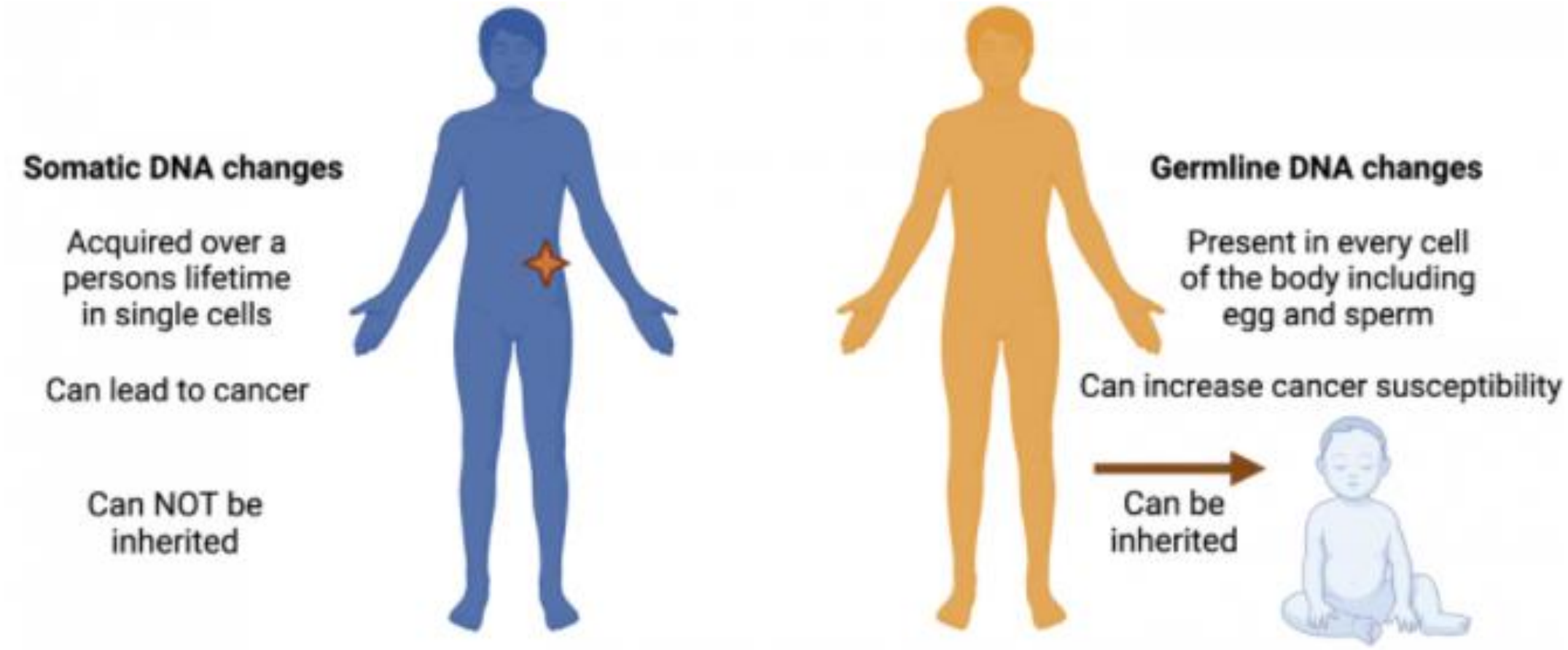
Proto-Oncogenes

Activación, mutación en al menos uno de los dos alelos, ganancia de función en una proteína que señaliza la división

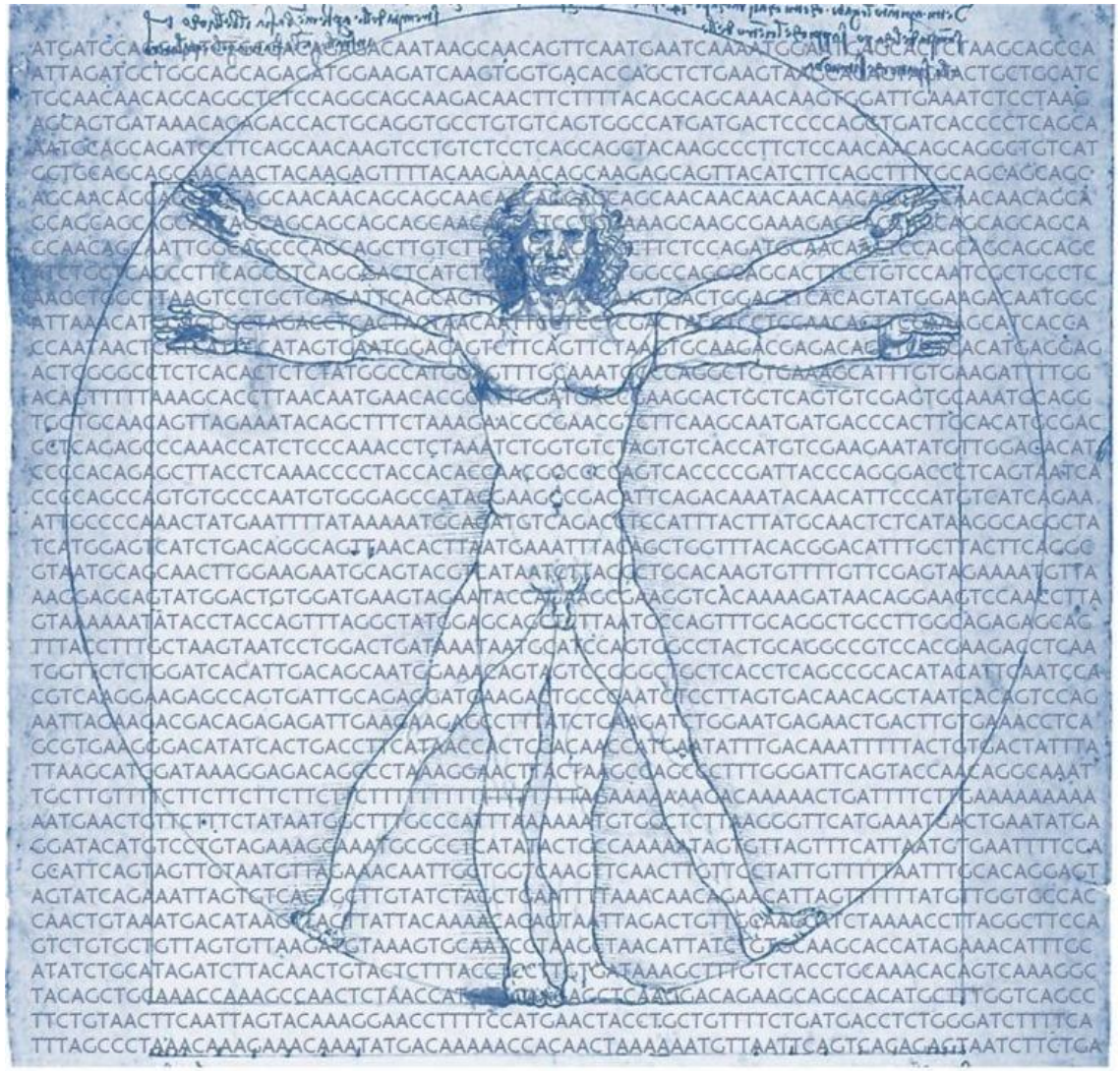




Cáncer y el Genoma

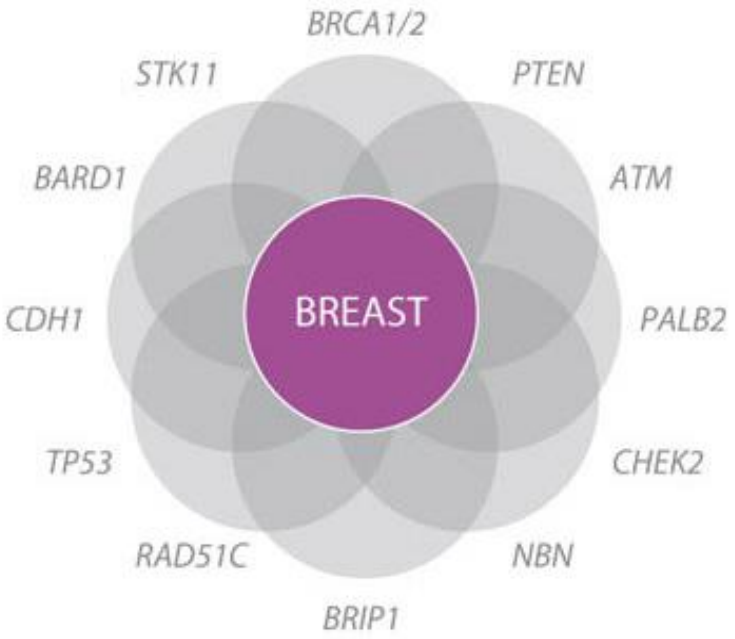


Cáncer y el Genoma

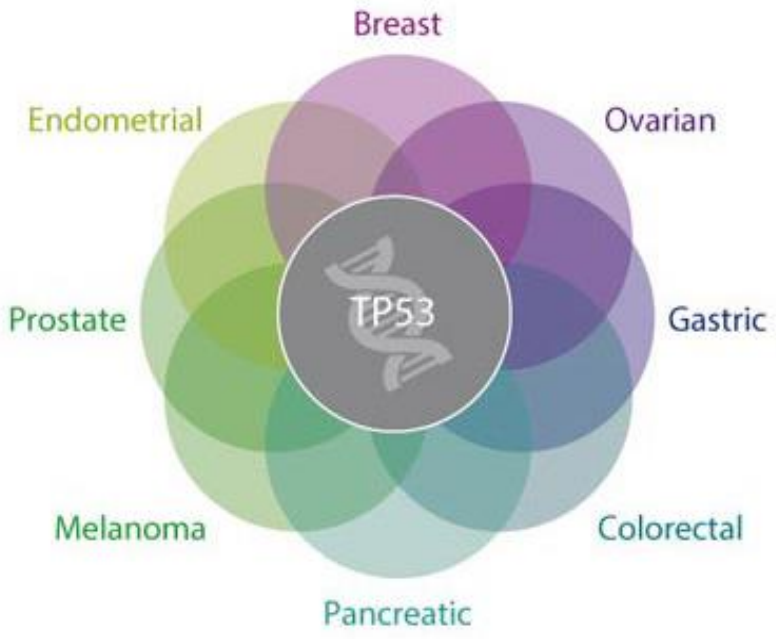


Cáncer y el Genoma

GENETIC OVERLAP



Multiple genes can increase the risk of a single cancer

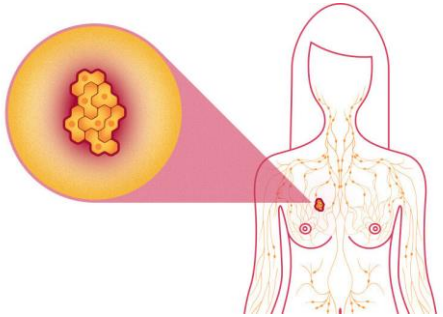


Multiple cancers can be associated with a single gene

Síndrome de Cáncer Hereditario de Mama y Ovario (SCHMO): Introducción

En el mundo

"En 2020, hubo 2,3 millones de mujeres diagnosticadas con cáncer de mama y 685 000 muertes en todo el mundo. A fines de 2020, había 7.8 millones de mujeres vivas a las que se les diagnosticó cáncer de mama en los últimos 5 años, lo que lo convierte en el cáncer más prevalente en el mundo"

