Cancer Genetics: A Vision for Precision

New Mexico Society of Clinical Oncology 2022

- **Jeffrey N. Weitzel, M.D.**
- **Professor, Latin American School of Oncology**
- **VP Medical Affairs Hereditary Cancer, Natera**

DISCLOSURE OF CONFLICTS OF INTEREST

Jeffrey N. Weitzel, M.D. has the following financial relationships to disclose:

- Employee, Natera
- Speaker fees, AstraZeneca

Timeline: Cancer Genomics

1910 — Payton Rous shows animal tumors can be transmissible via a virus. (Nobel Prize later awarded to Rous)[10]

1914 — Theodor Boveri proposes that chromosomal abnormalities cause cancer[11]

1971 — Alfred Knudson "two-hit hypothesis for genetic cause of hereditary cancer"[12]

Henry Lynch describes hereditary breast and ovarian cancer,[13] and Warthin's "family G" (ca. of colon, uterus, and other sites).

1973 — AJ Levine and others discover p53 proteins in virally transformed cells[15]

1979 — Identification of *RB* tumor suppressor genel[6]

1986 — armus and Bishop win Nobel Prize for discovery of cellular origin of retroviral oncogenes[17]

1989 — Vogelstein lab demonstrates *p53* is a tumor suppressor gene in colorectal cancer[18]

1990 — MC King maps breast cancer susceptibility locus to chromosome 17[19]

1991 — Cloning of *APC* colon cancer susceptibility gene MSI, Mismatch Repair Genes and Lynch Syndrome

1994 — Mark Skolnick and colleagues discover *BRCA1* as a cause of hereditary breast and ovarian cancer in families[21]

2000 — Initial sequencing and analysis of the human genome[24]

2001 — Prospective evidence preventive surgeries effective in *BRCA1/2* carriers[22,23]

2005 — Ashworth et al target PARP DNA repair pathway in *BRCA*-deficient cancers[26]

2007 — Easton and colleagues perform first genome-wide association study o breast cancer[27]

2009 — The Cancer Genome Atlas expands from a pilot to a large scale project[28]

2010 — Proof of Principle PARP inhibitor mono- therapy for *BRCA*-associated Breast and Ovarian Cancer

2013 — Supreme Court dissolution of Patent protection for genes

2014 — Beginning of widespread use of NGS-mediated multigene panels

2015 — Recognition of genetic associations with pancreatic and prostate cancers

2016 — Polygenic Risk Scores for Breast Cancer

2017 — Broader Application of Whole exome / genome studies to create general population base cohort (All of Us)

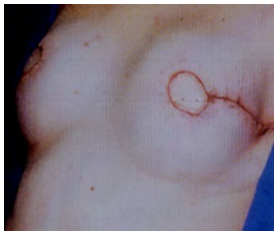
2022 — Polygenic Risk Scores as modifier of BRCA and other gene penetrance

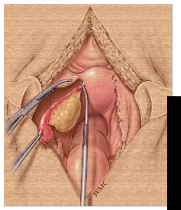
Clinical Management of *BRCA* Mutation-Positive Patient

Positive *BRCA1* or *BRCA2* test result

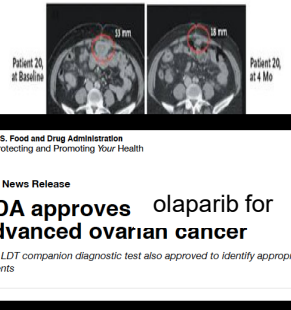
Possible testing for other adult relatives

Prophylactic surgery

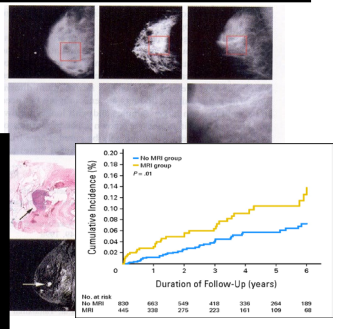




Targeted therapy

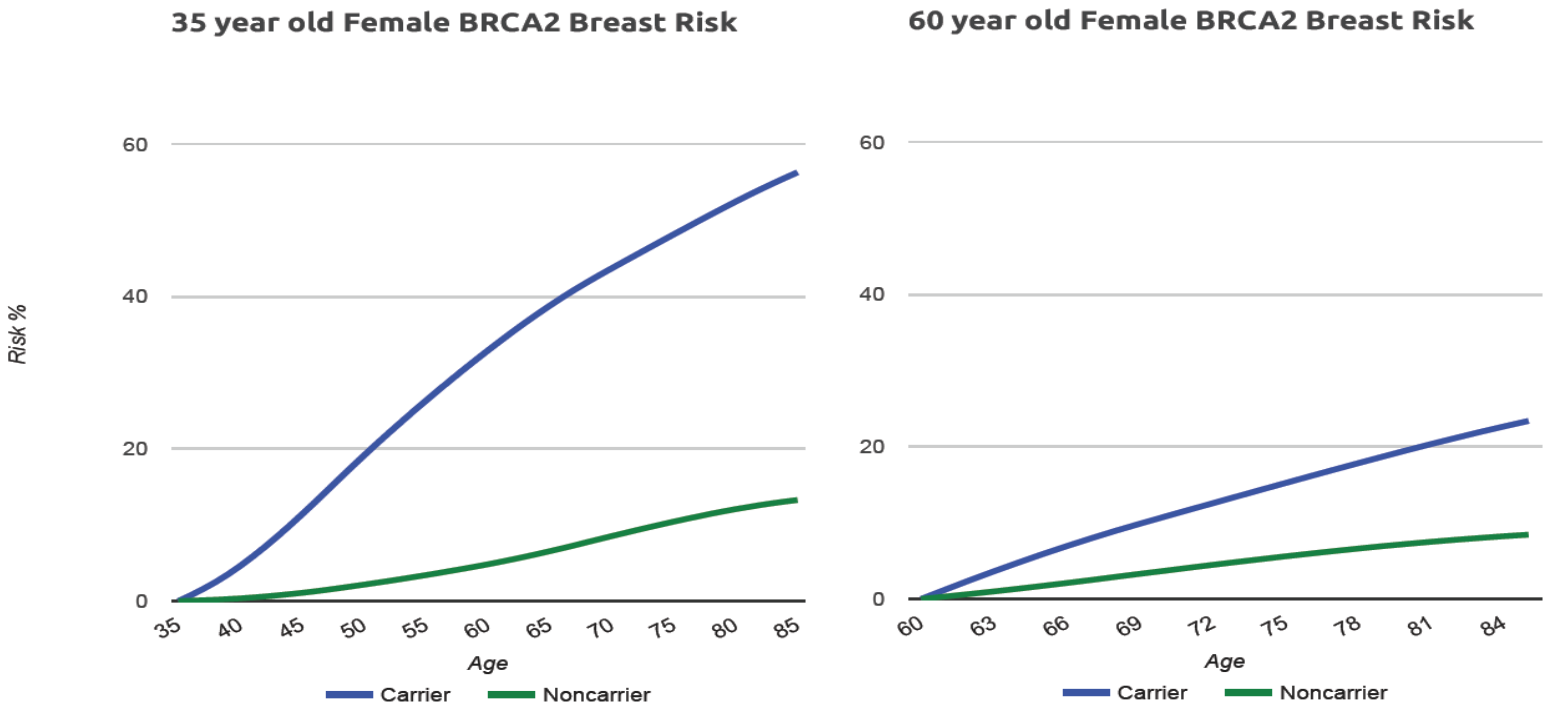


Increased surveillance

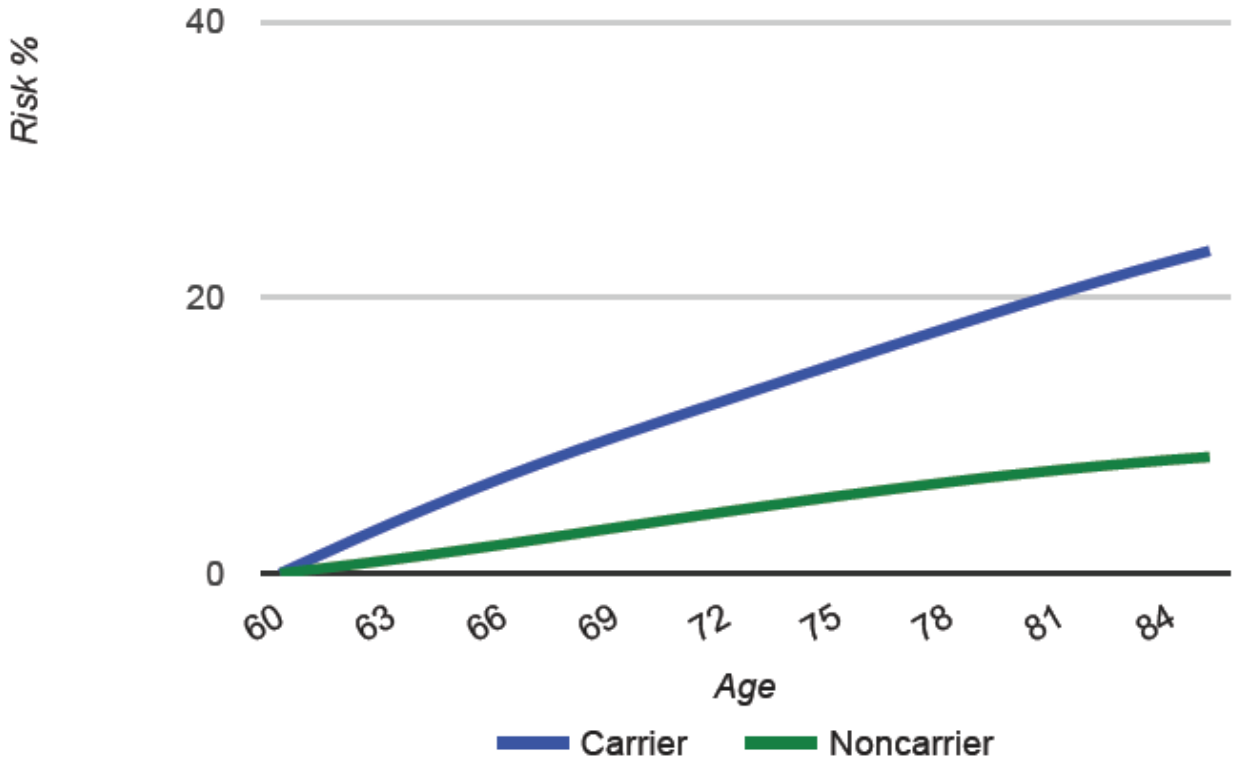


Chemo-prevention

Use disease status context- and Age-Specific Risk in Cancer Risk Counseling

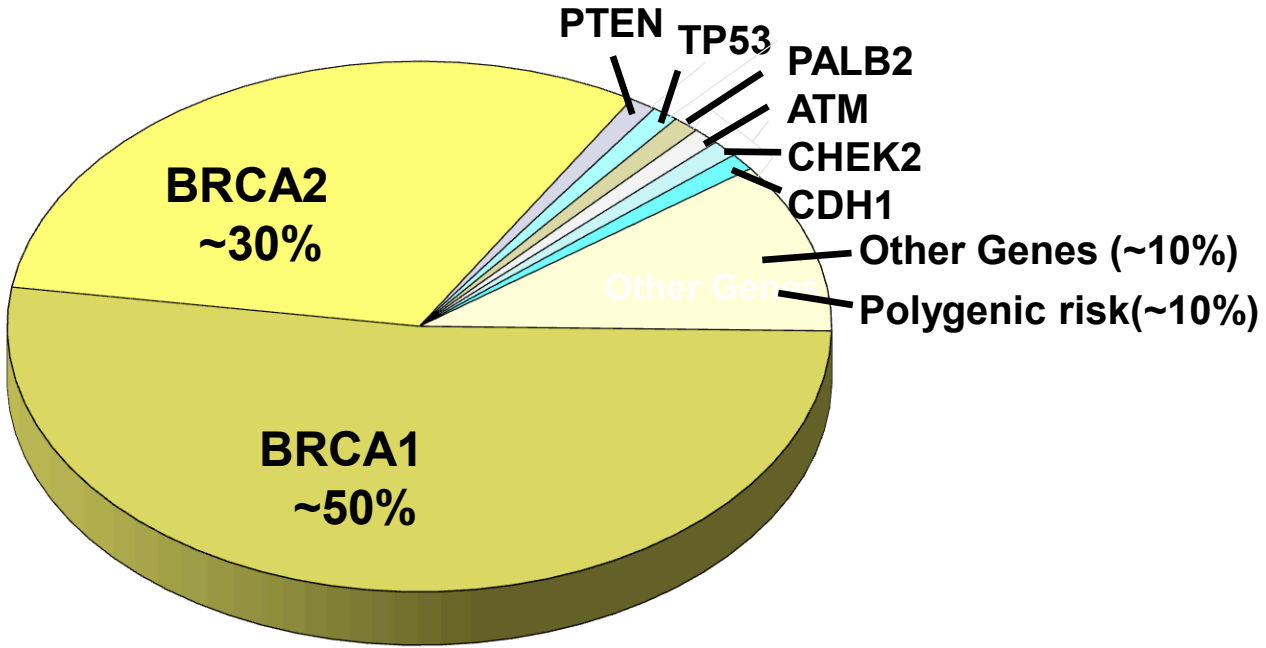


However: management of ovarian risk is ageless



60 year old Female BRCA2 Ovarian Risk

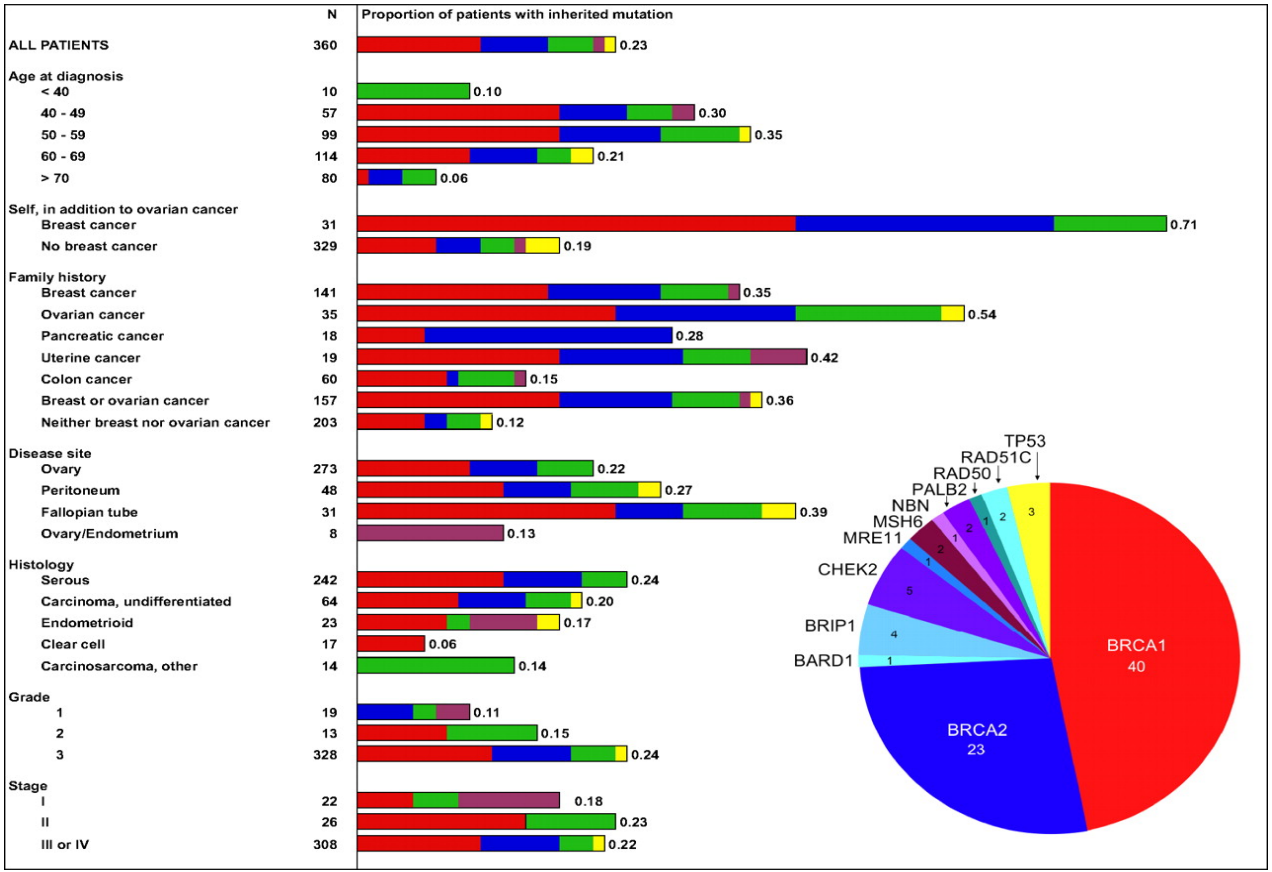
Genomic Epidemiology of Hereditary Breast Cancer



