Gene Panels: The Next Step in Hereditary Cancer Evaluation

Faculty

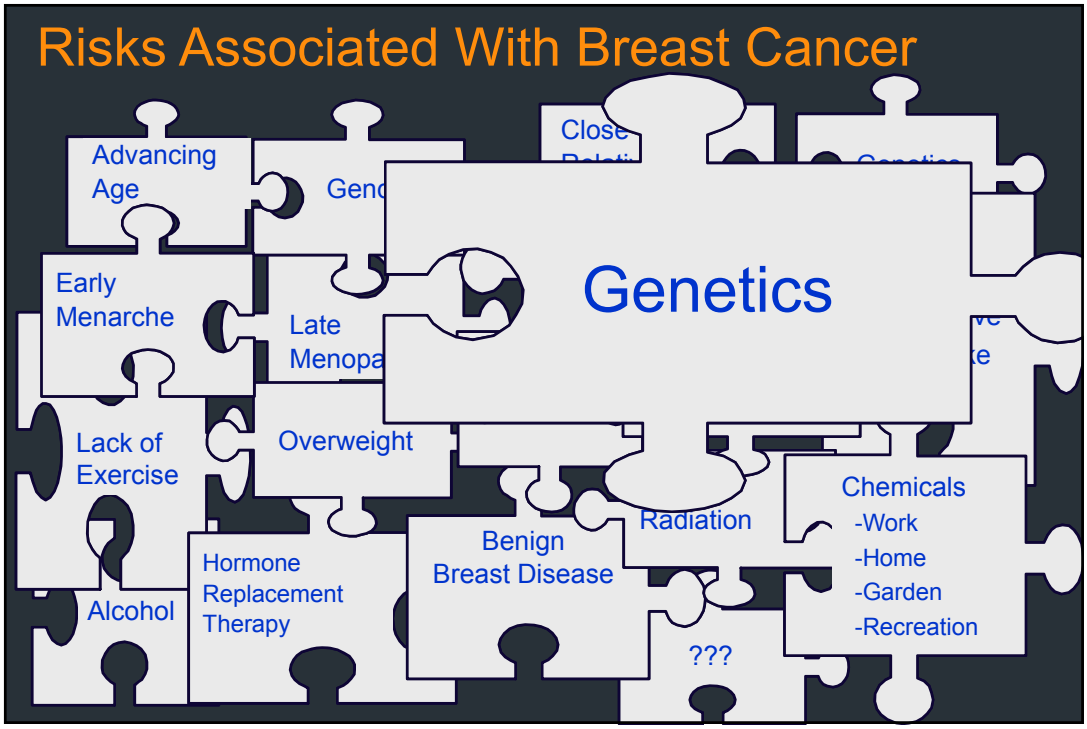
Julia Smith, MD, PhD (Moderator)
Clinical Director
Cancer Screening Program at the Laura and Isaac Perlmutter Cancer Center at NYU Medical Center
Director
NYU and Bellevue Lynne Cohen Foundation and
Caring Together Project for Woman with Increased Risk for Cancer
New York, NY

Jeffrey Weitzel, MD
Jeffrey Weitzel, MD
Director
Division of Clinical Cancer Genetics
City of Hope
Duarte, CA

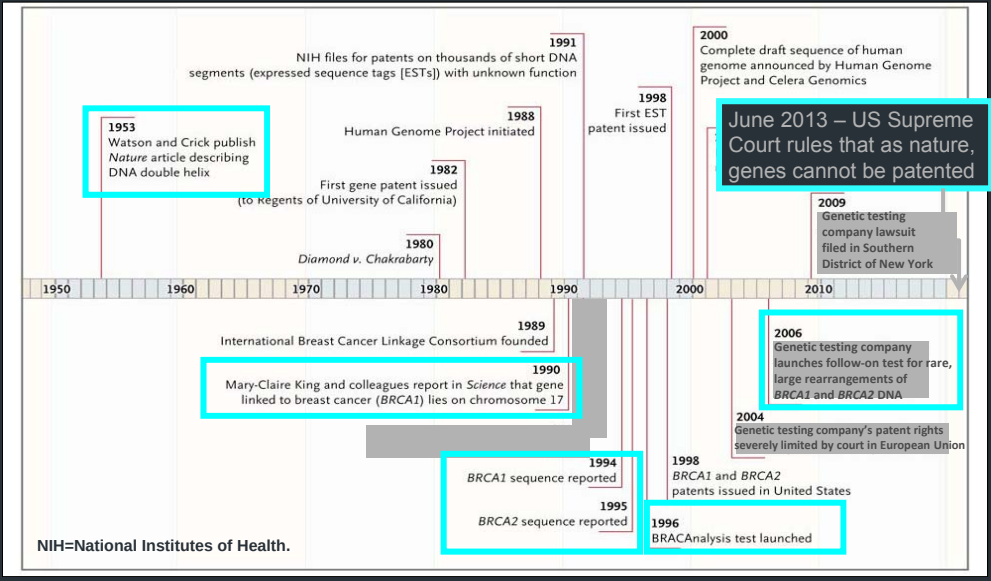
Adam Ofer, MD
Director of Gynecology
Norwalk Hospital
Norwalk, CT