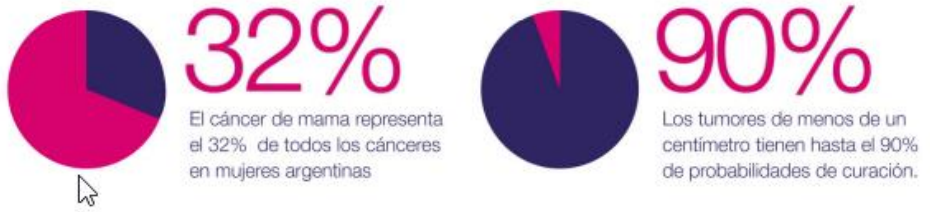


En Argentina

-El cáncer de mama es la primera causa de muerte por tumores en mujeres

-El cáncer de mama causa alrededor de 5600 muertes al año

-Anualmente se producen más de 19000 casos nuevos



https://www.who.int/news-room/fact-sheets/detail/breast-cancer

Síndrome de Cáncer Hereditario de Mama y Ovario (SCHMO) : Molecular

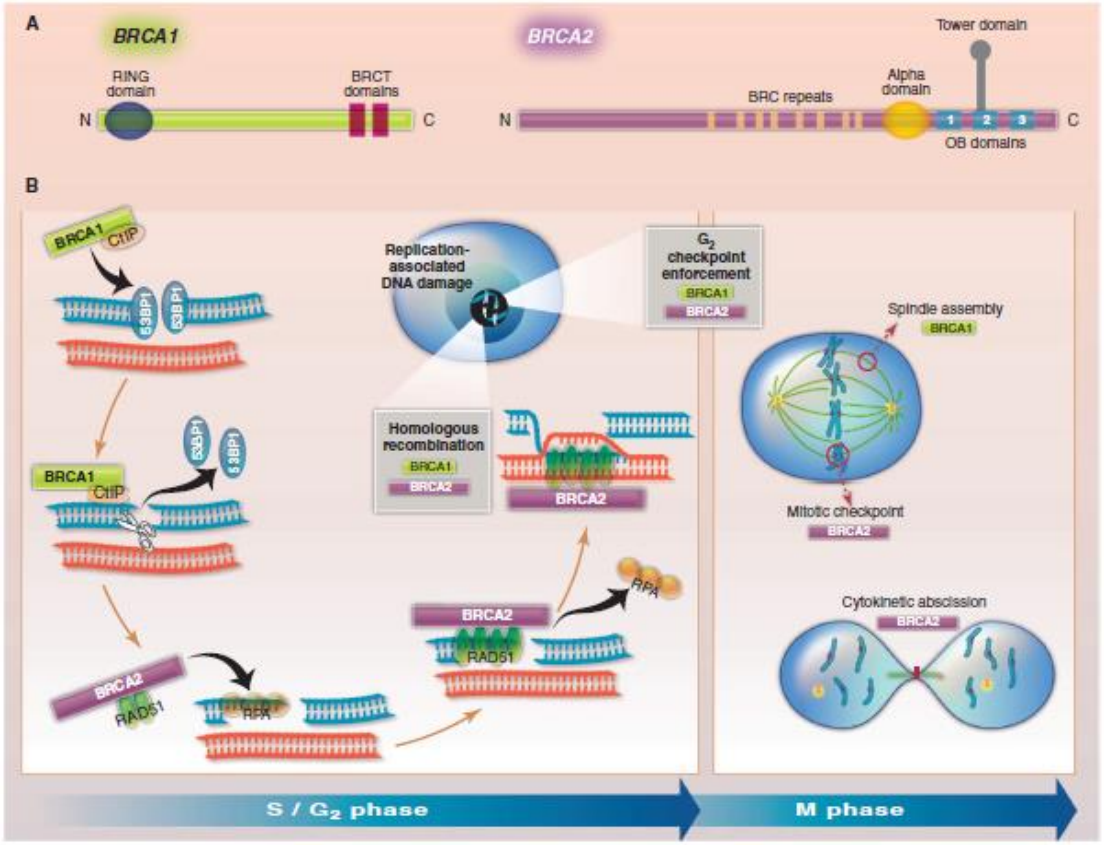
BRCA1/BRCA2

• Codifican para proteínas involucradas en la supresión tumoral

- BRCA1 se encuentra involucrado tanto en la reparación del ADN, como en la regulación de puntos de control del ciclo celular, en respuesta al daño en el ADN

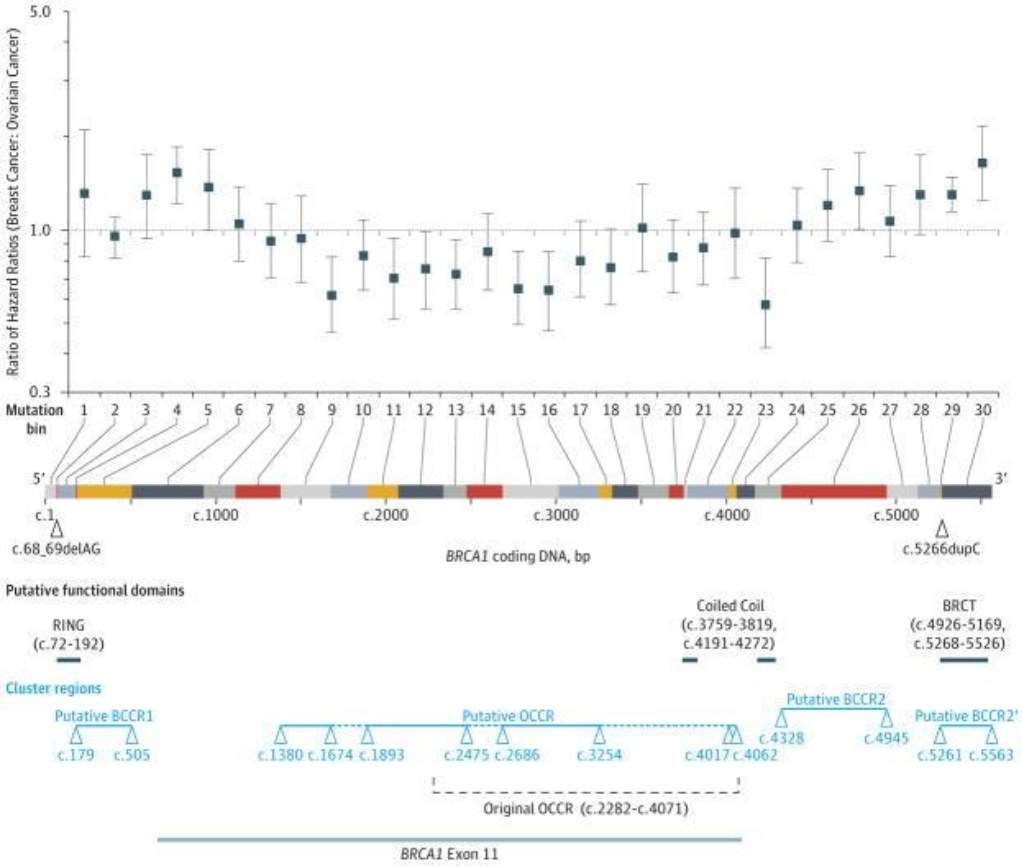
- BRCA2 participa en la reparación de rupturas de ADN doble cadena

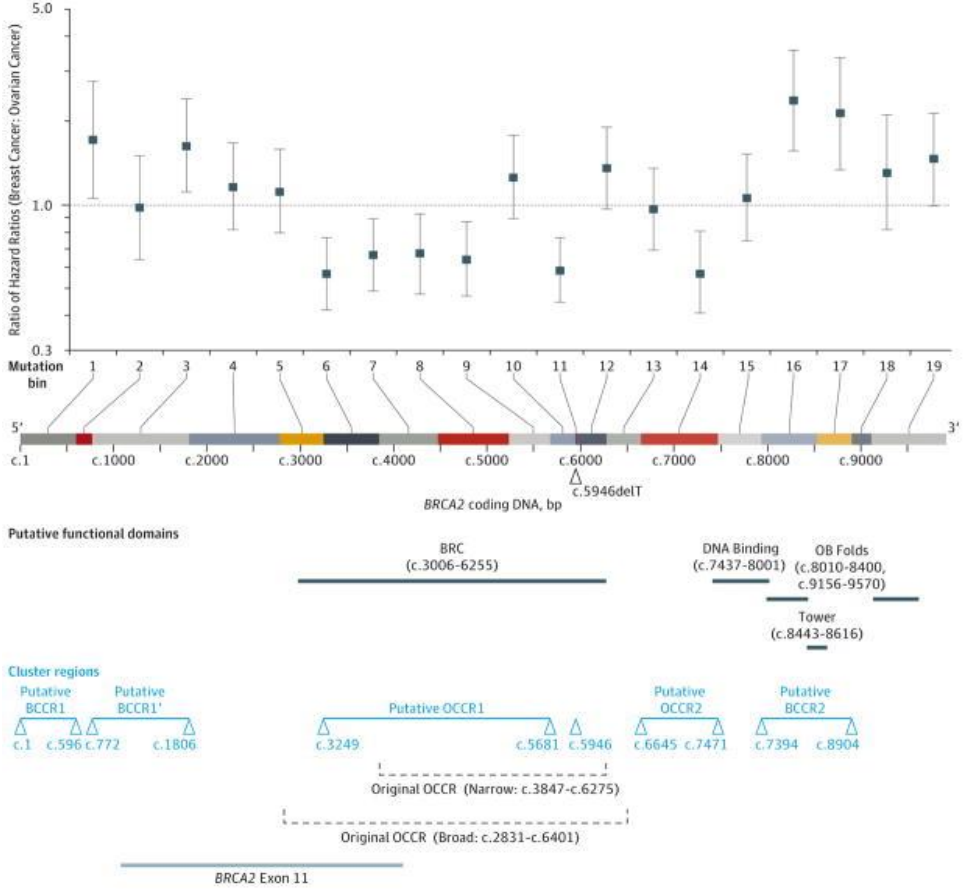
- BRCA1-BRCA2-RAD51: Mantenimiento y estabilidad del genoma