5-10% Hereditary

All Breast Cancer

Proportions ovarian, fallopian tube, or peritoneal cancer patients with respective germ-line loss-of-function mutations

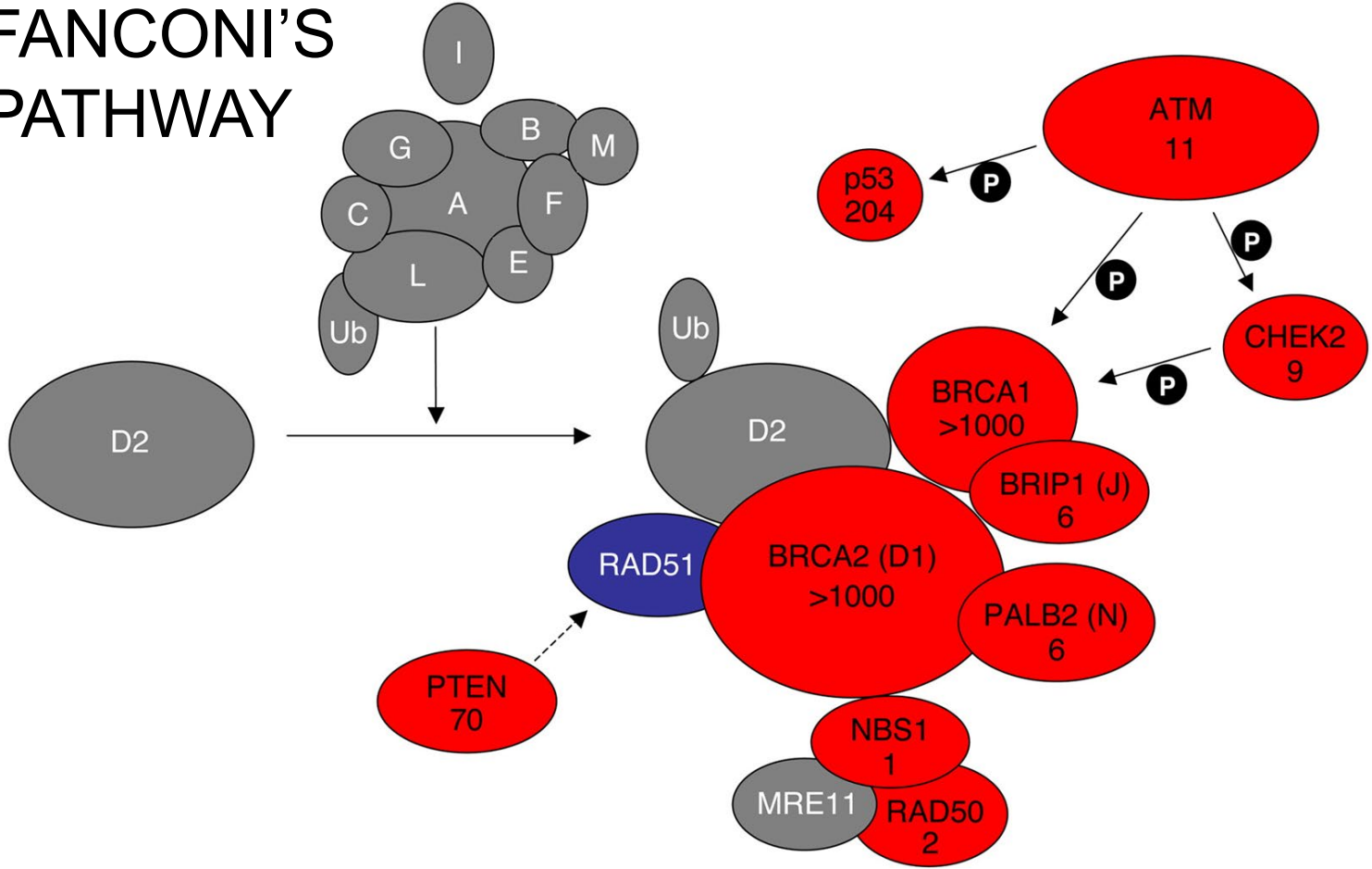


- Overall, germline mutation in 23% of unselected OC
- BRCA genes 74%
  - 10 genes for the next 26%

Observation does not = causality

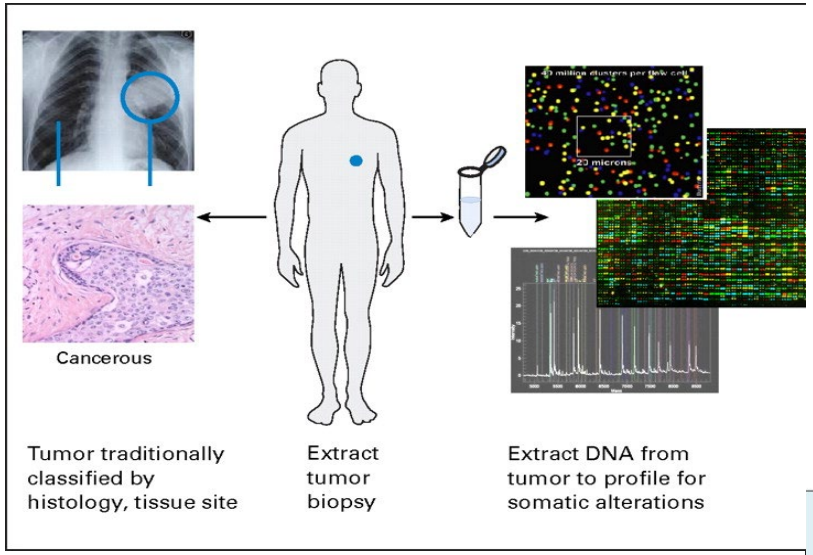
Walsh T et al. PNAS 2011;108:18032-18037

FANCONI'S PATHWAY

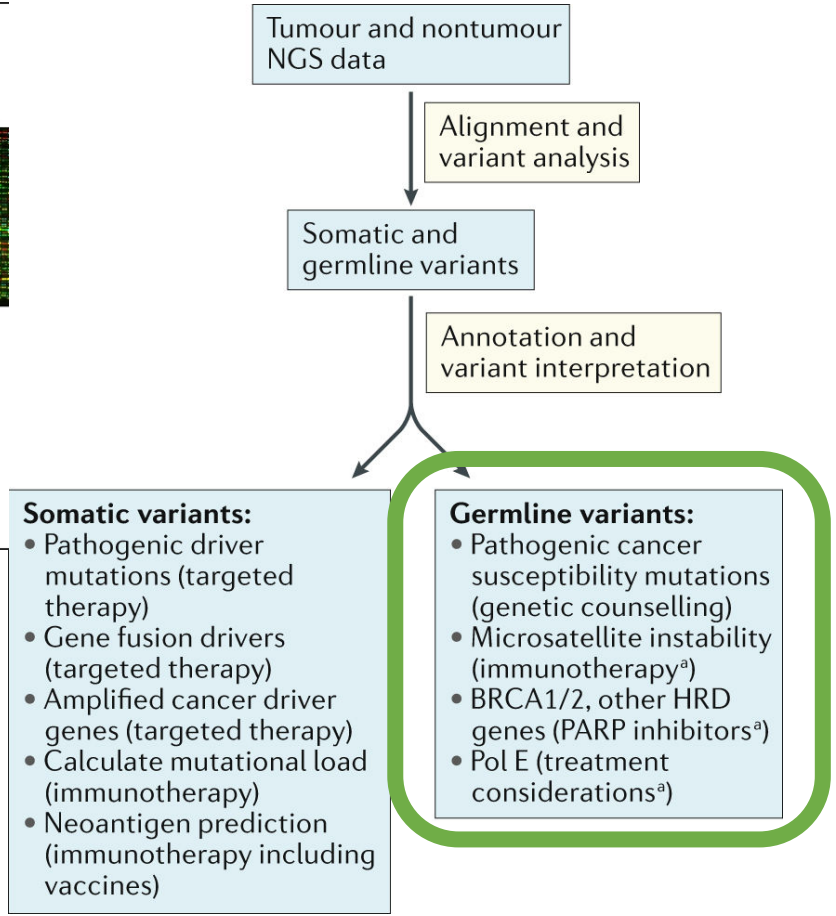


Walsh T, King M-C. Cancer Cell 2007;11(2):103-105

Emerging Clinical Utility of Genomic Assays

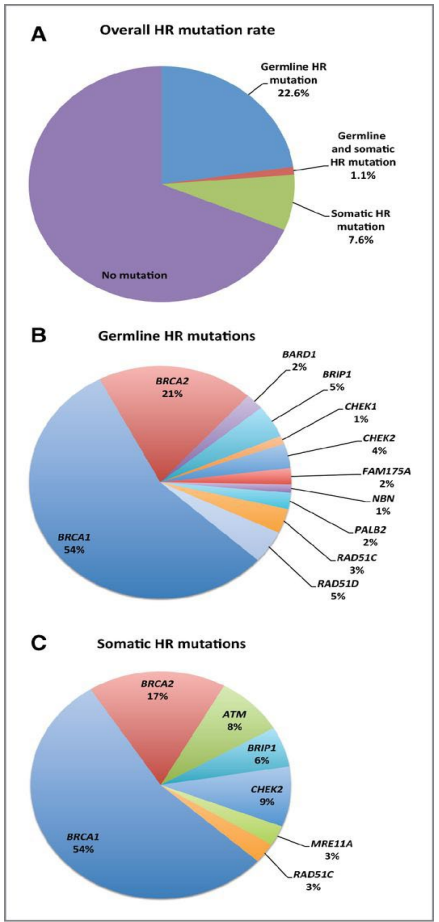


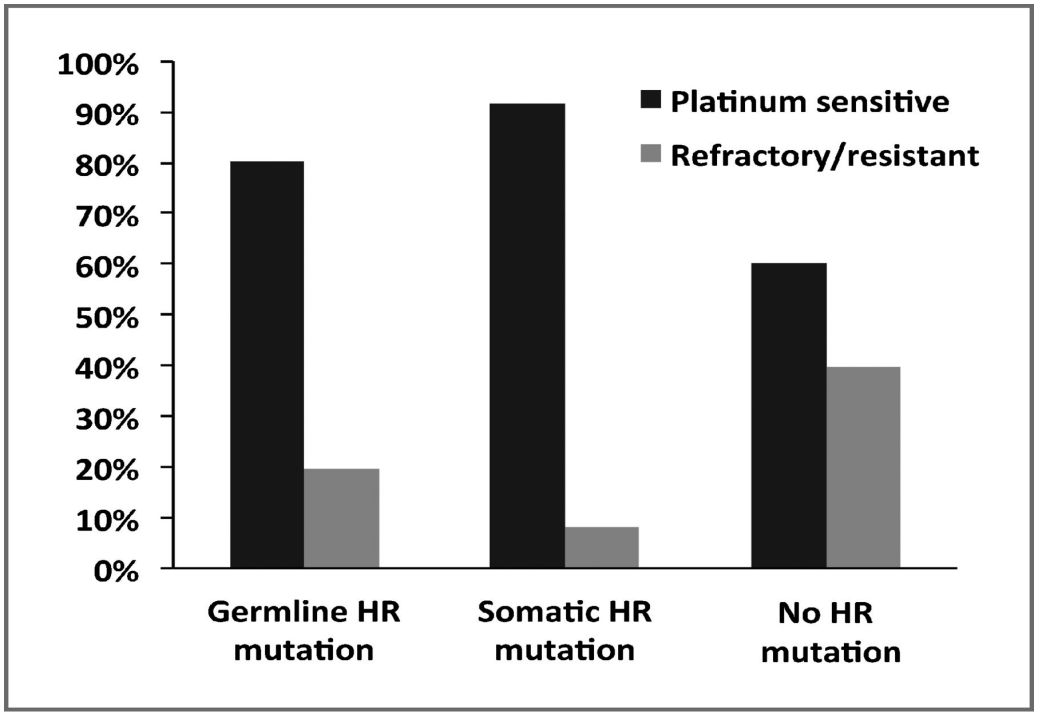
MacConaill & Garraway.
JCO 2010;28:5219-5228



Berger & Mardis. Nature Reviews 2018; 15:353-365.