Background on hereditary basis for cancer – Breast cancer as the exemplar

Risks Associated With Breast Cancer



Timeline of Important Events in DNA Patenting (Top) and the Discovery and Use of Genes Conferring Susceptibility to Breast and Ovarian Cancer (Bottom)



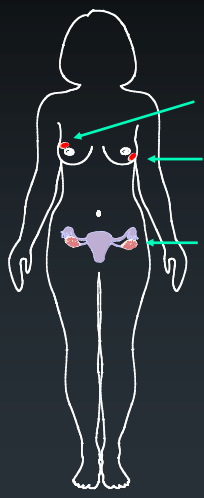
Adapted from the Kesselheim AS, Mello MM. *N Engl J Med*. 2010;362(20):1855-1858.

Scientists Identify a Mutant Gene Tied to Hereditary Breast Cancer

"…a genetic trophy so ferociously coveted and loudly heralded that it had taken on a near-mythic aura…"

Angier N. *The New York Times.* September 15, 1994.

BRCA1- and *BRCA2*-Associated Cancers: Lifetime Risk



Breast cancer 50%–85% (often early age at onset)

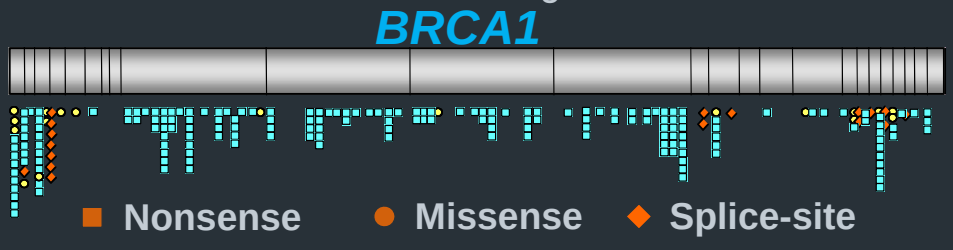
Second primary breast cancer 40%–60%

Ovarian cancer 15%–45%

- Absolute risk likely to be higher than 10%
  - Prostate cancer
- Absolute risk 10% or lower
  - Male breast cancer
  - Fallopian tube cancer
  - Pancreatic cancer