PMID: 24675954

Síndrome de Cáncer Hereditario de Mama y Ovario (SCHMO) : Molecular





Síndrome de Cáncer Hereditario de Mama y Ovario (SCHMO) : Molecular

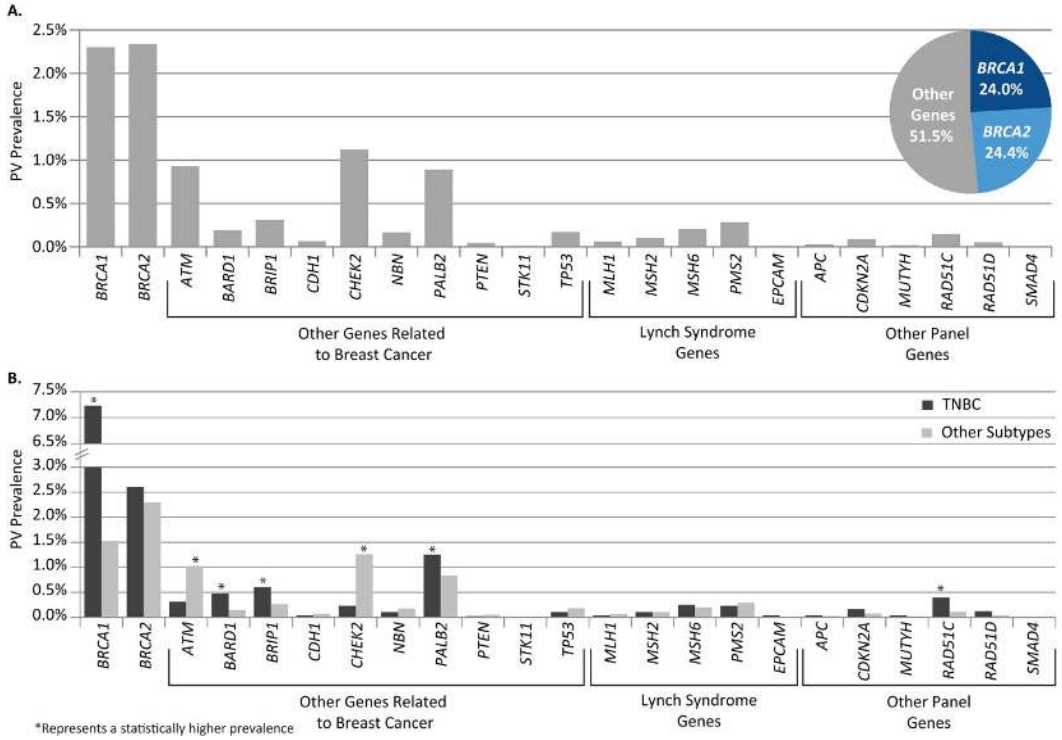
BRCA1/BRCA2

- **Riesgo *BRCA1***: 50-85% de desarrollar cáncer de mama en mujeres; 40-60% de desarrollar cáncer de ovario a los 85 años. Riesgo de otros tipos de cáncer en mujeres y hombres

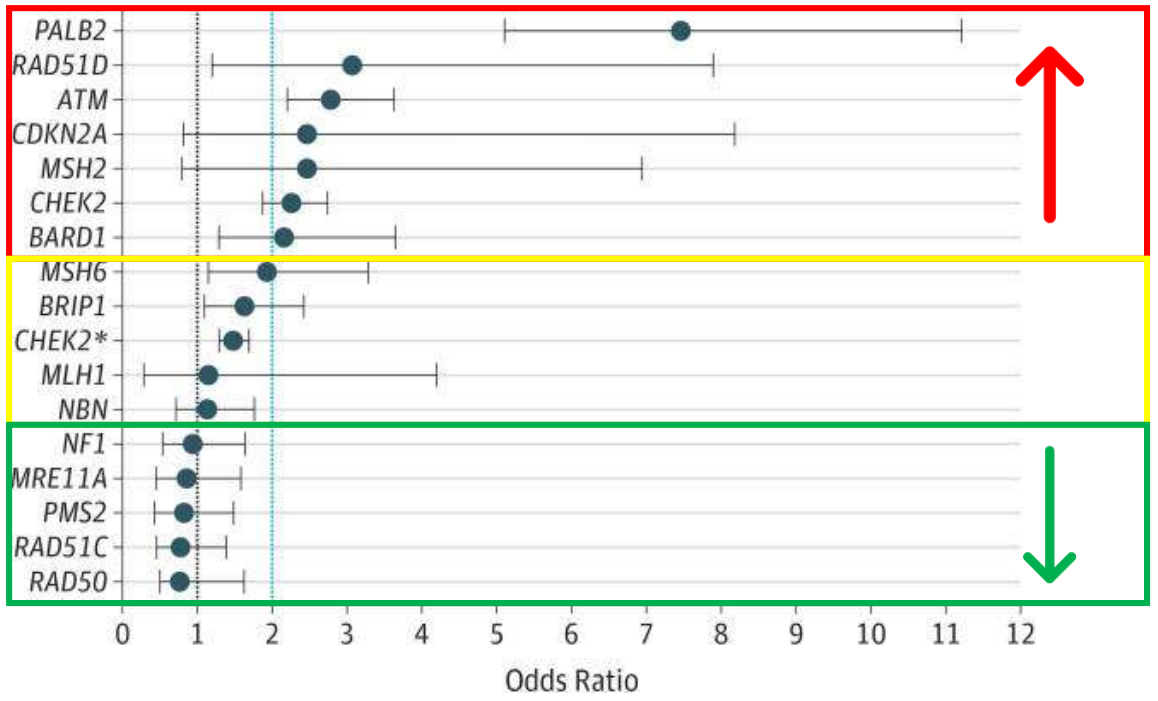
- **Riesgo *BRCA2***: 50-85% de desarrollar cáncer de mama en mujeres; 16-27% de desarrollar cáncer de ovario a edad avanzada. En hombres, riesgo incrementado para cáncer de mama y cáncer de próstata. Mujeres y hombres: riesgo de melanoma y cáncer de páncreas

Síndrome de Cáncer Hereditario de Mama y Ovario (SCHMO) : Molecular

¿OTROS GENES?



35000 pacientes con cáncer de mama
Panel de 25 genes



65057 pacientes
Non BRCA1/2 - Breast Cancer Risk: genes were categorized as high risk (OR > 5.0), moderate risk (OR = 2.0-5.0), or no clinical relevance (OR < 2.0).

Síndrome de Cáncer Hereditario de Mama y Ovario (SCHMO) : Molecular

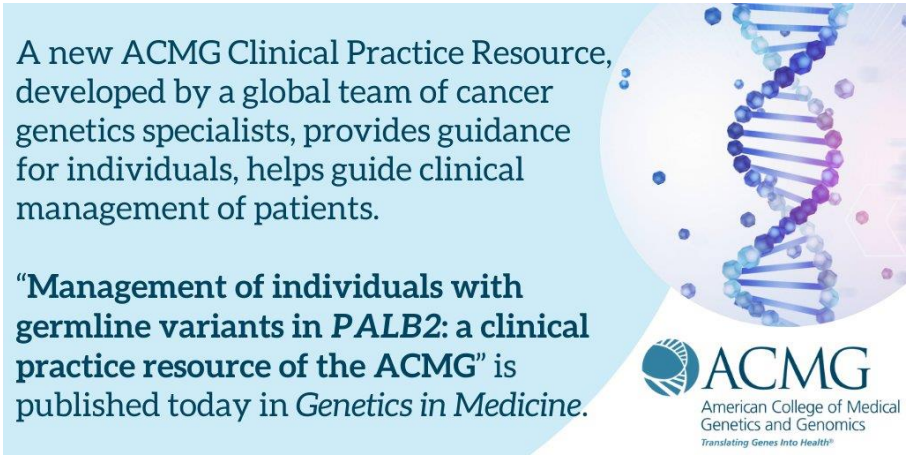
PALB2

- Desempeña un papel fundamental en la reparación por recombinación homóloga (HRR) a través de su capacidad para reclutar BRCA2 y RAD51 a las roturas del ADN

- PALB2 es un importante gen de susceptibilidad al cáncer de y existen importantes asociaciones entre las variantes patogénicas en línea germinal y los cánceres de ovario, páncreas , próstata y mama (femenino/masculino).

- Trabajos sugieren que el riesgo de cáncer de mama para los portadores de variantes patogénicas en PALB2 puede superponerse con el de los portadores de variantes patogénicas en BRCA2

NCCN GUIDELINES



¿Cuándo testear?

National Comprehensive Cancer Network®

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Specifically *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53*. See GENE-A)[a,d,e,f]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - By Age at Diagnosis and Family History
    - ≤45 y
    - 46–50 y with ANY:
      - Unknown or limited family history[g]
      - Multiple primary breast cancers (synchronous or metachronous)
      - ≥1 close blood relative[h] with breast, ovarian, pancreatic, or prostate cancer at any age
    - ≥51 y
      - ≥1 close blood relative[h] with ANY:
        - breast cancer at age ≤50 y or male breast cancer at any age
        - ovarian cancer any age
        - pancreatic cancer any age
        - metastatic,[i] intraductal/cribriform histology, or high- or very-high risk group (see NCCN Guidelines for Prostate Cancer) prostate cancer any age
      - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
      - ≥2 close blood relatives[h] with either breast or prostate cancer (any grade) at any age
    - Any Age
      - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k] (See NCCN Guidelines for Breast Cancer)
      - To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER-2 negative breast cancer[j]
      - Triple-negative breast cancer
      - Lobular breast cancer with personal or family history of diffuse gastric cancer. See NCCN Guidelines for Gastric Cancer
      - Male breast cancer
      - ≥1 close blood relative[g] with male breast cancer
  - By Ancestry
    - Ashkenazi Jewish ancestry
- Family history of cancer only
  - An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[m]
    - If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
  - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[n]

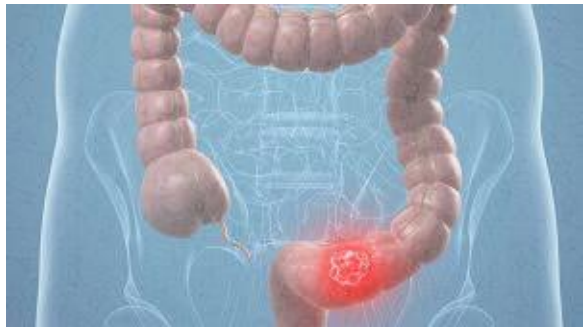
Síndrome de Cáncer Hereditario de Mama y Ovario (SCHMO) : Prevención

Cáncer Colorrectal (CCR) Hereditario: Molecular

CCR

Aproximadamente el 75% de los pacientes con CCR tienen una enfermedad esporádica.