Homologous recombination (HR) gene mutations in ovarian cancers and association with platinum sensitivity



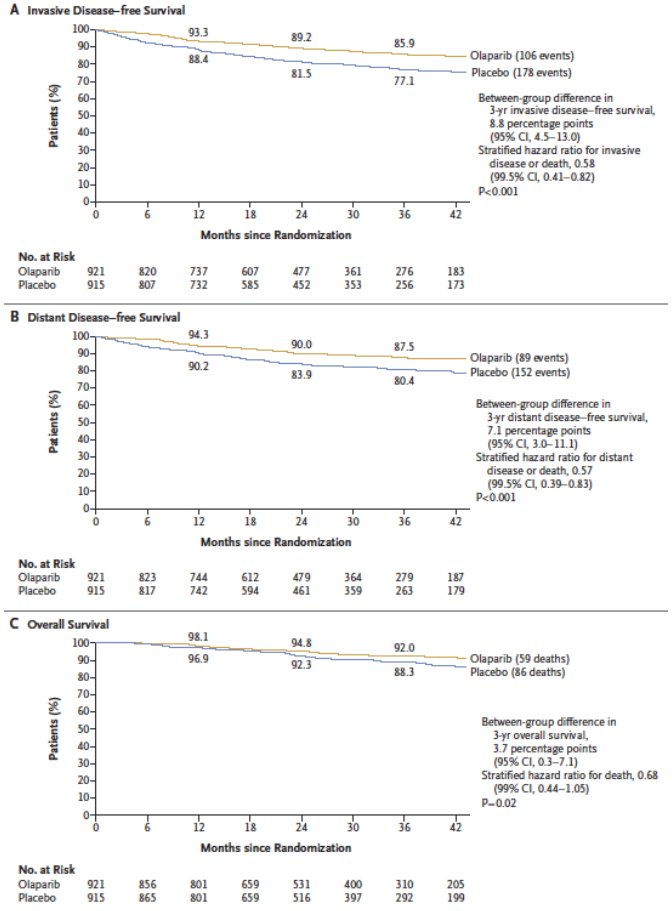


Pennington K P et al. Clin Cancer Res 2014;20:764-775

Adjuvant PARPi in high-risk early-stage HER2-negative *BRCA*-associated BC:

OympiaA

- Major advance moving PARPi forward in the treatment of *BRCA*-associated BC
- Supports expanded germline *BRCA* testing
- Prompted ASCO guideline rapid recommendations update



Tutt et al. NEJM 384:25, 2021
Tung et al. JCO 39:2959, 2021

NCCN Guidelines Version 1.2022
Hereditary Cancer Testing Criteria

National Comprehensive Cancer Network®

TESTING CRITERIA FOR HIGH PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES (Specifically BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53. See GENE-A)

Testing is clinically in in the following scenarios:

See General Testing Criteria on CRIT-1

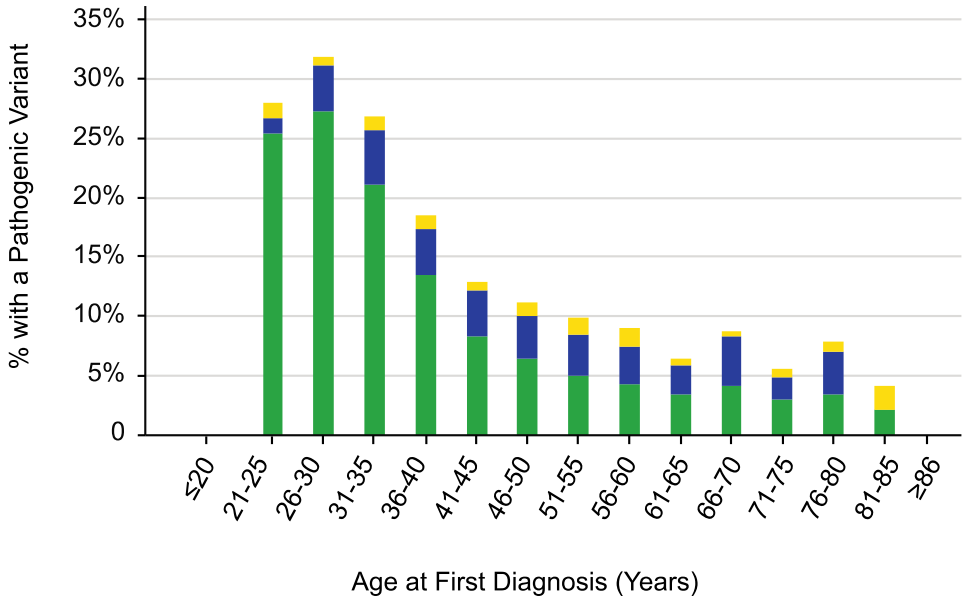
Personal history of breast cancer with specific features:

- By Age at Diagnosis and Family History
  - ≤45 y
  - 46-50 y with ANY:
    - Unknown or limited family history
    - Multiple primary breast cancers (synchronous or metachronous) at any age
    - ≥1 close blood relative with breast, ovarian, pancreatic, or prostate cancer at any age
  - ≥51 y
    - ≥1 close blood relative 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
    - To aid in adjuvant treatment decisions with olaparib for high-risk, HER-2 negative breast cancer*
    - Triple-negative breast cancer
    - Lobular breast cancer with personal or family history of diffuse gastric cancer. See NCCN Guidelines for Gastric Cancer
    - Metastatic breast cancer (See NCCN Guidelines for Breast Cancer)
    - Male breast cancer
    - ≥1 close blood relative[g] with male breast cancer
- By Ancestry
  - Ashkenazi Jewish ancestry

*

*OlympiaA

Persistent Prevalence of BC-associated variants across the age at diagnosis spectrum of women with multiple BCs



High Risk Genes: *BRCA1, BRCA2, PALB2, TP53, PTEN, CDH1, STK11*

Moderate Risk Genes: *CHEK2, ATM, BARD1, NBN*

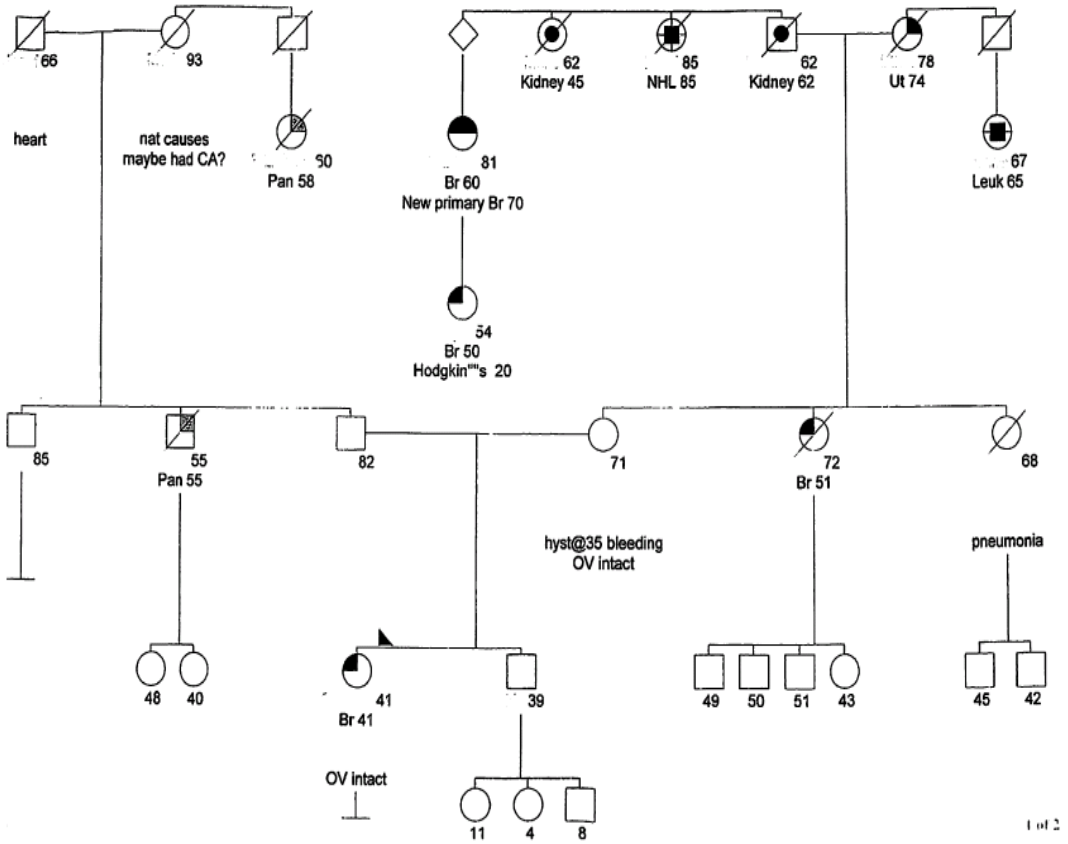
Non-Breast Cancer Risk Genes: *MSH6, MSH2, MLH1, EPCAM, PMS2, CDKN2A, APC, BRIP1, RAD51C, RAD51D*

Shift to *BRCA2* and moderate risk genes among women with later onset BC

>5% yield from MGPT after age 65

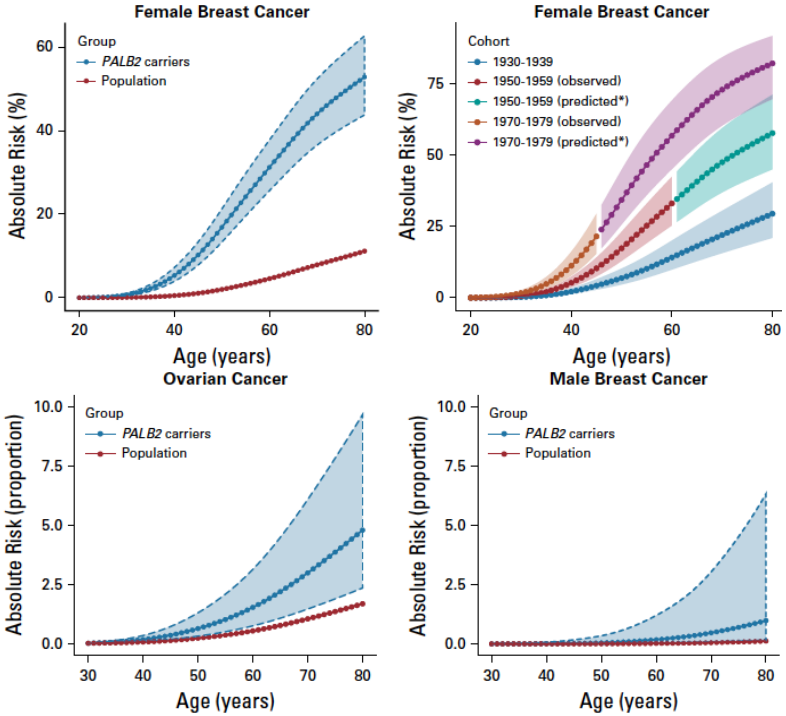
Weitzel et al. BCRT 2021

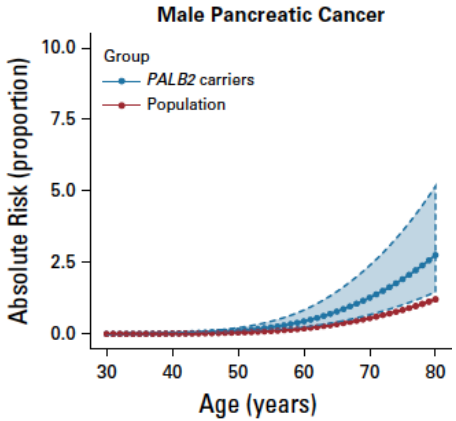
Beyond *BRCA* testing



- *BRCA* testing uninformative
- *PALB2* + on MGPT
- Could be either parental lineage
- Risk for new primary breast cancer not quantified
- Magnitude of ovarian cancer risk not clear
- Need to think about pancreatic cancer risk

Cancer Risks Associated With Germline *PALB2* Pathogenic Variants: An International Study of 524 Families

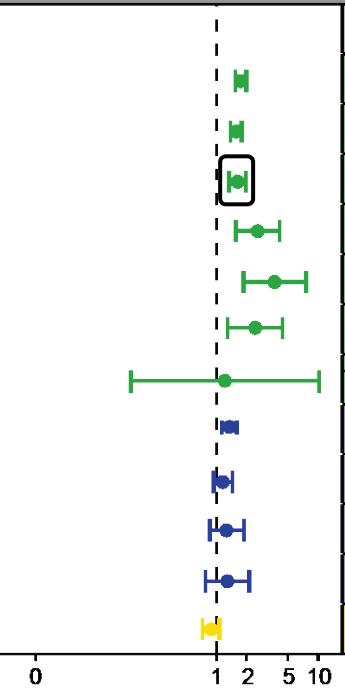




Yang et al. J Clin Oncol 2019

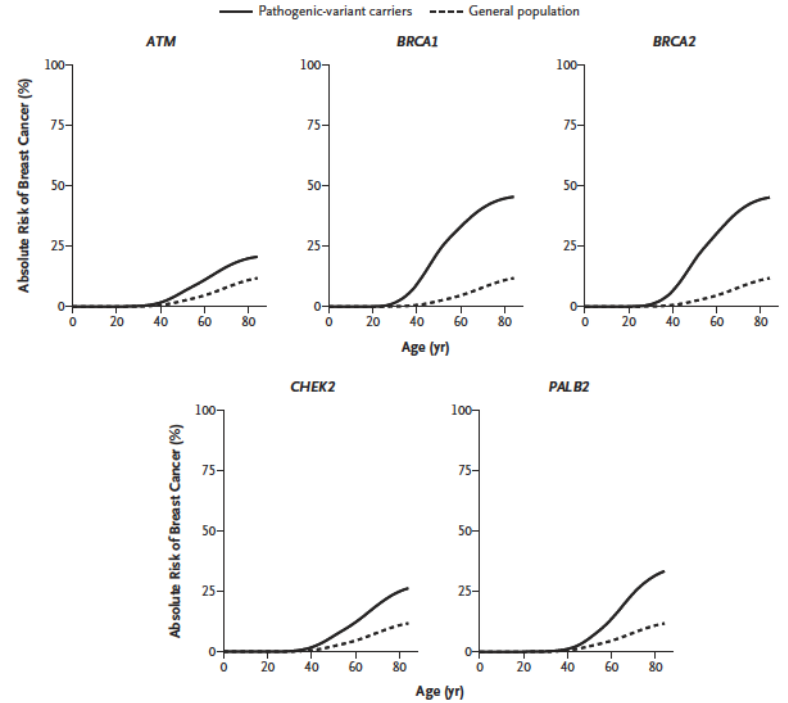
Multivariable logistic regression models of PV association (OR) with multiple breast cancers

Gene	≥ 2 Breast Cancers (N=10,220)		1 Breast Cancer (N=88,759)		Results from Multivariable Logistic Regression	
	N	% of Cohort	N	% of Cohort	Odds Ratio (95% CI)	p-value
Breast Cancer Risk Genes	1212	11.86	7165	8.07	**1.54 (1.44, 1.65)**	**<0.001**
BRCA1	359	3.51	1906	2.15	**1.74 (1.55, 1.97)**	**<0.001**
BRCA2	337	3.30	2007	2.26	**1.57 (1.39, 1.77)**	**<0.001**
PALB2	130	1.27	735	0.83	**1.62 (1.34, 1.96)**	**<0.001**
TP53	21	0.21	84	0.09	**2.56 (1.56, 4.20)**	**<0.001**
PTEN	13	0.13	26	0.03	**3.80 (1.88, 7.69)**	**<0.001**
CDH1	13	0.13	50	0.06	**2.42 (1.30, 4.52)**	**0.01**
STK11	1	0.01	8	0.01	1.22 (0.14, 10.35)	0.86
CHEK2	186	1.82	1236	1.39	**1.35 (1.15, 1.57)**	**<0.001**
ATM	102	1.00	772	0.87	1.17 (0.95, 1.45)	0.14
BARD1	30	0.29	212	0.24	1.27 (0.87, 1.87)	0.22
NBN	20	0.20	129	0.15	1.29 (0.78, 2.12)	0.32
Non-Breast Cancer Risk Genes	105	1.03	980	1.10	0.92 (0.75, 1.13)	0.45



Weitzel et al. BCRT 2021

A Population-Based Study of Genes Previously Implicated in Breast Cancer – what is the risk without ascertainment bias