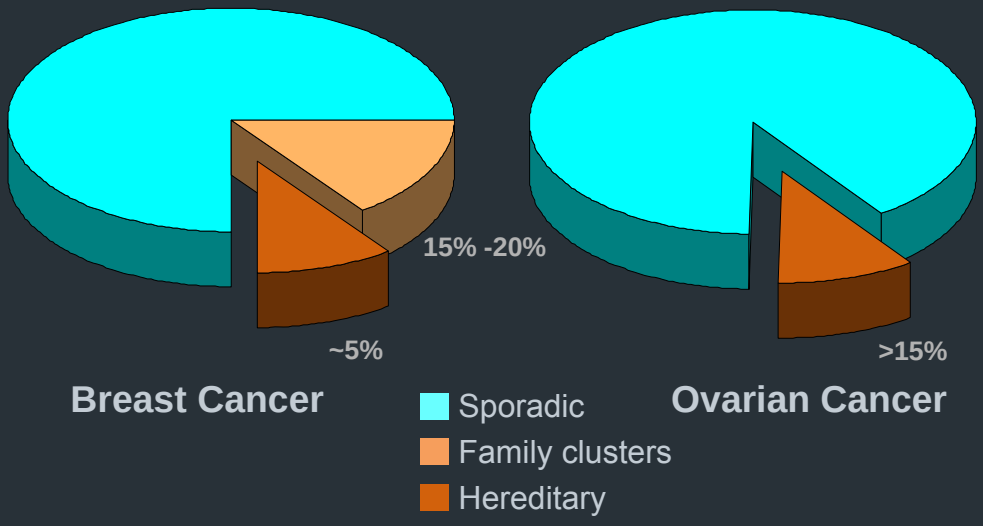
BRCA1 and *BRCA2*

- On chromosomes 17 and 13, respectively
- Autosomal dominant transmission
- Proteins have a role in genomic stability
- >2000 different mutations, polymorphisms, and variants distributed over both genes



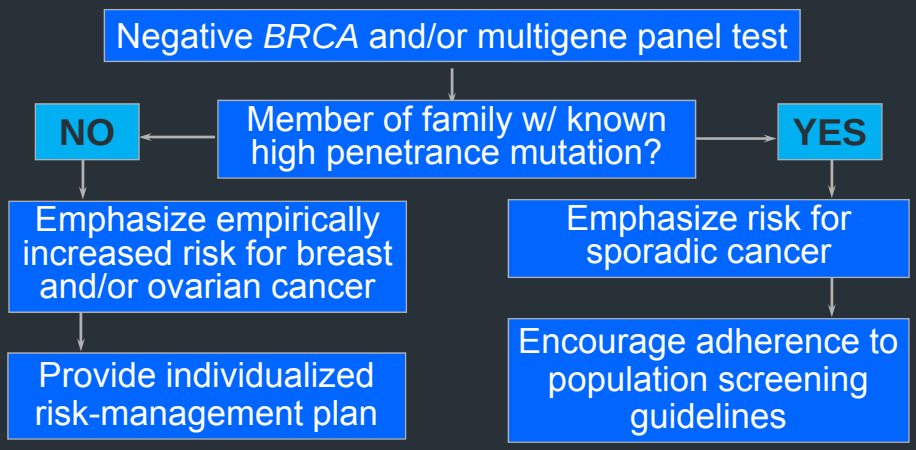
National Institutes of Health/National Human Genome Research Institute. Breast Cancer Information Core. https://research.nhgri.nih.gov/projects/bic/. Accessed May 6, 2015.

How Much Breast and Ovarian Cancer Is Hereditary?

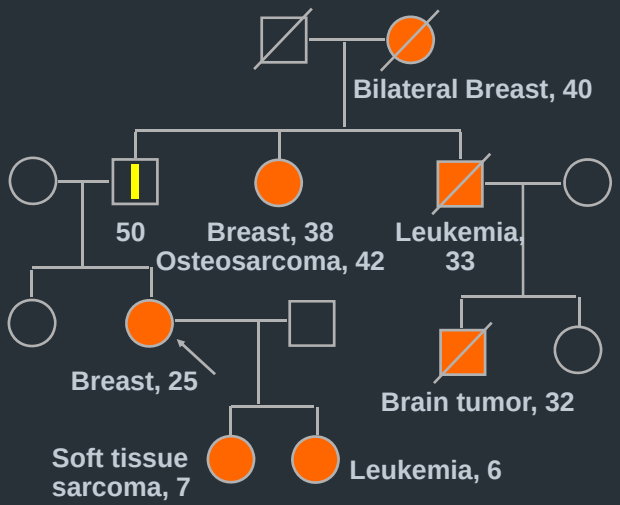


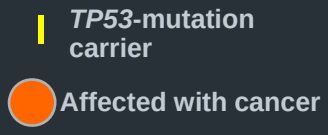
BRCA mutations prevalent in triple negative breast cancer (5%–21%) and medullary breast cancer

Clinical Management of Breast Cancer Susceptibility Gene Mutation-Negative Patients