El 10% al 30% restante de los pacientes tienen antecedentes familiares de CCR que sugieren una contribución hereditaria, exposiciones comunes o factores de riesgo compartidos entre los miembros de la familia, o una combinación de ambos.



Generalidades

El CCR hereditario tiene dos formas bien descritas:

- Síndromes polipósicos: poliposis adenomatosa familiar (FAP) y FAP atenuada (AFAP), que son causadas por variantes patogénicas en el gen APC ; y poliposis asociada a MUTYH

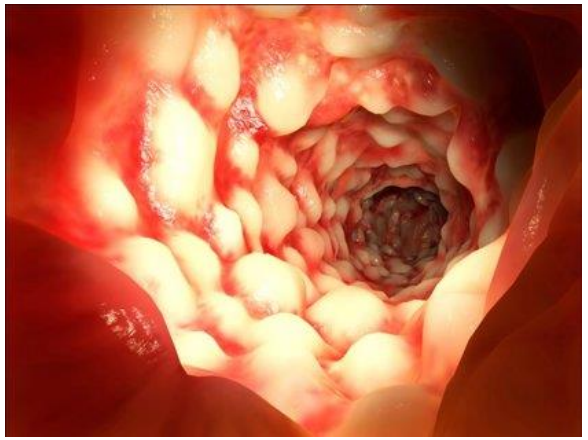
- Síndromes no polipósicos: Síndrome de Lynch, Síndrome POLE/POLD1

Otros síndromes de CCR

Cáncer Colorrectal (CCR) Hereditario: Molecular

El Síndrome de Lynch

Es el síndrome hereditario gastrointestinal más frecuente, responsable del 3-5% de todos los casos de CCR.



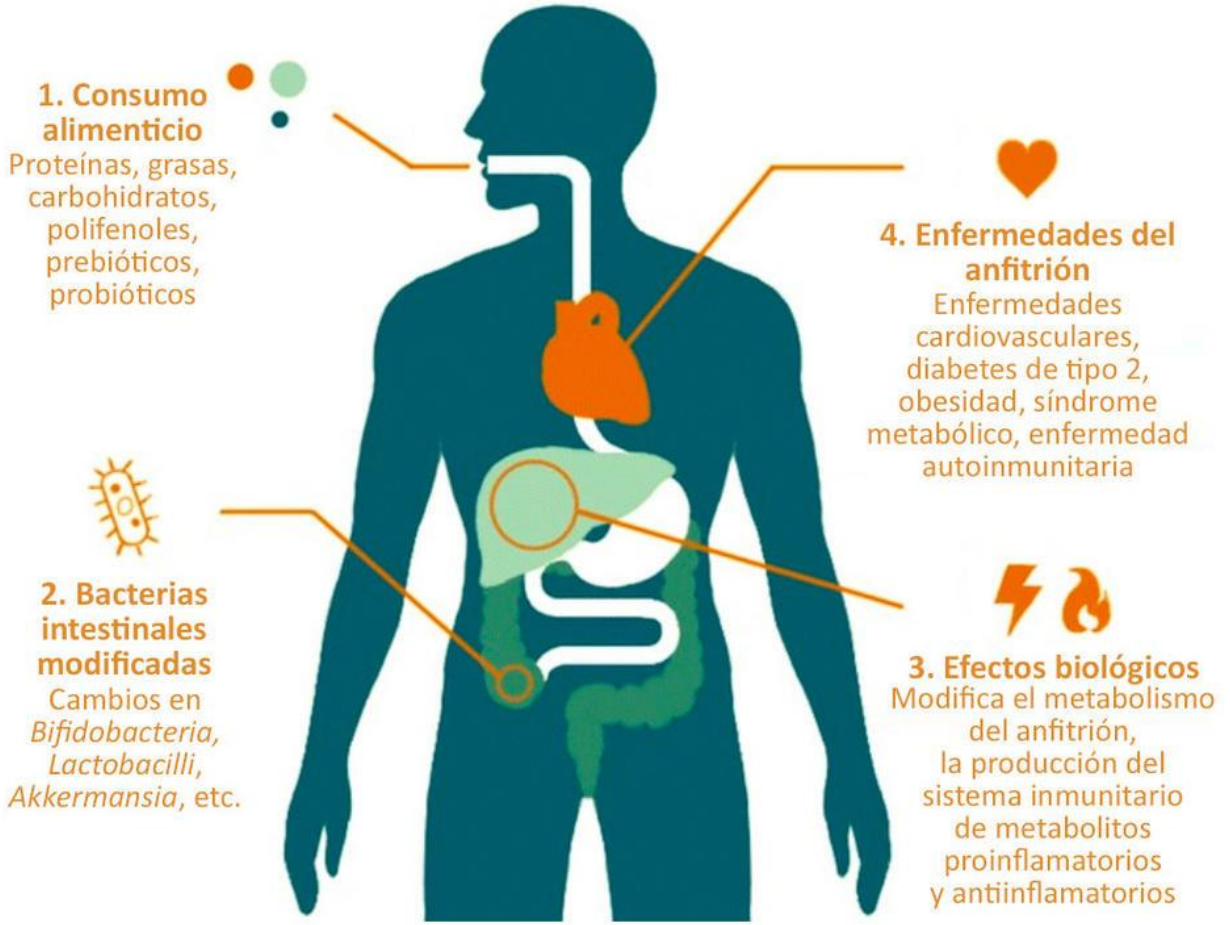
• De herencia autosómica dominante, se encuentra asociado a mutaciones germinales en 1 de los 4 genes implicados en la maquinaria de reparación del ADN: MLH1, MSH2, MSH6, PMS2.

• Deleciones en el gen EPCAM y la hipermetilación del promotor de MLH1.

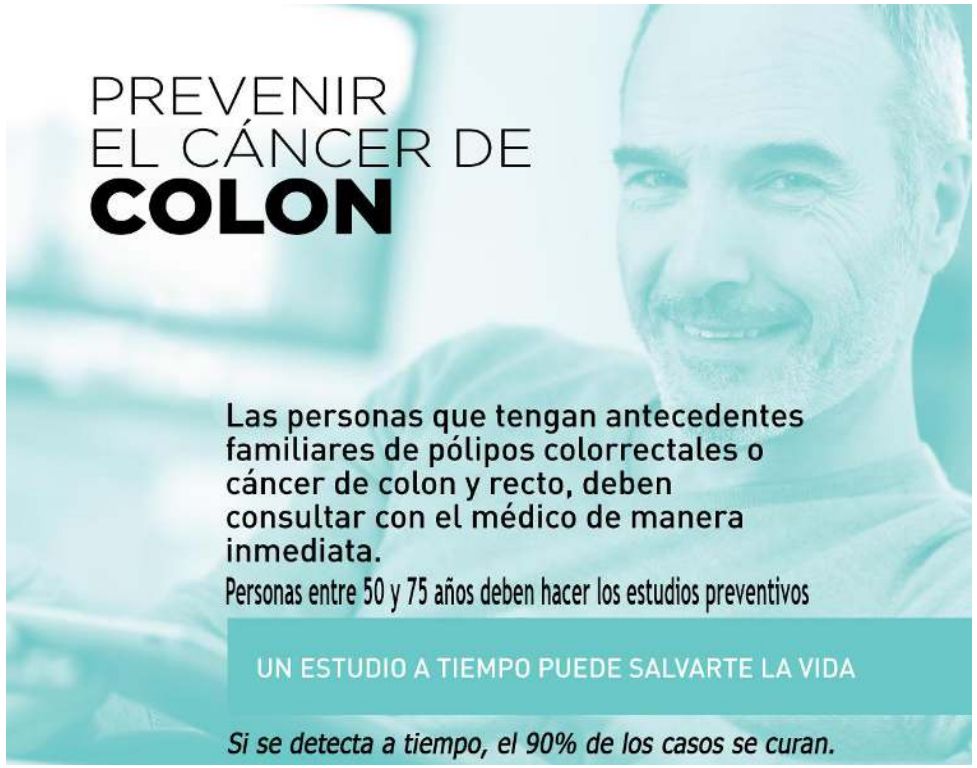
•Riesgo acumulado otros tipos de cáncer: endometrio (60%), ovario o estómago (10-15%), y un riesgo superior al de la población general para desarrollar tumores de las vías urinarias, intestino delgado, vía biliar y páncreas.

• La mayoría de los individuos afectados desconoce que es portador del síndrome.

Cáncer Colorrectal (CCR) Hereditario: Molecular

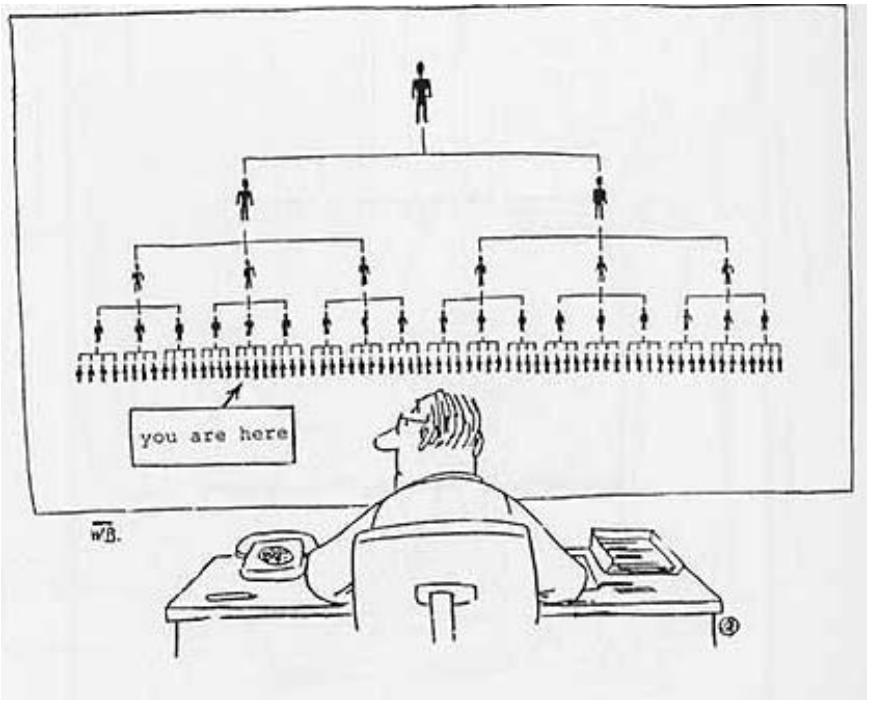


Cáncer Colorrectal (CCR) Hereditario: Introducción



Asesoramiento Genético : La importancia de la historia clínica

"El asesoramiento genético nace de la necesidad de ayudar a los individuos y a las familias con un diagnóstico o con riesgos de una condición genética hereditaria a comprender y adaptarse a las implicancias de los resultados de estudios genéticos, los que pueden determinar un diagnóstico definitivo de un síndrome o una predisposición a desarrollar una condición en el adulto"