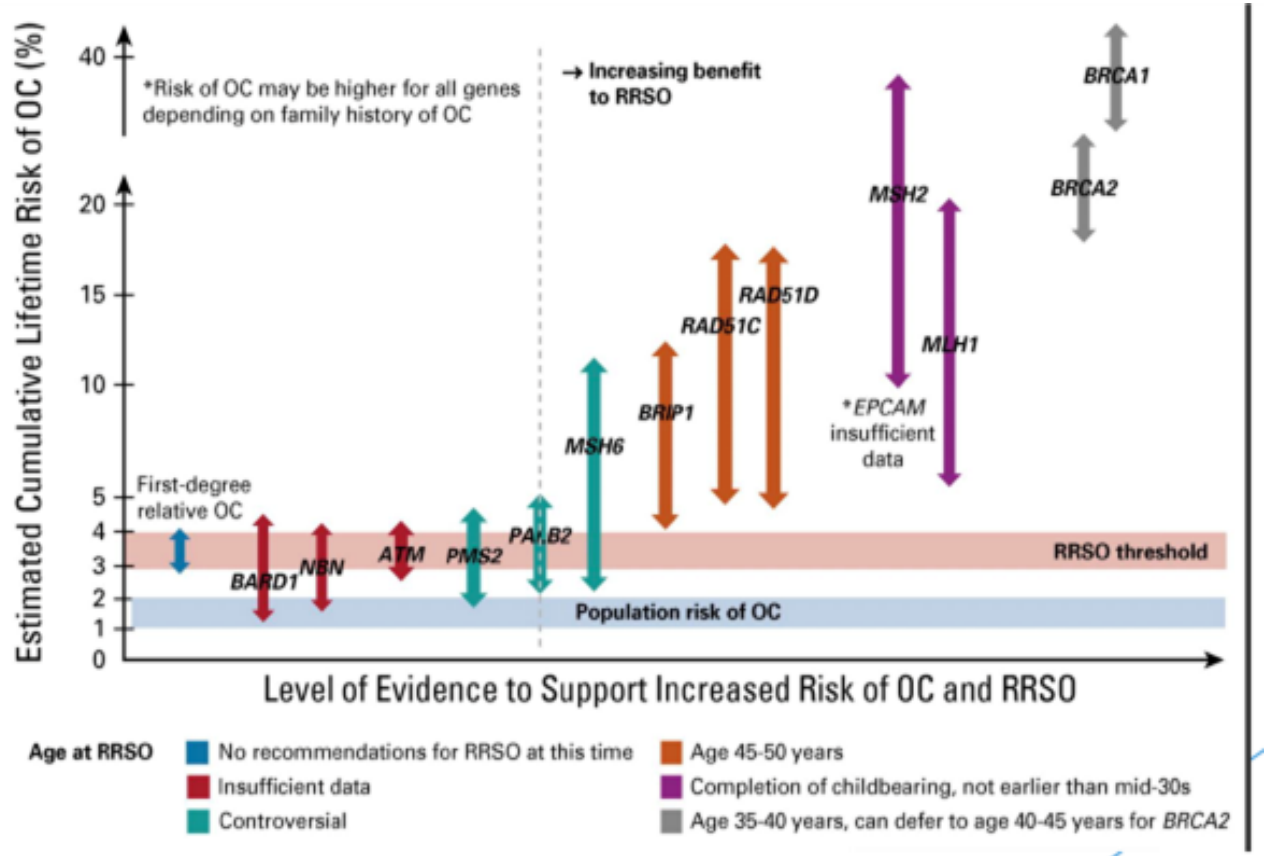


Demoted:

BLM	*MSH2*
BRIP1	*MSH6*
CDKN2A	*NBN*
ERCC3	*RAD50*
FANCC	*RECQL*
FANCM	*RINT1*
MLH1	*SLX4*
MRE11A	*XRCC2*

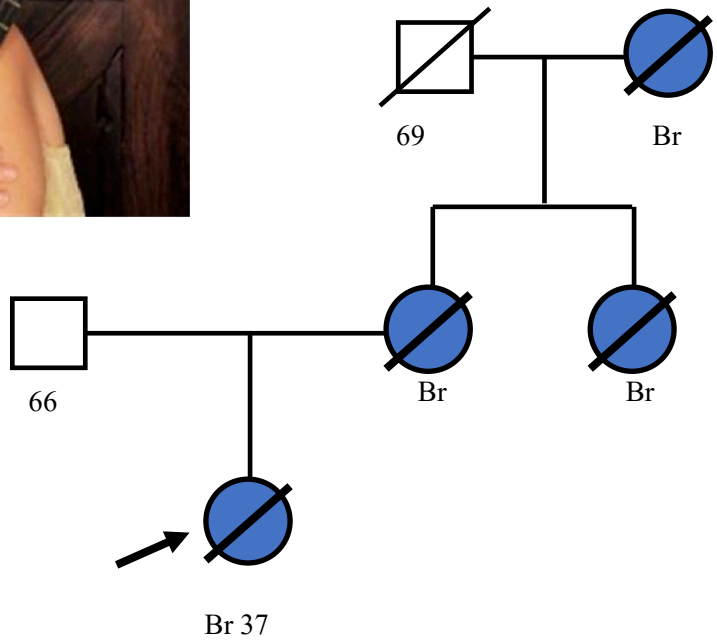
Hu *et al.* NEJM, 384:440, 2021

Risk of ovarian cancer

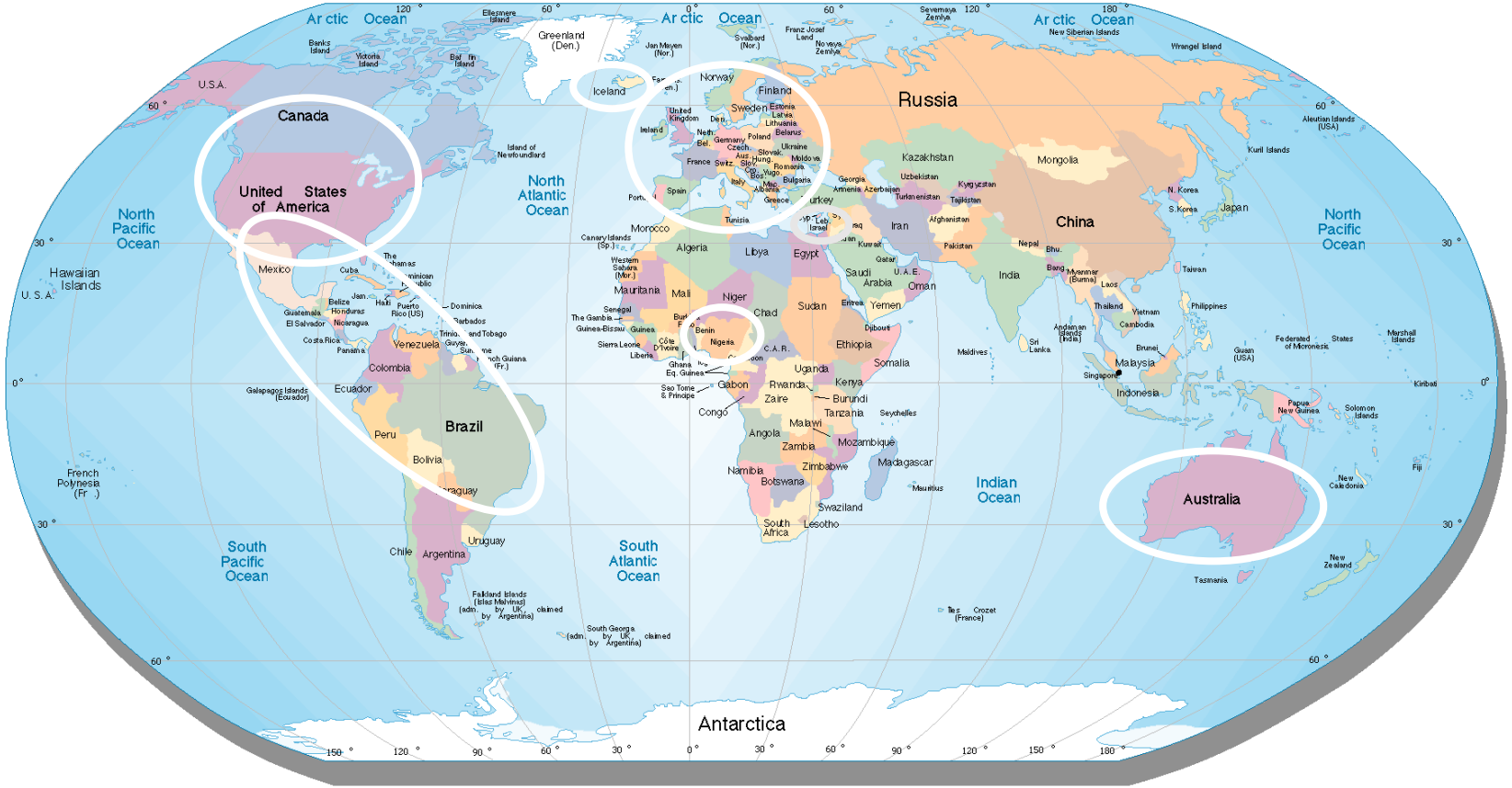


Liu, Y, et al, JCO Onc Prac, 2022, March 8, Volume 18, Issue 3

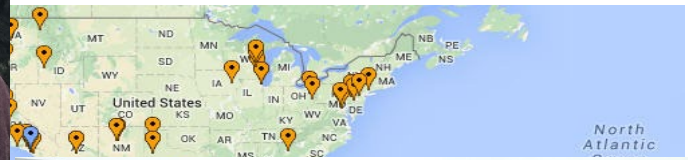
Colombia



Access to care influences knowledge of genetic epidemiology



The Clinical Cancer Genomics Community Research Network



- multi-generation pedigree, genomic data, biospecimens, and prospective F/U
- Global cancer genomics translational research

Significant clinical impact of recurrent *BRCA1* and *BRCA2* mutations in Mexico

Villarreal-Garza, C., R. M. Alvarez-Gómez, C. Pérez-Plasencia, L. A. Herrera, J. Herzog, D. Castillo, A. Mohar, C. Castro, L. N. Gallardo, D. Gallardo, M. Santibáñez, K. R. Blazer and J. N. Weitzel (2014). Cancer.

Clinical Profile of Disparity:

Young and advanced disease at diagnosis

Breast Cancer n=96		Ovarian Cancer n=92	
Age			
Range	26-63	Range	23-83
Mean	40	Mean	54
Stage			
I	1%	I	0%
II	27%	II	0%
III	67%	III	53%
IV	2%	IV	42%
Unknown	3%	Unknown	5%

BRCA mutations prevalent, and a possible partial explanation for excess of TNBC in Mexico

ER/PR/Her2 TNBC vs. non (any+)	No. (%) *BRCA* positive			Total No. of cases*
	BRCA1	*BRCA2*	Total	
TNBC cases	9	0	9 (27%)	33
Non-TNBC	2	3	5 (8%)	62
All cases	11	3	14 (15%)	95

ER: estrogen receptor, PR: progesterone receptor, TNBC: triple negative breast cancer. *Excluded one case with unknown tumor receptor status.

Villarreal *et al*. Cancer 2014

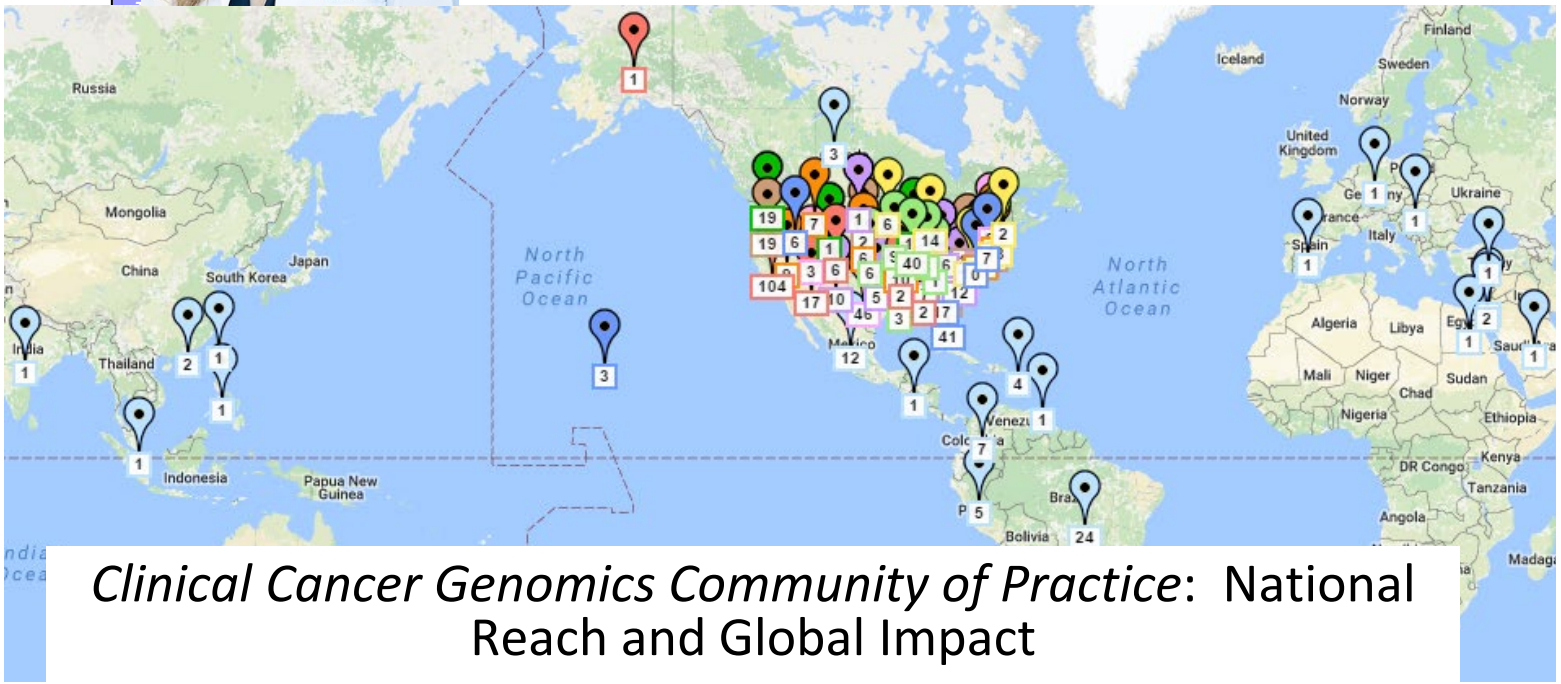
Mutation		Ovarian cancer (n=92)	Breast cancer (n=96)	Total (n=188)
BRCA1 (85%)	ex9-12del	9 (35%)	4 (29%)	13 (33%)
	IVS5+1G>A	2	0	2
	3977del4*	0	1	1
	R1699W*	1	0	1
	803delA*	1	0	1
	70insAG*	1	0	1
	A1708E	1	1	2
	4184del4	1	0	1
	R71G	1	0	1
	917delTT	0	1	1
	943ins10	1	0	1
	2925del4	0	1	1
	3878delTA	0	1	1
	185delAG	0	1	1
	R1443X	0	1	1
BRCA1 Large Rearrangements (*BRCA1*)**	ex8-9dup	2	0	2
	ex18-19del	2	0	2
	ex8-10del	1	0	1
BRCA2 (15%)	9463delG	1	0	1
	6244delG*	1	0	1
	2900delCT*	1	0	1
	6714del4*	0	1	1
	1803insA*	0	1	1
	6252insG	0	1	1
Total		26 (28%)	14 (15%)	40 (21%)

* Mutations detected by pyrosequencing; **detected by MLPA

EDUCATION REPORT

Personalized cancer genetics training for personalized medicine: Improving community-based healthcare through a genetically literate workforce

Kathleen R. Blazer, EdD, CGS[1], Deborah J. MacDonald, PhD, APNG[1], Julie O. Culver, MS[1], Carin R. Huizenga, MS[1], Robert J. Morgan, MD[2], Gwen C. Uman, PhD, RN[3], and Jeffrey N. Weitzel, MD[1,2]

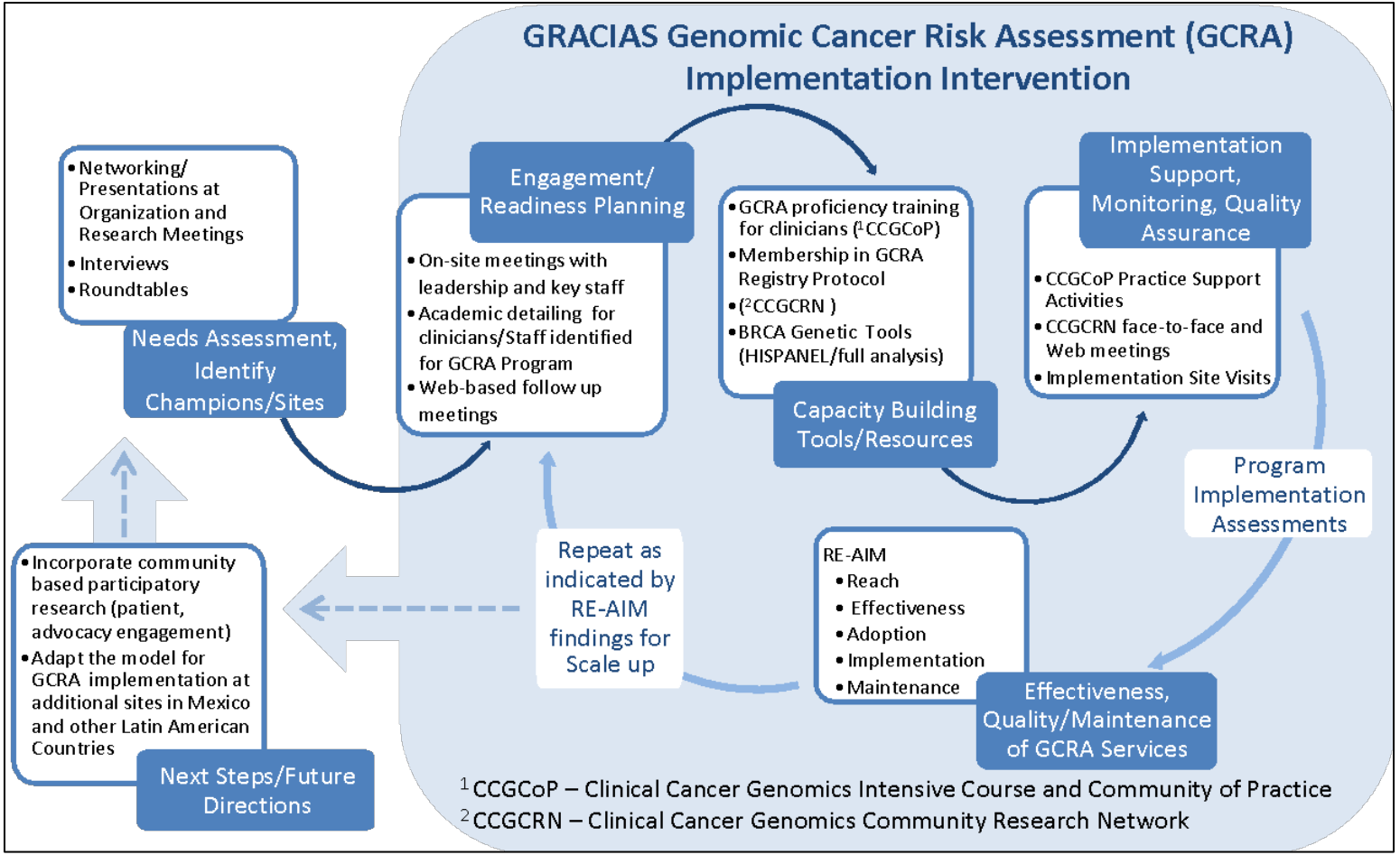


Clinical Cancer Genomics Community of Practice: National Reach and Global Impact

Genomic Risk Assessment for Cancer Implementation and Sustainment (GRACIAS)

- *Although genomic cancer risk assessment (GCRA) is a standard-of-care service in developed nations, access remains limited in Mexico and other low- and middle-income countries*
- *Roundtables identified limitations in healthcare finance, adequately trained workforce, and population-based registries*
- *We described the first project to use implementation science methods to develop and deliver an innovative multicomponent implementation intervention:*
  - *Comprehensive GCRA training and practice support (web-progeny)*
  - *low-cost BRCA testing*
  - *Academic detailing*
  - *GCRA registry protocol to enable testing and outcome measures*

***Genomic Risk Assessment for Cancer Implementation and Sustainment* (GRACIAS)**



Blazer, K.R, et al. JCO Global Oncology, 2021. 7: p. 992-1002.

Low cost platforms for clinical grade hereditary cancer testing – tool for GCRA implementation

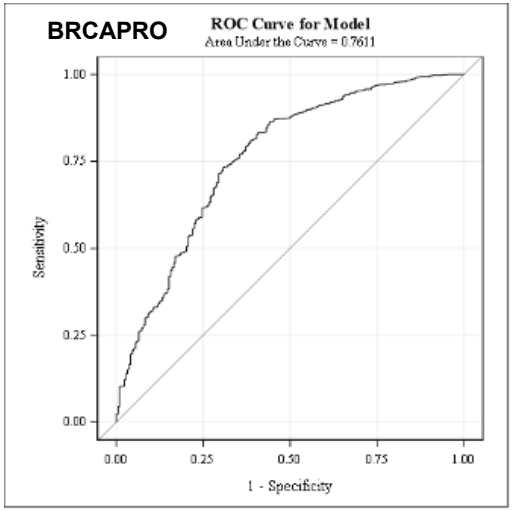
3-primer PCR assay for **MFM** Cummulative cost: $0.86

HISPANEL assay via Sequenom mass array: $20

Full BRCA Sequencing and CNV via NGS & MLPA: $60-80

Center	n	*HISPANEL* PVs	Non-*HISPANEL* Mutations	*HISPANEL* Sensitivity (Observed)	*PV Frequency by Center*
Bogotá, Colombia	225	12	9	0.57	0.09
Guadalajara, México	94	10	7	0.59	0.18
México City, México	538	53	40	0.57	0.17
Lima, Peru	653	25	57	0.30	0.13
San Juan, Puerto Rico	43	2	2	0.50	0.09
Porto Alegre, Brazil	74	10	9	0.53	0.26
TOTALS	**1627**	**112**	**124**	**0.47**	**0.14**

***HISPANEL* = Sequenom *BRCA* PV Panel (114 insertion/deletion or single nucleotide variants) and a PCR assay for the *BRCA1* exon9-12del CNV**



Multiplex amplicon multigene panel (CARRIERS I; 12 clinically actionable genes) $60

Multiplex amplicon multigene panel: 12 clinically actionable genes, 300 risk and ancestry snps) $80

Sanger re-sequencing of pathogenic variants, individual report, local site clinician disclosure to patients: **priceless**

Herzog et al. NPJ BC, 2021

- *GRACIAS* resulted in increased reach and sustainment of GCRA services at four major centers in Mexico
  - yield of *BRCA* pathogenic variants was comparable with the yield in US high-risk clinics.
- The project achieved similar benefits in Colombia (Bogota and Medellin) and Peru (INEN)
- GCRA risk stratification could inform allocation of limited resources and result in prevention of cancer
- The implementation science developed for GRACIAS may help scale up dissemination of GCRA in Latin America and for application in low resource settings, including rural communities and safety net hospitals in the United States

The Spanish Inquisition in Art

Torquemada before Isabella and Ferdinand

Galileo in front of his Inquisitors

(Prado, Madrid)

Illuminating genetic burden, shared ancestry and anthropology

Indigenous →
Jewish diaspora →
Colonial Spanish →

Recurrent PVs (≥3 obs) and Limited representation in public database (ClinVar)

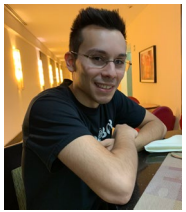
GENE	Variant (HGVS)	Brazil	Colombia	Mexico	Peru	Puerto Rico	Total
BRCA1	c.548-?_4185+?del[H]	0	0	23	0	0	23
	c.66_67del (p.Glu23fs)[H]	0	0	5	8	0	13
	c.5123C>A (p.Ala1708Glu)[H]	0	4	4	3	0	11
	c.815_824dup (p.Thr276fs)[H]	0	0	3	5	0	8
	c.5266dupC (p.Gln1756Profs)[H]	6	0	2	0	0	8
	c.-19-?_6325+?del[NC]	0	0	6	0	0	6
	c.4645_4646dup (p.Thr1550Lysfs)[NC]	0	0	0	4	0	4
	c.5075-?_5193+?del	0	0	4	0	0	4
	c.122A>T (p.His41Leu)	0	0	3	0	0	3
	c.3331_3334del (p.Gln1111fs)[H]	1	2	0	0	0	3
	c.5278-?_5467+?del	0	0	0	3	0	3
BRCA2	c.2808_2811del (p.Ala938Profs)[H]	3	1	2	0	0	6
	c.1219C>T (p.Gln407Ter)	0	0	0	3	0	3
	c.3264dupT (p.Gln1089Serfs)[H]	0	0	3	0	0	3
	c.5631del (p.Asn1877fs)	0	0	3	0	0	3
Recurrent PVs (% of total by country)		**10 (52.6)**	**7 (33.3)**	**58 (52.7)**	**26 (31.7)**	**0**	**101 (42.8)**

PVs: Pathogenic Variants; NC = Not in ClinVar; H = on *HISPANEL*

Herzog et al. NPJ BC, 2021

Pathogenic Variants in *PALB2*, *CHEK2* Genes Among 1054 *BRCA*-Negative Hispanics With Breast Cancer: The importance of an ancestry-matched reference population

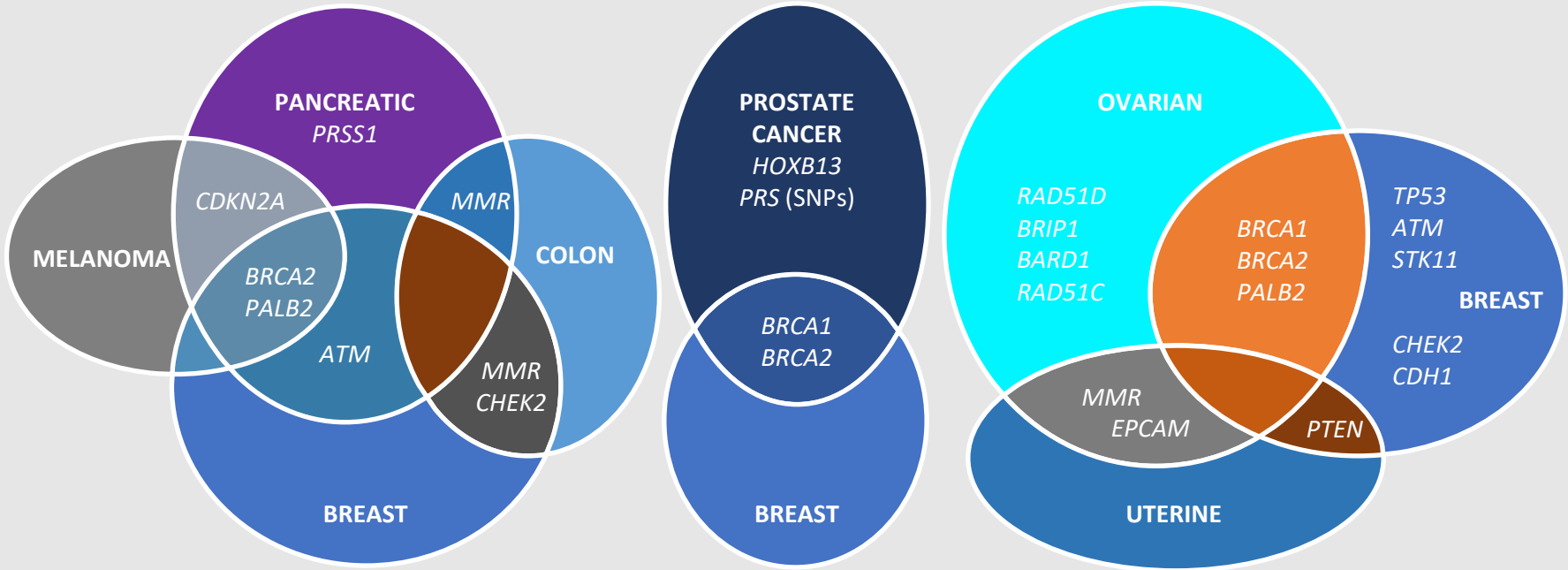
Analysis using ExAC Controls					
Gene	Variant	Cases with variant/ total ancestry matched cases (%)[#]	ExAC controls with variant/ total controls in ExAC (%)[&]	OR (95% CI)	*P* Value
CHEK2	c.707T>C: pL236P	12/ 612 (1.96)	35 / 5603 (0.63)	3.2 (1.5-6.5)	0.0016
PALB2	c.2167_2168del : p.M723fs	9 / 612 (1.14)	5 / 5608(0.09)	12.9 (3.5-51.2)	0.00005
PALB2	c.2411_2412del : p. S804fs	3 / 612 (0.49)	1 / 5601 (0.02)	27.5 (2.1 - 1431.2)	0.0035
Analysis using individually sequenced controls from City of Hope and the Multiethnic Cohort					
Gene	Variant	Cases with variant / total (%)*	Controls with variant / total (%)	OR (95% CI)	*P* Value
CHEK2	c.707T>C: pL236P	14 / 1045 (1.34)	4 / 1189(0.34)	4.1 (1.5 – 22.0)	0.039
PALB2	c.2167_2168del : p.M723fs	9 / 1045 (0.86)	0 / 1189 (0)		<0.0001
PALB2	c.2411_2412del : p. S804fs	3 /1045 (0.29)	1 / 1189 (0.08)	3.7 (0.0 - >100.0)	1.0