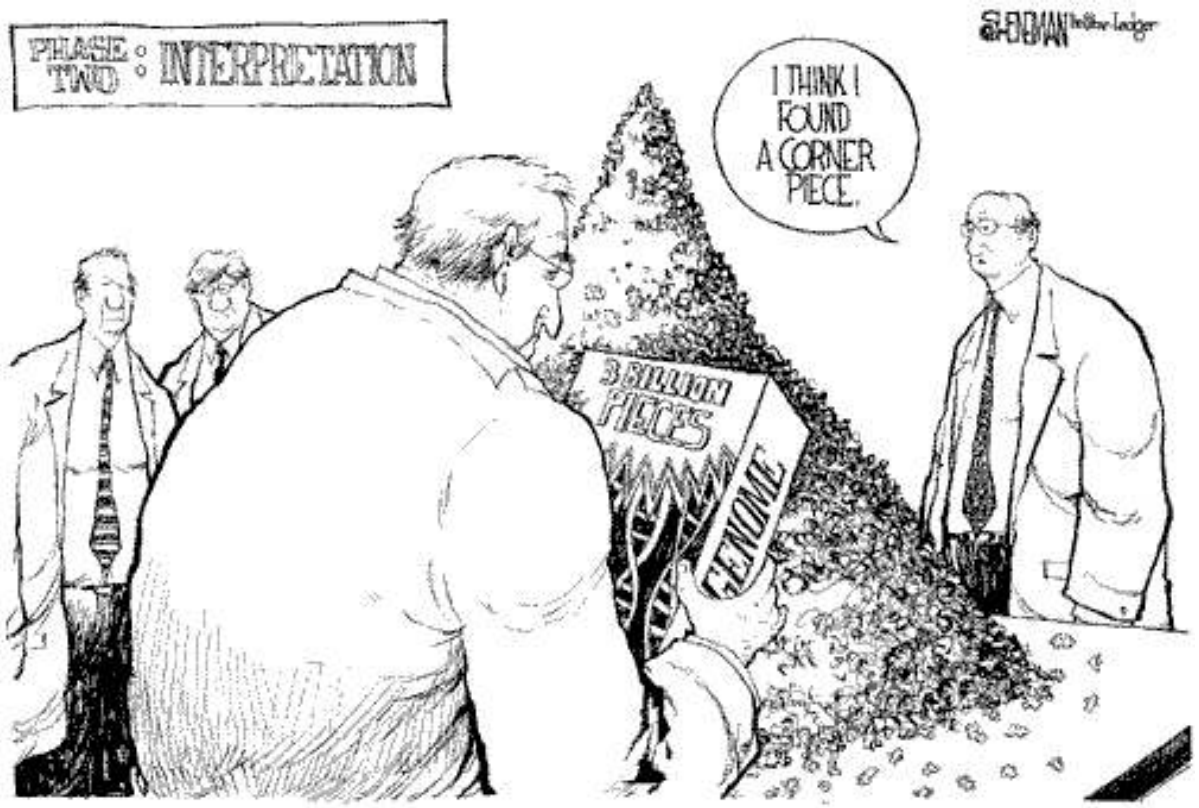
Este proceso integra:

•La interpretación de los antecedentes médicos y familiares para evaluar el riesgo de ocurrencia o de recurrencia de una enfermedad.

•La educación sobre la herencia, pruebas genéticas, manejo, prevención, recursos e investigación.

•El asesoramiento y apoyo psico-emocional para promover decisiones informadas adaptándose de la mejor manera al riesgo o condición genética.

Bioinformática y el análisis de variantes




ONCE YOU UNFOLD ONE OF THESE THINGS, IT'S NEVER THE SAME.
Ethical Questions
MAP OF THE HUMAN GENOME
Medical Dilemmas
Legal Tangles
Privacy concerns
Moral Issues
Insurance Applications

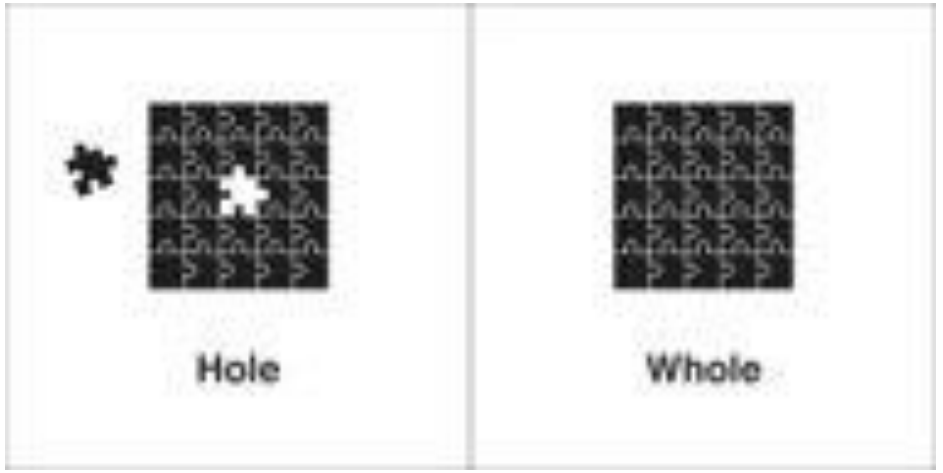
¿Analistas de variantes, curadores de variantes o los Sherlock Holmes del laboratorio?

- Las bases de conocimiento de las variantes y sus modelos asociados desempeñan un papel cada vez más importante en la interpretación de variantes en cáncer.

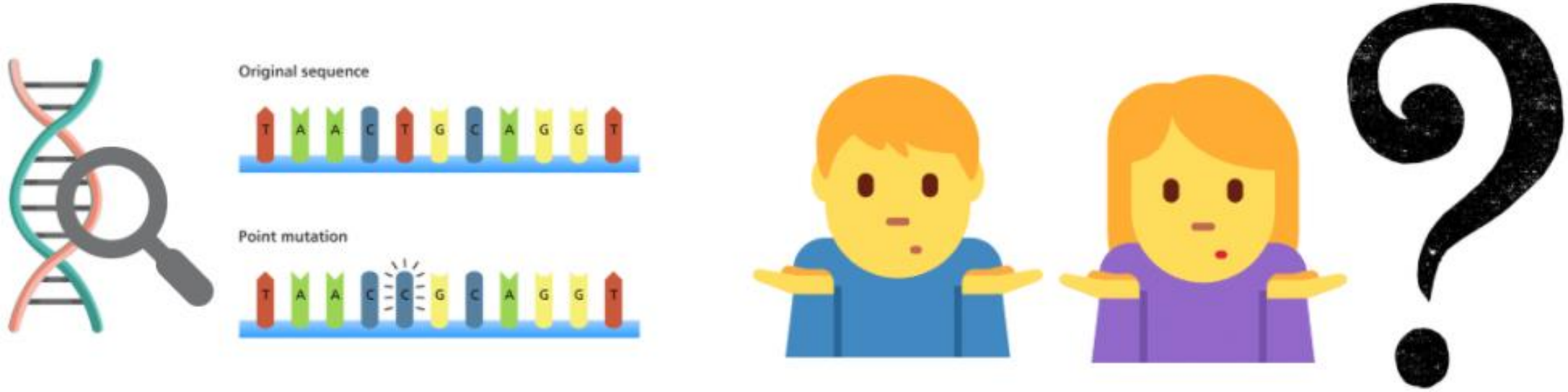
- Estas bases de conocimientos varían en su nivel de accesibilidad pública y la complejidad de los modelos utilizados para capturar el conocimiento clínico y estructural de las variantes.

- Existen paneles de expertos que determinan como y con que severidad aplicar las reglas establecidas a cada gen

- Las variantes seleccionadas por los paneles de expertos en curación de variantes como el caso de *ClinGen* han sido reconocidas por la FDA como una fuente de evidencia científica válida que puede respaldar la validez clínica.



Interpretación de variantes germinales en cáncer



y ahora qué?

Interpretación y curaduría de variantes germinales en cáncer

ACMG/AMP (2015)

Guideline > Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5.

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

Sue Richards [1], Nazneen Aziz [2], Sherri Bale [3], David Bick [4], Soma Das [5], Julie Gastier-Foster [6], Wayne W Grody [7], Madhuri Hegde [8], Elaine Lyon [9], Elaine Spector [10], Karl Voelkerding [9], Heidi L Rehm [11], ACMG Laboratory Quality Assurance Committee

Affiliations + expand

PMID: 25741868 PMCID: PMC4544753 DOI: 10.1038/gim.2015.30

Free PMC article

Pathogenic criteria

Rule		Specification type	Rule description
VS	PVS1	Removed	Null variant in gene with established LOF as disease mechanism
Strong	PS1	No change	Different nucleotide change (same amino acid) as a previously established pathogenic variant
	PS2	Disease/gene	De novo (paternity confirmed) in a patient with disease and no family history
	PS3	Disease/gene	Functional studies of mammalian knock-in models supportive of a damaging effect on the gene or gene product
	PS4	Disease/gene	Prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls - OR - Variant identified in ≥15 probands with consistent phenotypes
	PP1_Strong	Modif. strength	Variant segregates with ≥7 meioses
Moderate	PM1	Disease/gene	Hotspot/est. functional domain (amino acids 181–937) without benign variation
	PM2	Disease/gene	Absent/extremely rare (<0.004%) from large population studies
	PM3	Removed	Detected in *trans* with a pathogenic variant (recessive)
	PM4	No change	Protein length changes due to in-frame deletions/insertions of any size in a nonrepeat region or stop-loss variants
	PM5	No change	Missense change at an amino acid residue where a different missense change previously established as pathogenic
	PM6	Disease/gene	Confirmed de novo without confirmation of paternity
	PVS1_Moderate	Modif. strength	Null variant in gene with evidence supporting LOF as disease mechanism
	PS4_Moderate	Modif. strength	Variant identified in ≥6 probands with consistent phenotypes
	PP1_Moderate	Modif. strength	Variant segregates in ≥5 meioses
Supporting	PP1	Disease/gene	Variant segregates in ≥3 meioses
	PP2	Removed	Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease
	PP3	No change	Multiple lines of computational evidence support a deleterious effect on the gene or gene product
	PP4	Removed	Phenotype specific for disease with single genetic etiology
	PP5	Removed	Reputable source reports as pathogenic
	PS4_Supporting	Modif. strength	Variant identified in ≥2 probands with consistent phenotypes

Benign criteria

Rule		Specification type	Rule description
SA	BA1	Disease/gene	Allele frequency is ≥0.1% based on the filtering allele frequency in ExAC
Strong	BS1	Disease/gene	Allele frequency is ≥0.02% based on the filtering allele frequency in ExAC provided there is no conflicting information
	BS2	Removed	Observed in healthy adult with full penetrance expected at an early age
	BS3	No change	Functional studies of mammalian knock-in models supportive of no damaging effect on protein function or splicing
	BS4	Disease/gene	Nonsegregation in affected members of a family
Supporting	BP1	Removed	Missense variant in gene where only LOF causes disease
	BP2	Disease/gene	Observed as comp het (in *trans*) or double het in genes with overlapping function (e.g., sarcomere genes) without increased disease severity or observed in *cis* with a pathogenic variant in any inheritance pattern
	BP3	Removed	In-frame deletions/insertions in a repetitive region without a known function
	BP4	No change	Multiple lines of computational evidence suggest no impact on gene or gene product
	BP5	Disease/gene	Variant found in a case with an alternate molecular basis for disease
	BP6	Removed	Reputable source reports as benign
	BP7	No change	A silent variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site -AND- the nucleotide is not highly conserved

ACMG/AMP, American College of Medical Genetics and Genomics/Association for Molecular Pathology; LOF, loss of function; Modif. strength, modified rule strength; Removed, not applicable to *MYH7*-associated disease; SA, standalone; VS, very strong.