Also recurrent in Mexico

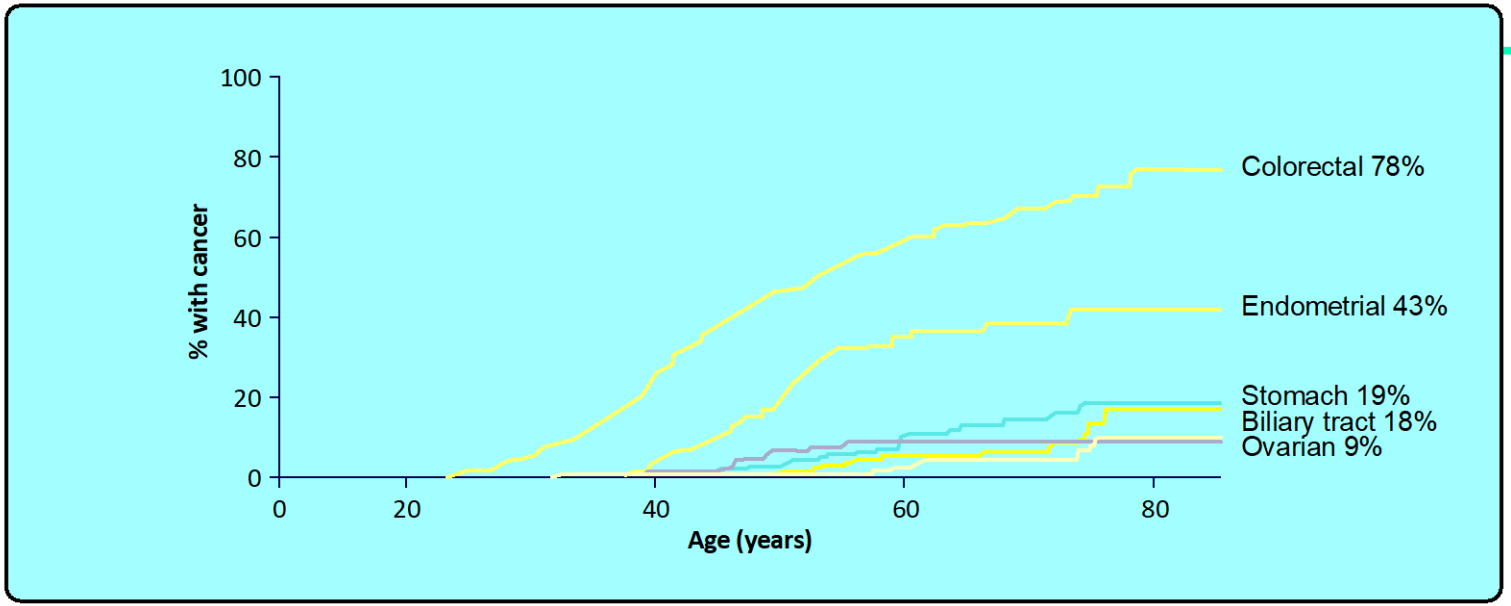
Weitzel et al, Cancer 2019

Genetic Heterogeneity and Overlapping Phenotypes



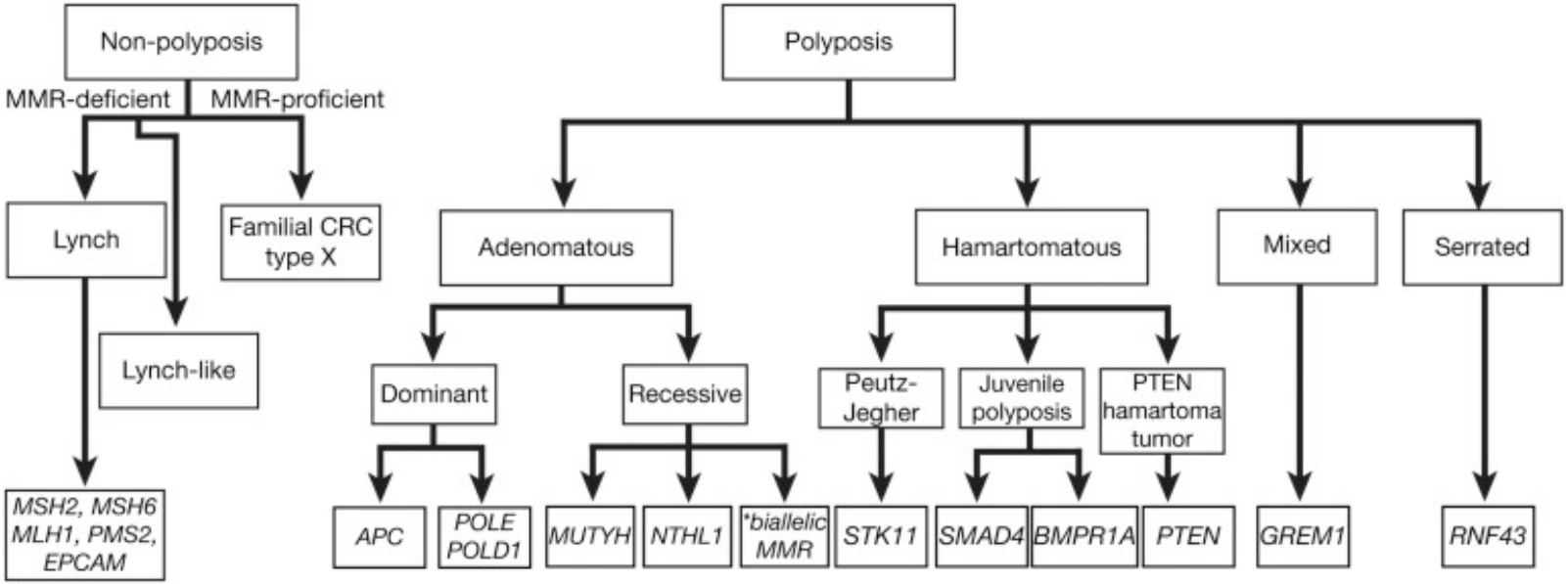
Multi-gene panels (All included on Empower)

Cancer Risks in Lynch Syndrome



Critical: Decreased CRC risk and decreased CRC-mortality by risk appropriate surveillance (e.g., more frequent colonoscopy)

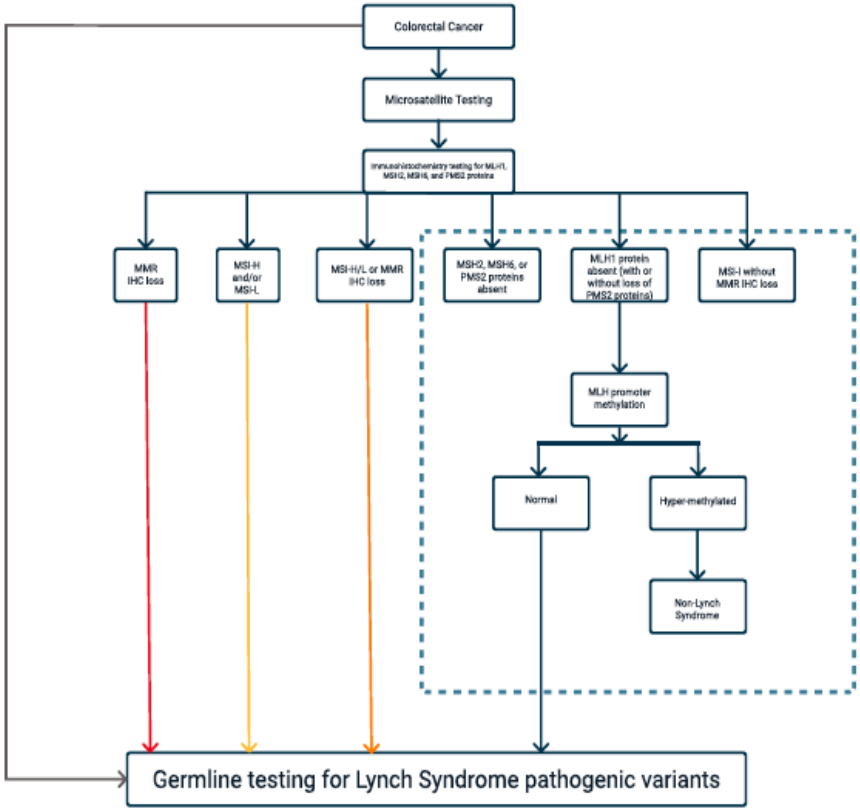
Colorectal cancer predisposition genes



Valle L *Clin Gastro Hep* 2017

Identifying more patients with Lynch syndrome (LS) through universal testing

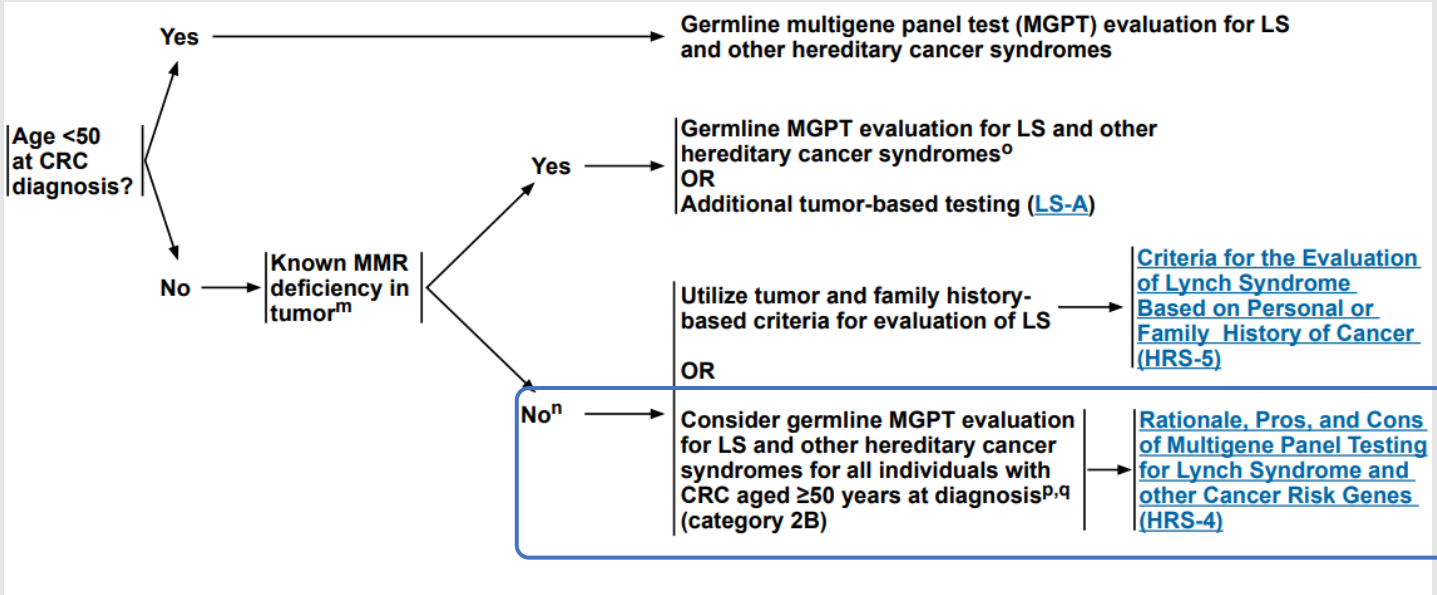
- LS prevalence across multiple ethnic, geographic, and clinical populations is similar
- Universal germline testing of cancer patients reveals that most hereditary colorectal cancers are attributed to Lynch syndrome
- Young patients presenting with CRC and those who fulfill criteria for a familial risk provide the highest returns for LS identification
- Most effective strategy is going directly to germline testing for all CRC



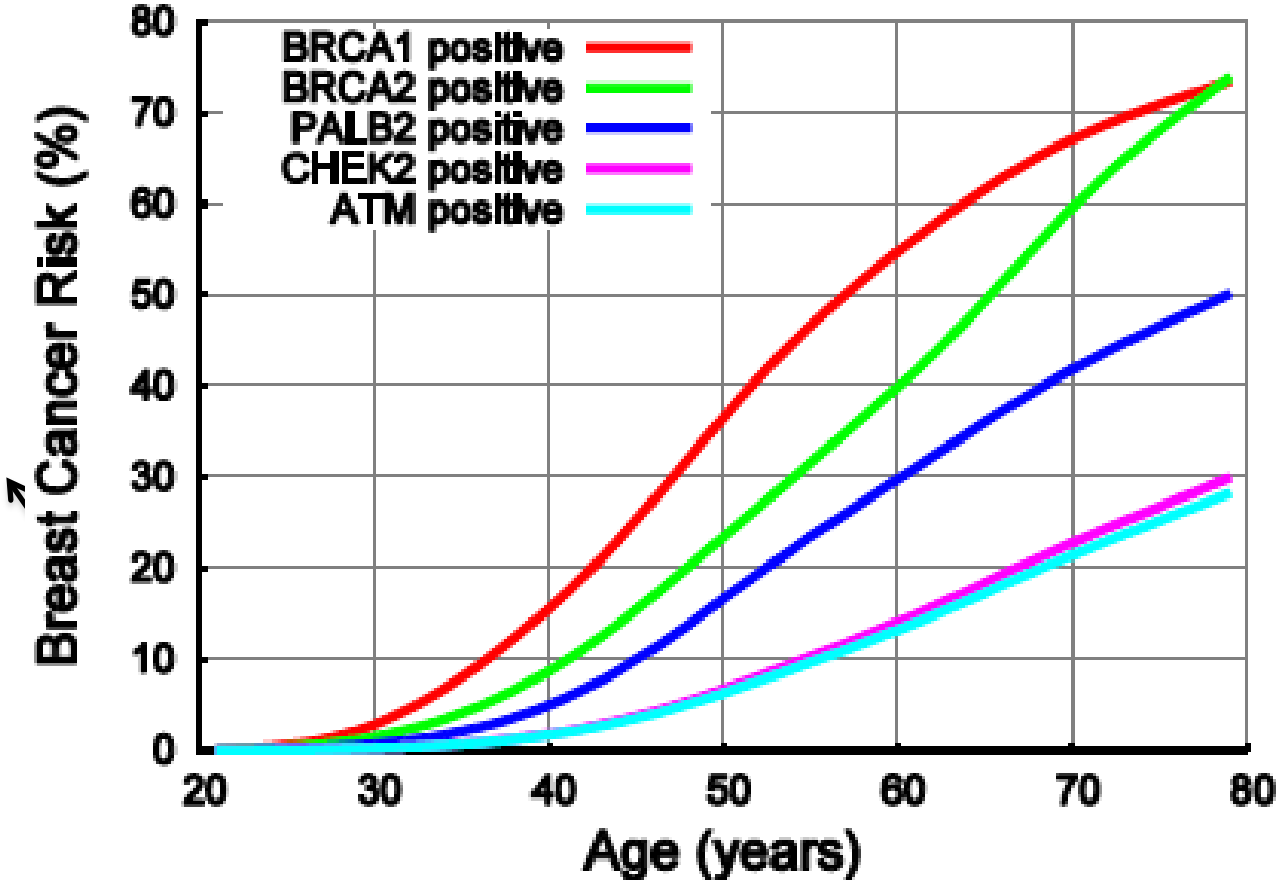
Abu-Ghazaleh et al. Genetics in Medicine (2022) , 1–15

NCCN Guidelines Version 1.2022
Lynch syndrome screening

Criteria for evaluation of Lynch syndrome and other cancer risk genes among individuals with a personal history of colorectal cancer