ACMG
American College of Medical Genetics and Genomics

Interpretación y curaduría de variantes germinales en cáncer

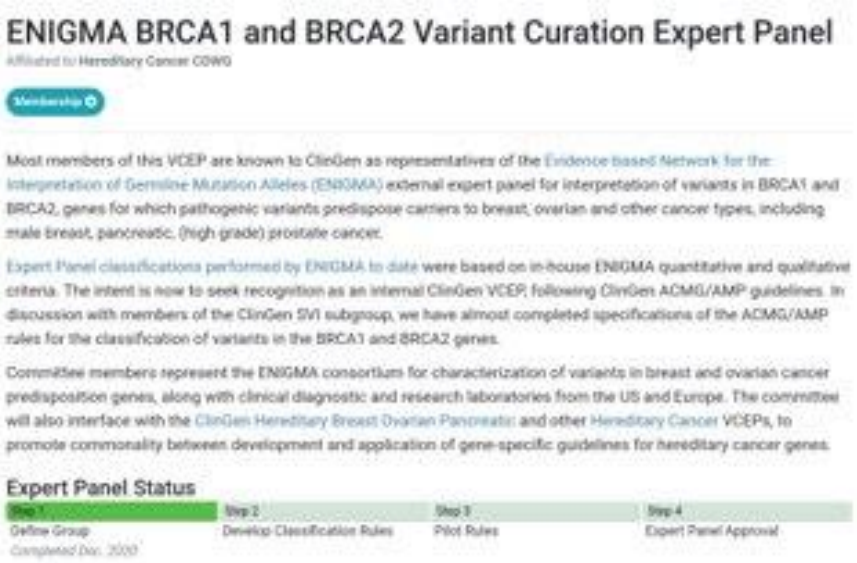
ACMG/AMP (2015)

	Benign		Pathogenic			
	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			

Interpretación y curaduría de variantes germinales en cáncer

CLINGEN (2013)
National Institutes of Health (NIH)

Evidence based Network for the Interpretation of Germline Mutant Alleles y International Societ
y for Gastrointestinal Hereditary


ENIGMA BRCA1 and BRCA2 Variant Curation Expert Panel

Most members of this VCEP are known to ClinGen as representatives of the Evidence based Network for the Interpretation of Germline Mutation Alleles (ENIGMA) external expert panel for interpretation of variants in BRCA1 and BRCA2, genes for which pathogenic variants predispose carriers to breast, ovarian and other cancer types, including male breast, pancreatic, (high grade) prostate cancer.

Expert Panel classifications performed by ENIGMA to date were based on in-house ENIGMA quantitative and qualitative criteria. The intent is now to seek recognition as an internal ClinGen VCEP, following ClinGen ACMG/AMP guidelines. In discussion with members of the ClinGen SVI subgroup, we have almost completed specifications of the ACMG/AMP rules for the classification of variants in the BRCA1 and BRCA2 genes.

Committee members represent the ENIGMA consortium for characterization of variants in breast and ovarian cancer predisposition genes, along with clinical diagnostic and research laboratories from the US and Europe. The committee will also interface with the ClinGen Hereditary Breast Ovarian Pancreatic and other Hereditary Cancer VCEPs, to promote commonality between development and application of gene-specific guidelines for hereditary cancer genes.

Expert Panel Status

Step 1	Step 2	Step 3	Step 4
Define Group	Develop Classification Rules	Pilot Rules	Expert Panel Approval


A Collaborative Effort to Define Classification Criteria for *ATM* Variants in Hereditary Cancer Patients

Recommendations for application of the functional evidence PS3/BS3 criterion using the ACMG/AMP sequence variant interpretation framework


ClinGen TP53 Variant Curation Expert Panel Guidelines Finalized

Subscribe

New classification guidelines for germline variants of the tumor suppressor gene *TP53* were published online in Human Mutation in March 2021. Inherited variants in *TP53* are the cause of the cancer predisposition syndrome known as Li-Fraumeni Syndrome (LFS).

The rule specifications, developed by the ClinGen *TP53* Variant Curation Expert Panel (VCEP), follow the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) guidelines for germline variant classification. The updated TP53-specific classification guidelines provide critical information for the health care providers engaged in clinical management of LFS patients as well as those who receive genetic testing results that indicate an alteration in *TP53* that

Interpretación y curaduría de variantes germinales en cáncer

CANVIG/CANVAR (2017)

Clinical Scientists, Cancer Genetics, and the Cancer Variant Interpretation Group (CanVIG)

GenQA Genomics Quality Assessment
Member of UK NEQAS consortium

ICR The Institute of Cancer Research

CANCER RESEARCH UK

CanGene CanVar

Data Resources, Clinical and Educational Tools

to leverage Cancer Susceptibility Genetics for

Early Detection and Prevention of Cancer

HDI healthdatainsight

UNIVERSITY OF CAMBRIDGE

UNIVERSITY OF OXFORD

MANCHESTER 1824

UNIVERSITY OF Southampton

St George's University of London

CanVIG-UK Consensus Specification for Cancer Susceptibility Genes ACGS Best Practice Guidelines for Variant Classification (v2.12)

NEW DOCUMENT
CanVIG-UK Consensus Specification for Cancer Susceptibility Genes
Approved: 22nd June 2021

Current Version

CanVIG-UK Gene Specific Recommendations: BRCA1/BRCA2

NEW GUIDANCE
Version 1.10
CanVIG-UK gene specific recommendations for BRCA1/BRCA2 variants.
Approved: 23rd June 2021

CanVIG-UK Gene Specific Recommendations: TP53

NEW GUIDANCE
Version 1.30
CanVIG-UK gene specific recommendations for TP53 variants.
Approved: 23rd June 2021

Interpretación y curaduría de variantes germinales en cáncer

ACGS (2017)

The Association for Clinical Genomic Science

Genomics Quality Assessment

Member of UK NEQAS consortium

ACGS

Association for Clinical Genomic Science

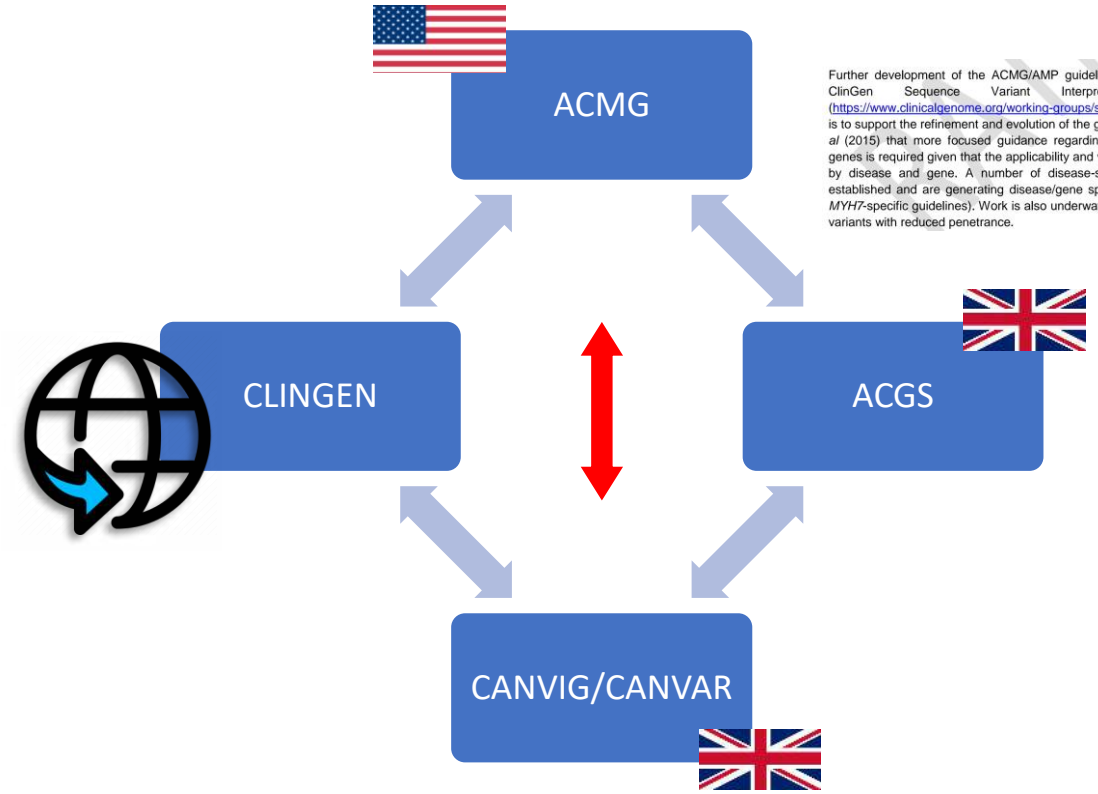
ACGS Best Practice Guidelines for Variant Classification 2019

Sian Ellard[1,2], Emma L Baple[2,3,4], Ian Berry[5], Natalie Forrester[6], Clare Turnbull[4], Martina Owens[1], Diana M Eccles[7], Stephen Abbs[8], Richard Scott[4,9], Zandra C Deans[10], Tracy Lester[11], Jo Campbell[12], William G Newman[13,14] and Dominic J McMullan[15]

1. Department of Molecular Genetics, Royal Devon & Exeter NHS Foundation Trust, Exeter, EX2 5DW, UK.
2. University of Exeter Medical School, Exeter, EX2 5DW, UK.
3. Department of Clinical Genetics, Royal Devon & Exeter NHS Foundation Trust, Exeter, EX2 5DW, UK.
4. Genomics England, William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ, UK
5. Leeds Genetics Laboratory, St James's University Hospital, Leeds LS9 7TF, UK.
6. Bristol Genetics Laboratory, North Bristol NHS Trust, Bristol BS10 5NB, UK.
7. Wessex Clinical Genetics Service, University Hospital Southampton, Southampton SO16 5YA, UK.
8. East Anglian Medical Genetics Service, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.
9. Department of Clinical Genetics, Great Ormond Street Hospital for Children NHS Foundation Trust, London, WC1N 3JH, UK.
10. UK NEQAS for Molecular Genetics, Department of Laboratory Medicine, Royal infirmary of Edinburgh, Edinburgh EH16 4SA, UK.
11. Oxford Genetic Laboratories, Oxford University Hospitals NHS Foundation Trust, Oxford OX3 7LE, UK.
12. Viapath Genetics Laboratory, Viapath Analytics LLP, 5th Floor Tower Wing, Guy's Hospital, London SE1 9RT, UK.
13. Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester M13 9WL, UK.
14. Evolution and Genomic Science, University of Manchester, Manchester M13 9PL
15. West Midlands Regional Genetics Laboratory, Birmingham Women's NHS Foundation Trust, Birmingham, B15 2TG, UK.