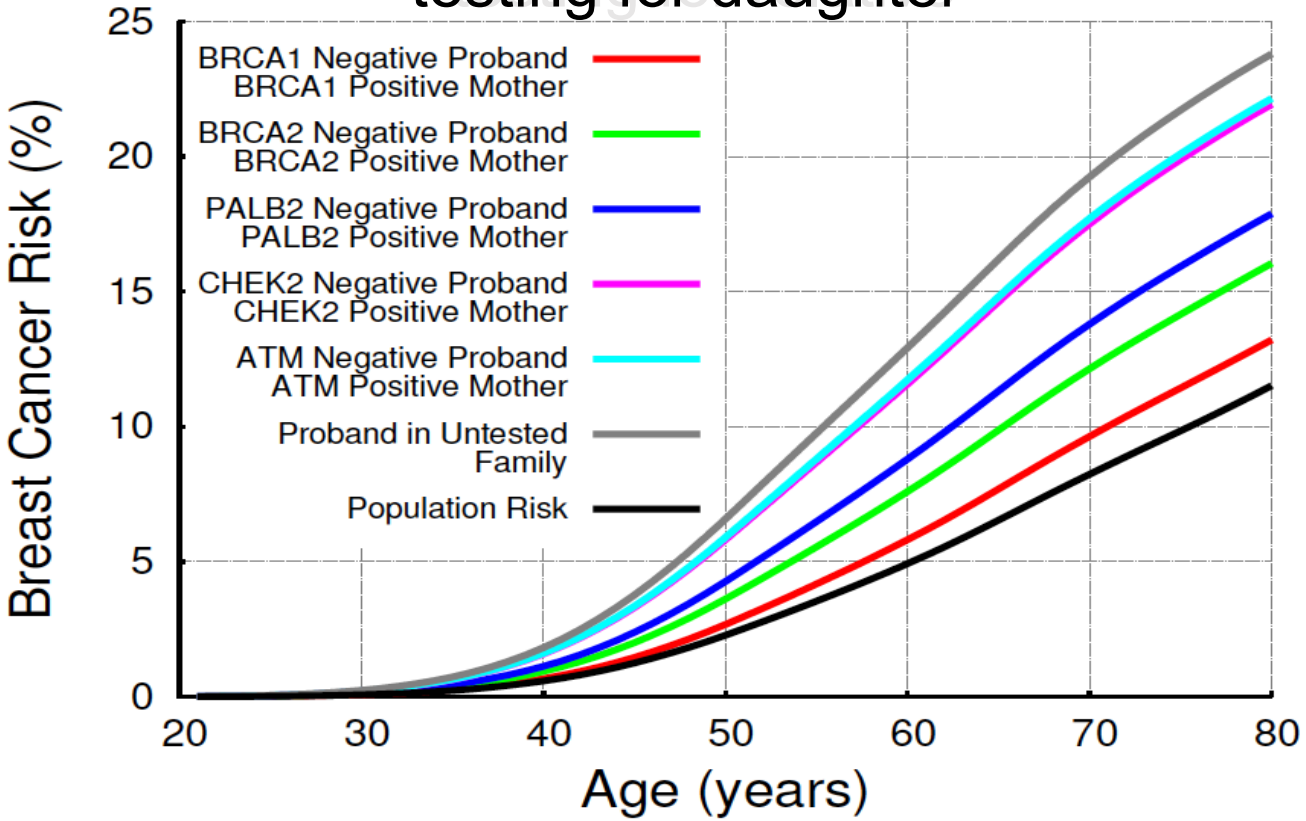


Implications for woman with positive test result



BOADICEA model. Lee et al. Genet Med April 14, 2016; doi:10.1038/gim.2016.31

Negative predictive value of "informative" testing for daughter

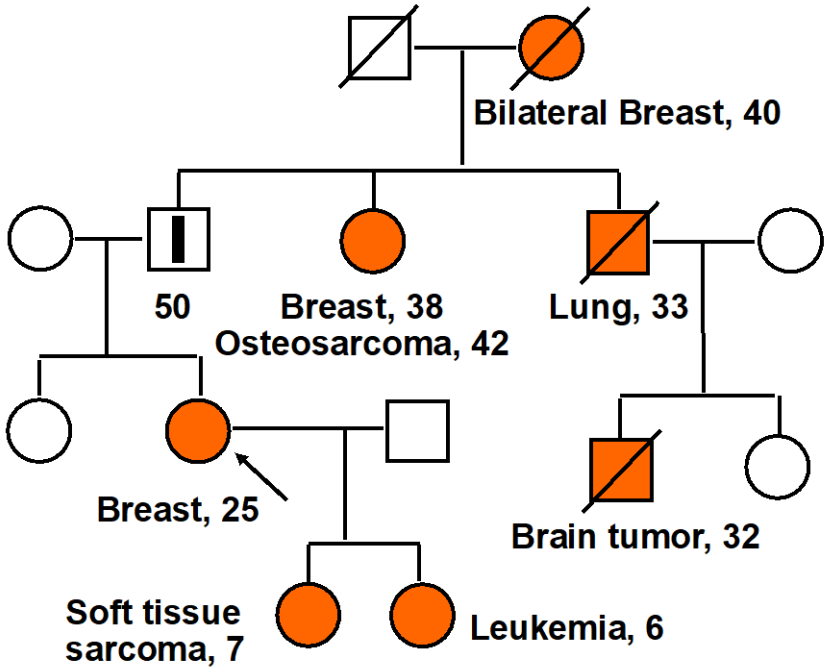


BOADICEA model. Lee et al. Genet Med April 14, 2016; doi:10.1038/gim.2016.31

Cancer Multigene Panel Testing
Levels of Possible Information

Genes associated with a well-known syndrome	• Highest cancer risks • Risk for most associated cancers well defined • Screening and management guidelines well defined • Clear implications for other family members
Genes not associated with a well known syndrome, but well researched	• Moderate to high cancer risks • Risk fairly well defined for some, but not all cancers • Screening and management guidelines dependent upon test results and family history • Implications for family members nuanced
Newer genes	• Cancer risk(s) not well defined (most moderate) • Management guidelines not well defined • Implications to family members not clear • Frequent Variants of Uncertain Significance • May not change medical management

Li-Fraumeni Syndrome (LFS)



TP53-mutation carrier

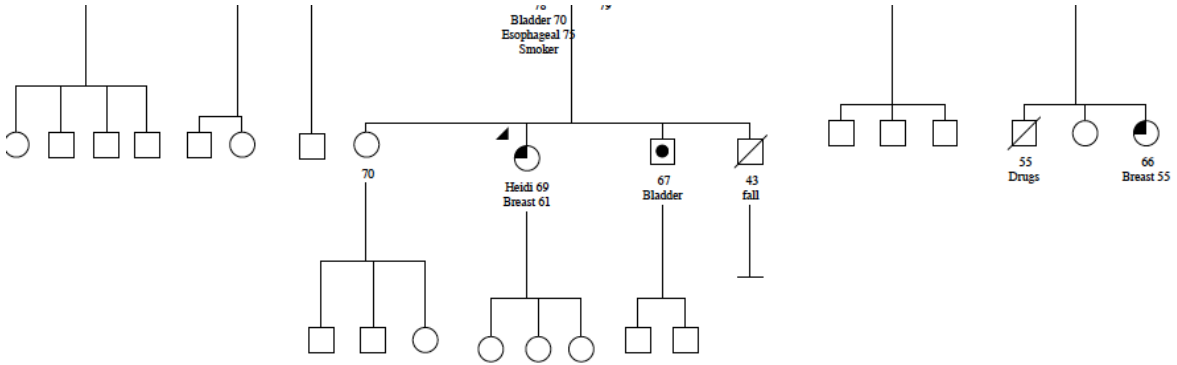
Affected with cancer
Often triple positive BC
(>60% are ER+, HER2+)

LFS Core Cancers:
Brain tumors (choroid plexus)
Sarcoma (rhabdoid, lipo)
Adrenal cortical carcinoma
Breast cancer (young onset)

TP53	**Increased risk of breast cancer** • See Li-Fraumeni Syndrome Management	**No increased risk of ovarian cancer**

JAMA Oncology | Original Investigation

Baseline Surveillance in Li-Fraumeni Syndrome Using Whole-Body Magnetic Resonance Imaging A Meta-analysis



TP53 p.R248Q (c.743G>A) Research Study Findings

RESULTS

Tissue Site	*NGS Genotype*	*NGS Read Depth (Het Ratio)*	*Sanger Genotype*
DNA from eyebrow pluck	Wild-type	10293x	Wild-type

Somatic *TP53* variants frequently confound germ-line testing results

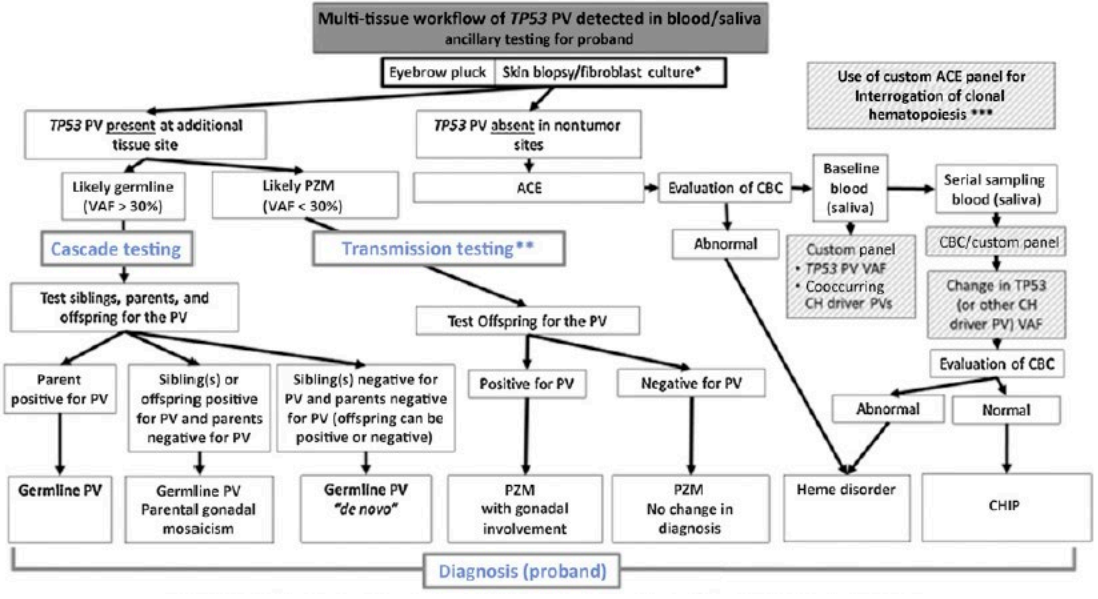
Jeffrey N. Weitzel, MD[1], Elizabeth C. Chao, MD[2,3], Bita Nehoray, MS[1], Lily R. Van Tongeren, BA[1], Holly LaDuca, MS[2], Kathleen R. Blazer, EdD, MS[1], Thomas Slavin, MD, DABMD FACMG[1], Tina Pesaran, MS[2], Christina Rybak, MS[1], Ilana Solomon, ScM, MA[1], Mariana Niell-Swiller, MS[1], Jill S. Dolinsky, MS[2], Danielle Castillo, BSc[1], Aaron Elliott, PhD[2], Chia-Ling Gau, PhD[2], Virginia Speare, PhD[2] and Kory Jasperson, MS[2]

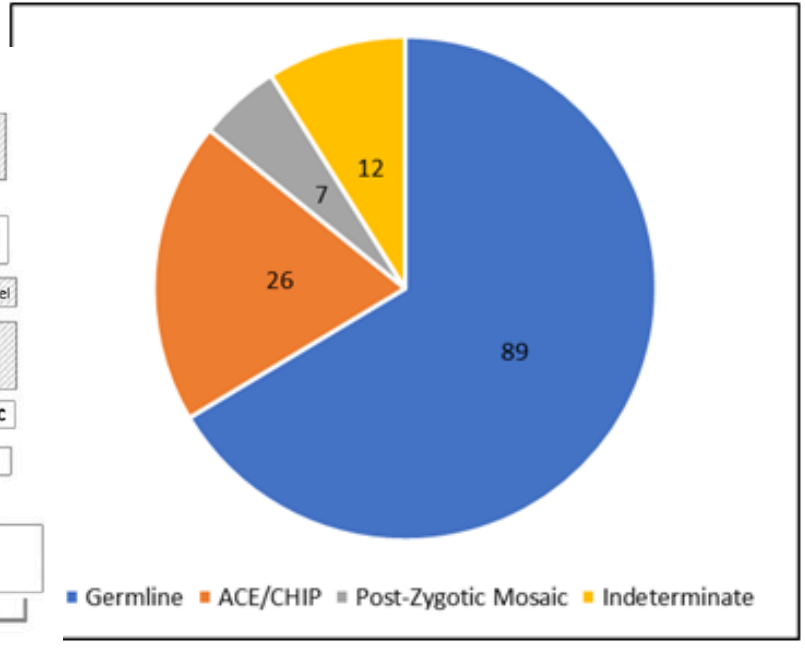
	Totals, *n* (%)	MGPT	*TP53* gene-specific	*P* value
Total testing inclusive of *TP53*	116,084	114,630	1,454	
Total *TP53*-positive cases	353	285	68	
Evidence for ACE	72 (20.4%)	66 (23.2%)	6 (8.8%)	$P = 0.005$
Average age at testing (years)	57	58.5	39.5	$P = 0.009$
Meets criteria for *TP53* testing				
Breast cancer diagnosis <31 years	7 (9.7%)	6 (9.1%)	1 (16.7%)	ns
Chompret criteria	4 (5.6%)	2 (3%)	2 (33.3%)	$P = 0.002$
Results of ancillary testing				
Evidence confirming ACE	32 (91.4%)	29 (96.7%)	3 (60%)	$P = 0.007$
Evidence supporting germ line	3 (8.6%)	1 (3.3%)	2 (40%)	ns

Weitzel et al. Genetics In Medicine, 2017

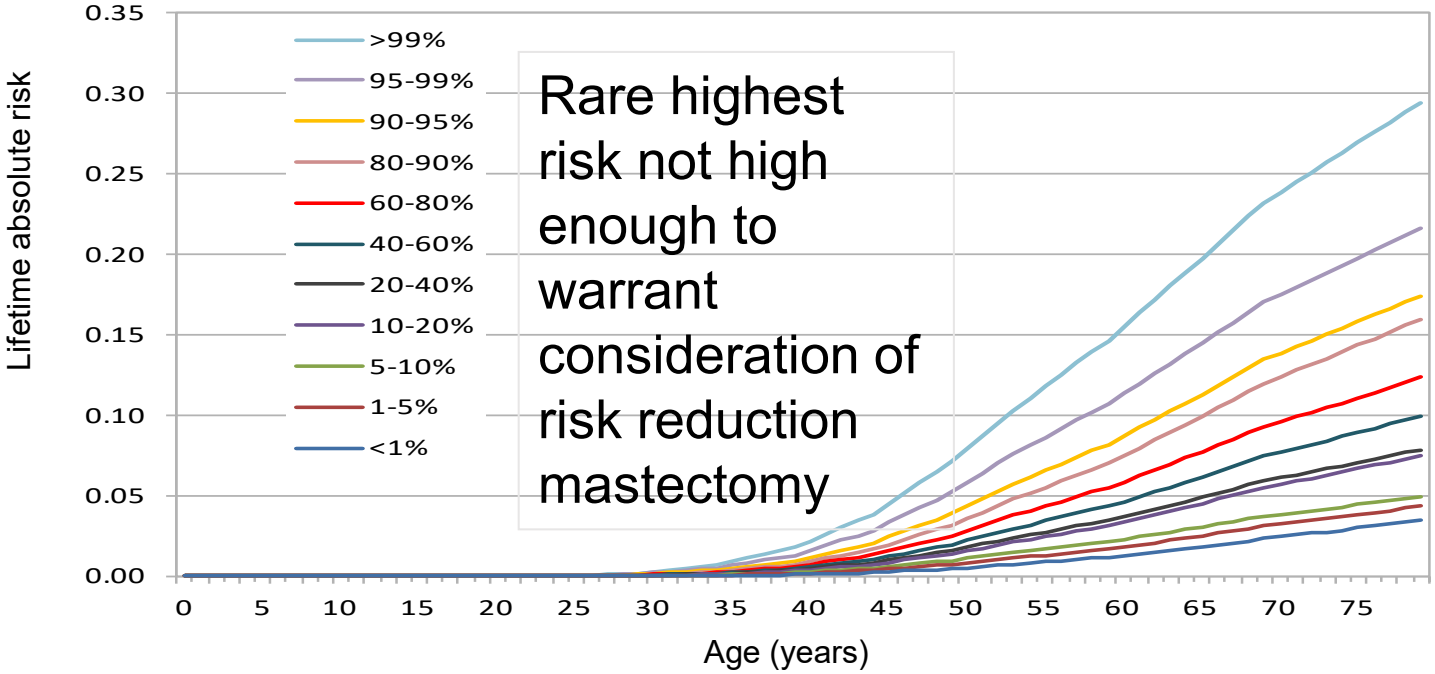
Clonal Hematopoiesis and Mosaicism Revealed by a Multi-Tissue Analysis of Constitutional *TP53* Status

Danielle Castillo[1], Tze-An Yuan[1], Bita Nehoray[1], Aleck Cervantes[1], Kevin K. Tsang[1], Kai Yang[1], Sharon R. Sand[1], Janet Mokhnatkin[1], Josef Herzog[1], Thomas P. Slavin[1], Sophie Hyman[2], Alison Schwartz[2], Benjamin L. Ebert[2], Christopher I. Amos[3], Judy E. Garber[2], and Jeffrey N. Weitzel[1,4]





77-SNP Polygenic Risk Score (PRS) Can Stratify Groups for Absolute Risk Assessment With Age



Mavaddat N et al. J Natl Cancer Inst. 2015;107(5)

Health Equity and Benefits of GWAS Insights

Emerging challenges to health equity include the need to go beyond the majority/European populations

validate GWAS and promising tools such as polygenic risk scores (PRS) for cancer and chronic medical illnesses

PRSs are subject to the same biases that affect virtually all clinical genomic information, including that of the limited ethnic diversity of the data used in their development, relevant to global efforts in cancer prevention.

ARTICLE

Received 8 May 2014 | Accepted 12 Sep 2014 | Published 20 Oct 2014

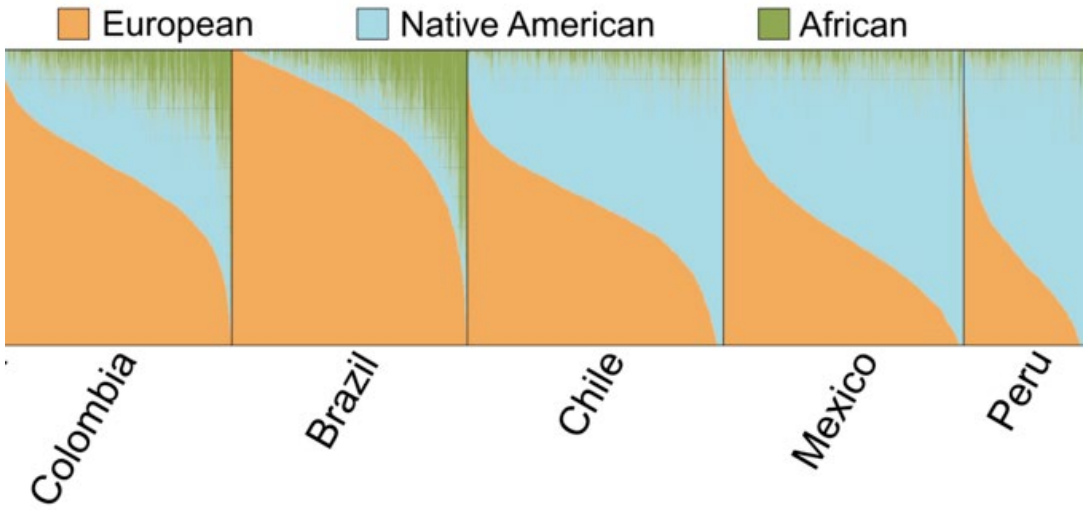
DOI: 10.1038/ncomms6260 OPEN

Genome-wide association study of breast cancer in Latinas identifies novel protective variants on 6q25

Laura Fejerman[1], Nasim Ahmadiyeh[2], Donglei Hu[1], Scott Huntsman[1], Kenneth B. Beckman[3], Jennifer L. Caswell[1], Karen Tsung[2], Esther M. John[4,5], Gabriela Torres-Mejia[6], Luis Carvajal-Carmona[7,8], María Magdalena Echeverry[7], Anna Marie D. Tuazon[7], Carolina Ramirez[8], COLUMBUS Consortium[†], Christopher R. Gignoux[9], Celeste Eng[10], Esteban Gonzalez-Burchard[10], Brian Henderson[11], Loic Le Marchand[12], Charles Kooperberg[13], Lifang Hou[14], Ilir Agalliu[15], Peter Kraft[16], Sara Lindström[16], Eliseo J. Perez-Stable[1], Christopher A. Haiman[11] & Elad Ziv[1]

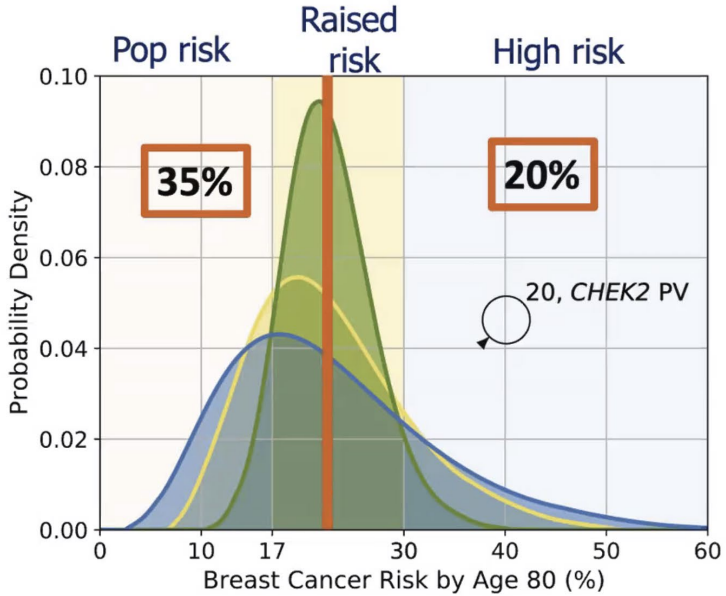
- minor allele for this variant is strongly protective (rs140068132: odds ratio (OR) 0.60, 95% confidence interval (CI) 0.53-0.67, P=9 x 10-18)
- originates from Indigenous Americans and is uncorrelated with previously reported risk variants at 6q25

Latin American Populations are Highly Admixed, with varying European origin



Ruiz-Linares et al. 2014

Combining PRS & risk factors altogether: reclassification – *CHEK2*



Average *CHEK2* Risk

Polygenic Risk Score

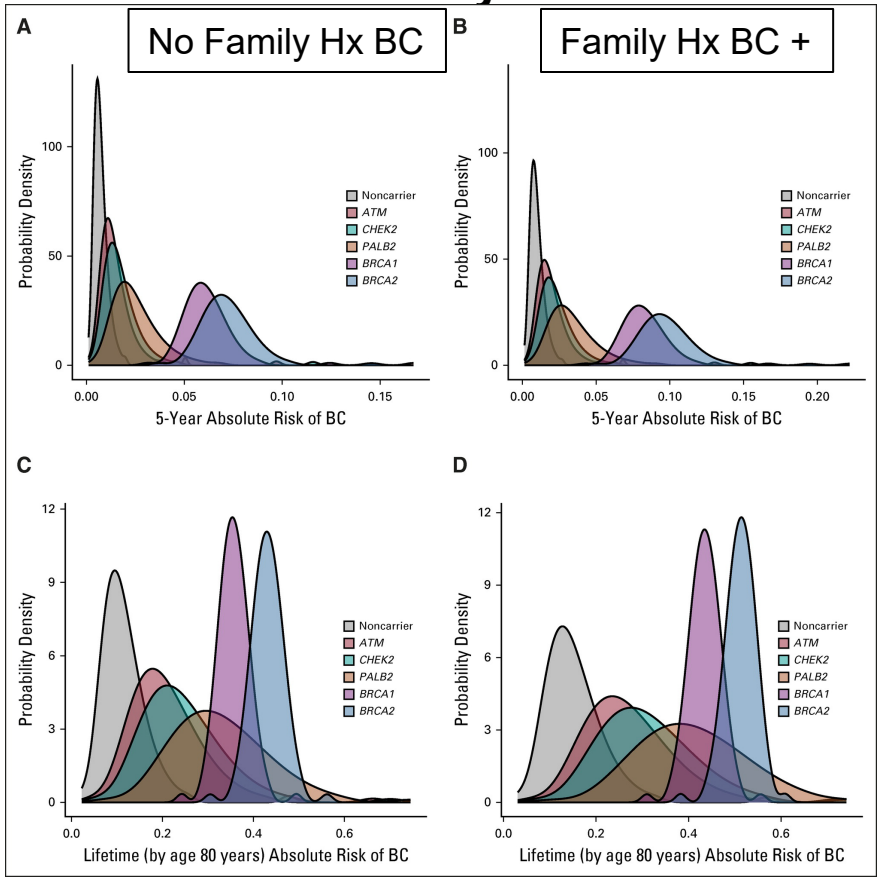
Lifestyle/hormonal risk factors

Full model

Lee et al, Genet Med 2019

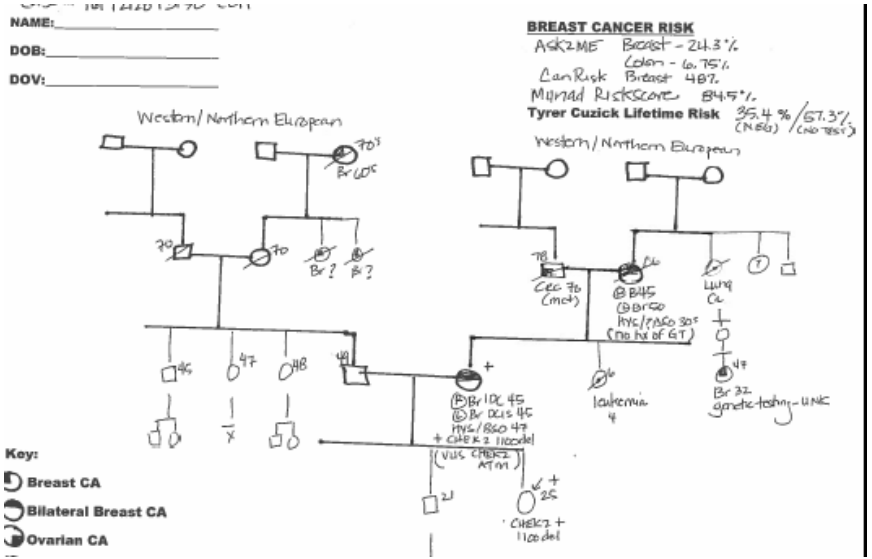
CARRIERS Study: population-based study of multigene panel variant risk modification by PRS

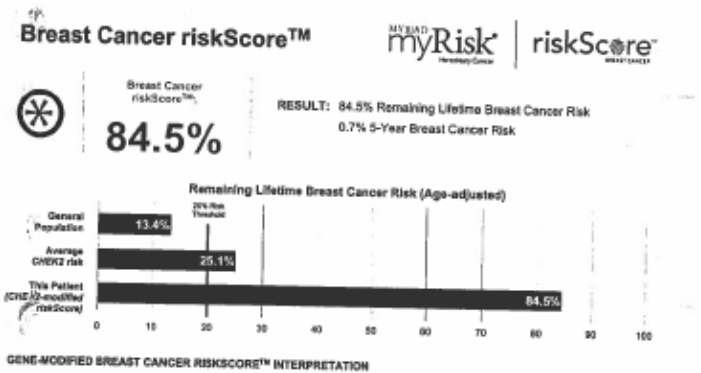
Distribution of the 5-year and lifetime (by age 80 years) absolute risk for women at age 40 years, with/without first-degree family history of BC



Gao et al; *Journal of Clinical Oncology* 2021. Ahead of Print DOI: 10.1200/JCO.20.01992

Exemplar case…What about the outlier?





Multigene panel test, combined with PRS and empiric risk model

Challenges to incorporation of PRS in multifactorial cancer risk assessment

- Feasibility - no commercial access to "best PRS" (313 snp; or Mavaddat 77).
- Need global population representation in GWAS
- Technical challenges of integration in risk model programs (e.g., CANRISK)
- Acceptability for patients and clinicians alike; especially "extreme" risk estimates
- Uptake of interventions
- Impact on clinical outcomes and health systems

Genomic Cancer Risk Assessment

- Hereditary breast and ovarian cancer affects all world populations
- Common ancestry, geography and world history are reflected in the presence and prevalence of founder mutations
- There are guidelines for screening (MRI), risk reduction (RRSO, RRM), and emerging indications for genetically targeted precision therapeutics, and *BRCA* testing influences surgical decisions in a risk-appropriate way
- Multigene panel tests are efficient and sensitive, but be prepared for the unexpected (e.g., *CDH1*, mosaic *TP53*)

Precision Prevention

- Surveillance and prevention can improve survival in at-risk individuals
  - Protocols will need to be adapted to lower risk
- PRS holds the promise of further precision estimating BC risk; the greatest early benefit likely to be:
  - ability to discern higher (and lower…) risk ATM and CHEK2 carriers
  - justification for high risk screening for some women with limited family structure, no PV, and borderline empiric risk model estimates

Summary

- Representative populations are needed for variant curation and genetic risk estimation
- Training in genomic cancer risk assessment and counseling is important for dissemination and implementation of GCRA
- The remarkable advances in genetic analysis technologies, with ever more economy, should be brought to bear to enhance access globally
- International collaboration essential, and can influence care locally

Acknowledgements:

- Breast Cancer Research Foundation (#20-172)
- Conquer Cancer Research Professorship in Breast Cancer Disparities
- Clinical Cancer Genomics Community of Practice and GCRA training courses supported by NCI R25-CA171998-01A1
- Clinical Cancer Genomics Community Research Network; NCI RC4CA153828
- NCI R01 CA242218