Recommendations ratified by ACGS Quality Subcommittee on 06 05 2019

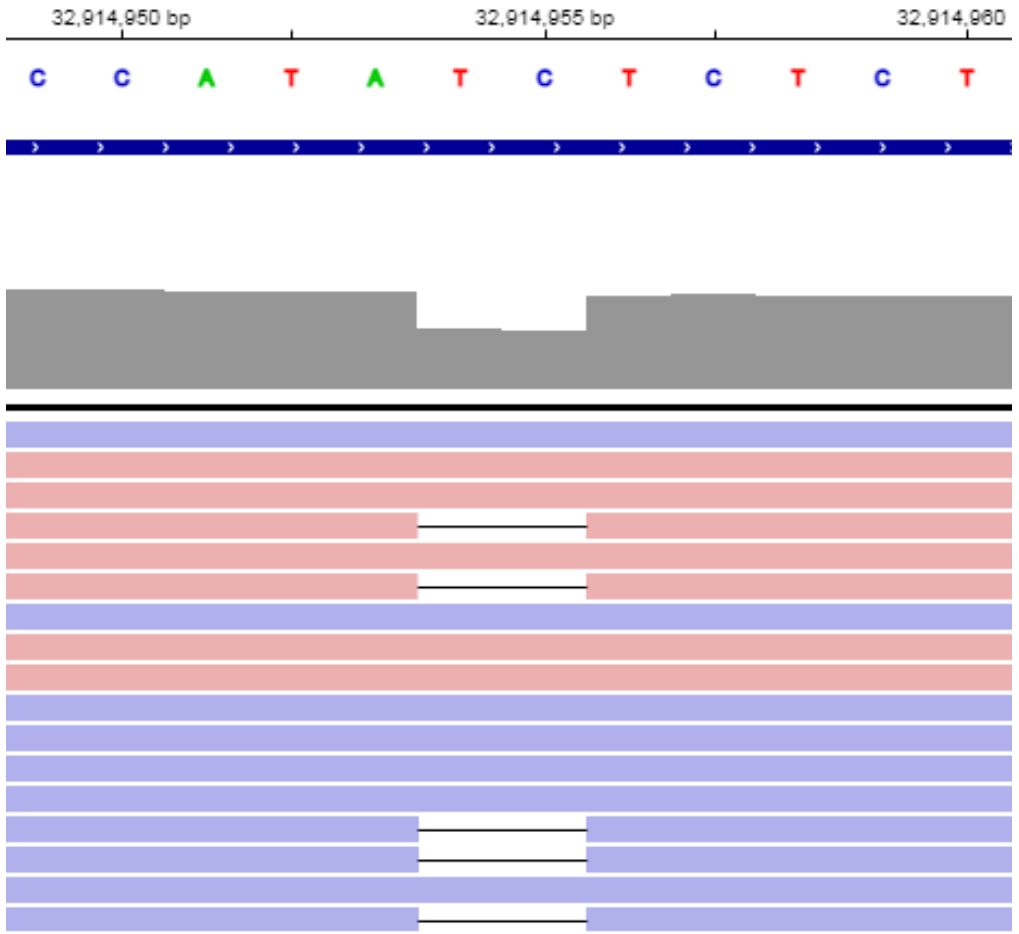
Interpretación y curaduría de variantes germinales en cáncer



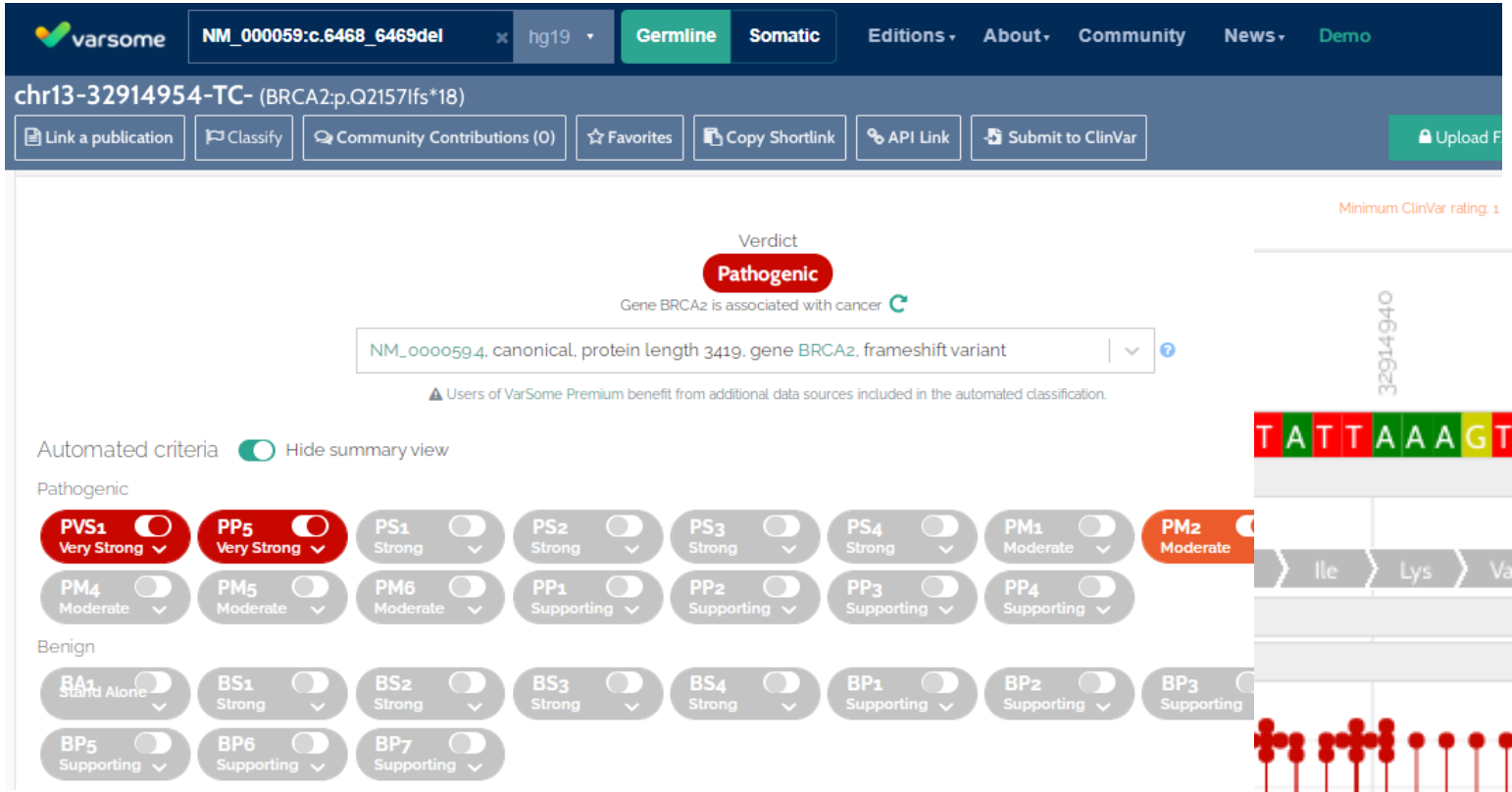
Further development of the ACMG/AMP guidelines is being undertaken through the US ClinGen Sequence Variant Interpretation (SVI) Working Group (https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation/). Their goal is to support the refinement and evolution of the guidelines. It was recognised by Richards *et al* (2015) that more focused guidance regarding the classification of variants in specific genes is required given that the applicability and weight assigned to certain criteria may vary by disease and gene. A number of disease-specific variant expert panels have been established and are generating disease/gene specific guidelines (see Kelly *et al* 2018 for *MYH7*-specific guidelines). Work is also underway to consider interpretation and reporting of variants with reduced penetrance.

Aplicando

HGVS:
BRCA2(NM_000059.4):c.6468_6469del
(p.Gln2157IlefsTer18)



Interpretación y curaduría de variantes germinales en cáncer



https://varsome.com/
https://franklin.genoox.com/clinical-db/home

Interpretación y curaduría de variantes germinales en cáncer

Datos población control

gnomAD

Genome Aggregation Database

BRCA2:c.6468_6469del ----> not found in gnomAD

Ejemplo de variante benigna:
BRCA2:c.8851G>A

Frequencies

gnomAD Exomes Version: 2.1.1 f = 0.00955

Population frequencies

Population	Allele Count	Allele Number	Homozygotes
African	20	16.220	-
Ashkenazi Jewish	16	10.054	-
East Asian	3	18.376	-
European (Finnish)	17	21.638	-
European (Non-Finnish)	559	113.326	2
Latino	1306	34.512	31
South Asian	433	30.554	7
Other	41	6116	1
Total	**2395**	**250.796**	**41**
Male	1201	135.576	19
Female	1194	115.220	22

https://gnomad.broadinstitute.org/

Interpretación y curaduría de variantes germinales en cáncer

Predictores In Silico

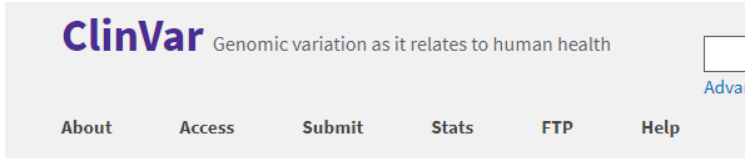
Programas computacionales, evalúan diversos aspectos:

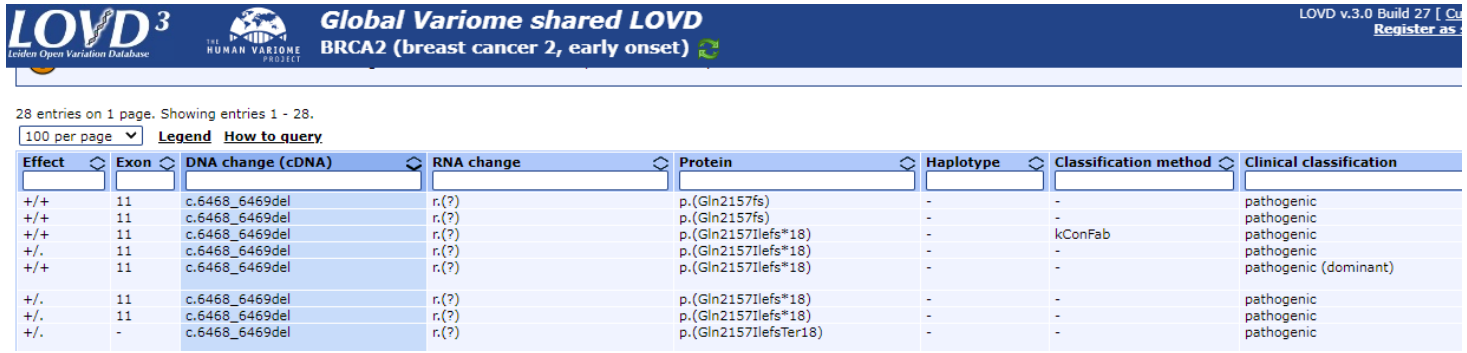
- Conservación entre especies
- Estructura proteica
- Función proteica
- Modificaciones transcripcionales (splicing)

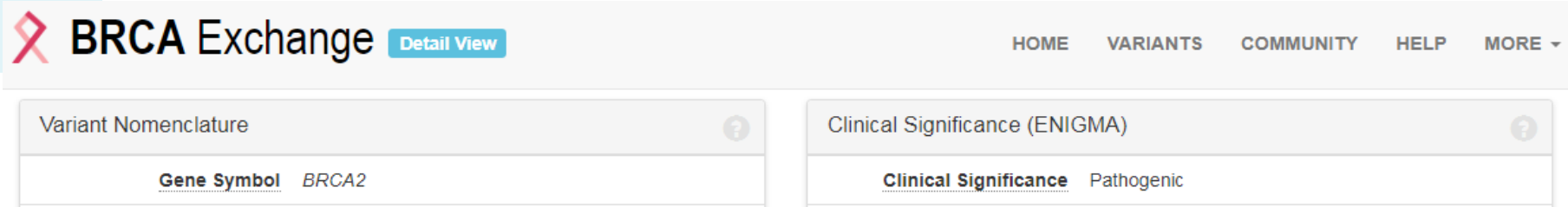
Category	Name	Website	Basis
Missense prediction	ConSurf	http://consurftest.tau.ac.il	Evolutionary conservation
	FATHMM	http://fathmm.biocompute.org.uk	Evolutionary conservation
	MutationAssessor	http://mutationassessor.org	Evolutionary conservation
	PANTHER	http://www.pantherdb.org/tools/csnpScoreForm.jsp	Evolutionary conservation
	PhD-SNP	http://snps.biofold.org/phd-snp/phd-snp.html	Evolutionary conservation
	SIFT	http://sift.jcvi.org	Evolutionary conservation
	SNPs&GO	http://snps-and-go.biocomp.unibo.it/snps-and-go	Protein structure/function
	Align GVGD	http://agvgd.iarc.fr/agvgd_input.php	Protein structure/function and evolutionary conservation
	MAPP	http://mendel.stanford.edu/SidowLab/downloads/MAPP/index.html	Protein structure/function and evolutionary conservation
	MutationTaster	http://www.mutationtaster.org	Protein structure/function and evolutionary conservation
	MutPred	http://mutpred.mutdb.org	Protein structure/function and evolutionary conservation
	PolyPhen-2	http://genetics.bwh.harvard.edu/pph2	Protein structure/function and evolutionary conservation
	PROVEAN	http://provean.jcvi.org/index.php	Alignment and measurement of similarity between variant sequence and protein sequence homolog
	nsSNPAnalyzer	http://snpanalyzer.uthsc.edu	Multiple sequence alignment and protein structure analysis
	Condel	http://bg.upf.edu/fannsdb/	Combines SIFT, PolyPhen-2, and MutationAssessor
	CADD	http://cadd.gs.washington.edu	Contrasts annotations of fixed/nearly fixed derived alleles in humans with simulated variants
Splice site prediction	GeneSplicer	http://www.cbcb.umd.edu/software/GeneSplicer/gene_spl.shtml	Markov models
	Human Splicing Finder	http://www.umd.be/HSF/	Position-dependent logic
	MaxEntScan	http://genes.mit.edu/burgelab/maxent/Xmaxentscan_scoreseq.html	Maximum entropy principle
	NetGene2	http://www.cbs.dtu.dk/services/NetGene2	Neural networks
	NNSplice	http://www.fruitfly.org/seq_tools/splice.html	Neural networks
	FSPLICE	http://www.softberry.com/berry.phtml?topic=fsplice&group=programs&subgroup=gfind	Species-specific predictor for splice sites based on weight matrices model
Nucleotide conservation prediction	GERP	http://mendel.stanford.edu/sidowlab/downloads/gerp/index.html	Genomic evolutionary rate profiling
	PhastCons	http://compgen.bscb.cornell.edu/phast/	Conservation scoring and identification of conserved elements
	PhyloP	http://compgen.bscb.cornell.edu/phast/	
		http://compgen.bscb.cornell.edu/phast/help-pages/phyloP.txt	Alignment and phylogenetic trees: Computation of *P* values for conservation or acceleration, either lineage-specific or across all branches

Interpretación y curaduría de variantes germinales en cáncer

Bases de datos







- ClinVar
- LOVD
- BRCA Exchange (específico)

Interpretación final

VUS : El elemento sorpresa y la incertidumbre

- Una "variante de significado incierto" o VUS es un cambio genético cuyo impacto no se conoce todavía. En algunos casos, no tenemos suficiente información para determinar si una variante es benigna o patogénica.

Journal of Community Genetics (2020) 11:139–145
https://doi.org/10.1007/s12687-019-00434-7

REVIEW

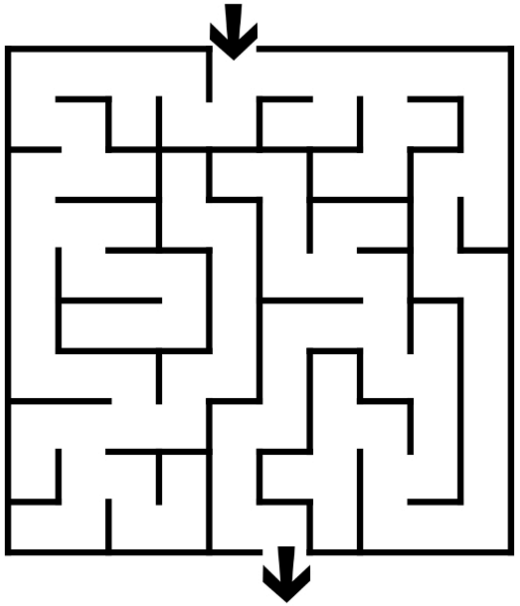
Check for updates

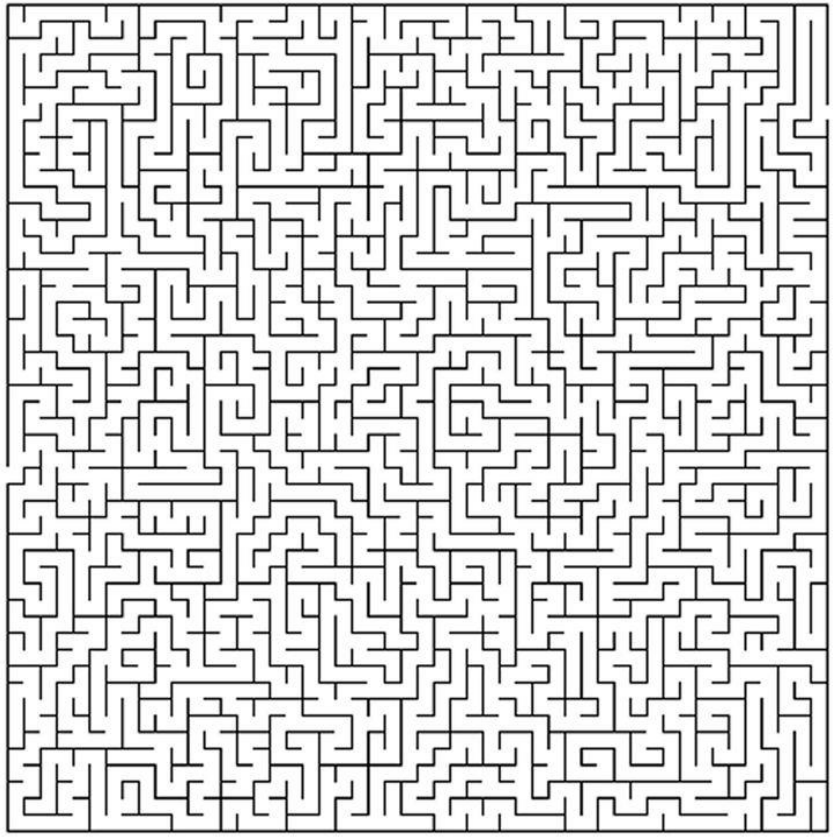
Patients' views on variants of uncertain significance across indications

Kristin Clift[1] · Sarah Macklin[2] · Colin Halverson[3] · Jennifer B. McCormick[4] · Abd Moain Abu Dabrh[5] · Stephanie Hines[6]

Received: 14 August 2018 / Accepted: 12 August 2019 / Published online: 20 August 2019

Interpretación y curaduría de variantes germinales en cáncer





Resumen

- Alteraciones genéticas pueden ser de origen germinal o somático. **Cuando es germinal podemos analizar sangre.**
- Las variantes germinales son heredables. **Podemos evaluar portadores en la familia.**
- Ser portador de una variante patogénica en cáncer, aumenta el riesgo de desarrollar **PERO no determina que lo va a tener.**
- No toda variante es patogénica.
- La clasificación es dinámica y cambia con el tiempo.

Equipo PGM


focus
EXOMA CLÍNICO DIRIGIDO
vision
PRENATAL NO INVASIVO
clear
CANCER HEREDITARO
chromo
MICRO ARRAY CROMOSÓMICO

Héritas
Medicina de precisión

CIRCULO MEDICO DE ROSARIO 1910

¡Muchas gracias!

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