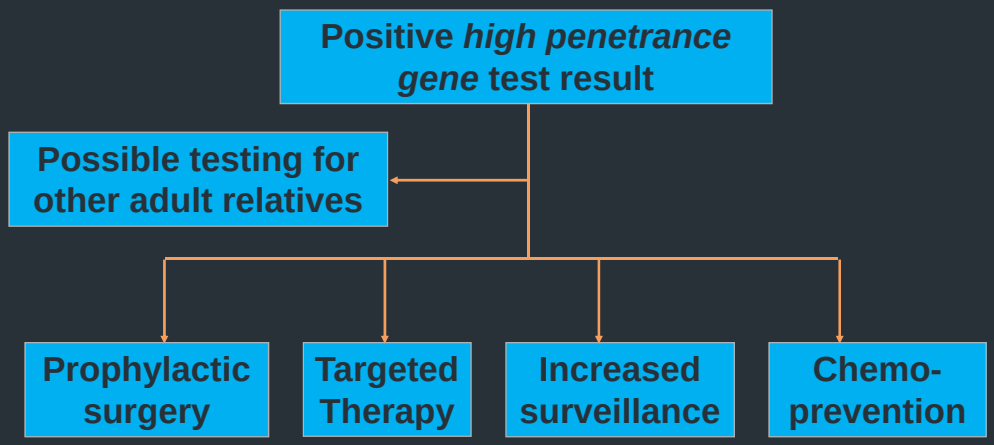
Li-Fraumeni Syndrome (LFS)





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

Clinical Management of Mutation-Positive Patient



Angelina Jolie's Double Mastectomy Puts Genetic Testing in the Spotlight

An effective intervention:

Study of 483 BRCA carriers: >90% risk reduction

Rebbeck TR et al. *J Clin Oncol*. 2004;22(6):1055-1062.

Prospective Study of Breast Cancer Incidence in Women With a *BRCA1* or *BRCA2* Mutation Under Surveillance With and Without Magnetic Resonance Imaging

Annual surveillance with MRI is associated with a significant reduction in the incidence of advanced-stage breast cancer in *BRCA1* and *BRCA2* carriers.

Warner E et al. *J Clin Oncol*. 2011;29(13):1664-1669.

Oophorectomy Reduces Ovarian Cancer, Breast Cancer, and All-Cause Mortality

Greatest breast cancer risk reduction among *BRCA1* mutation carriers without a prior dx of breast cancer who had their oophorectomy < age 50

HR: 0.15 (95% CI 0.04–0.63)

All-cause mortality after risk-reducing salpingo-oophorectomy, HR (98% CI)	0.40 (0.26–0.61)
Age < 50y	0.41 (0.25–00.67)
Age ≤ 50y	0.37 (0.15–0.94)

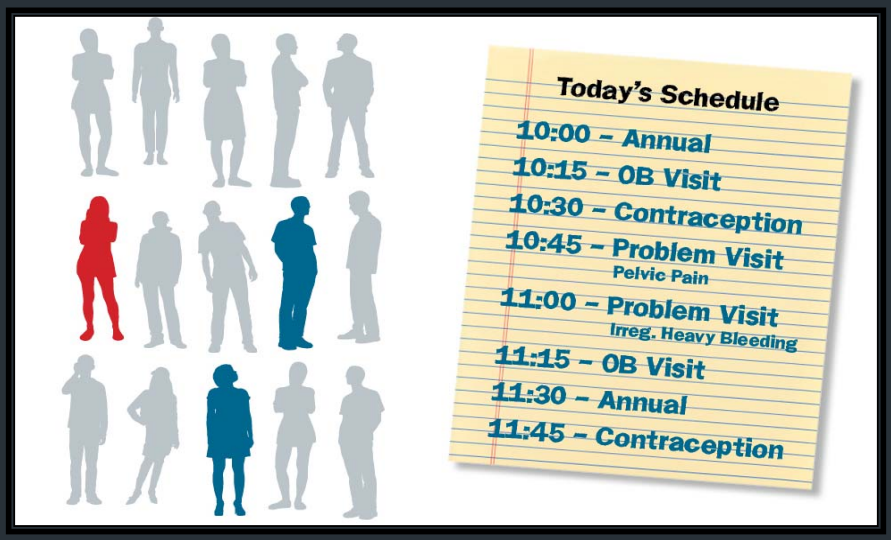
CI=confidence interval; HR=hazard ratio.

Adapted from Clague J et al. *PloS One*. 2011;6(9):e25632.

Genetic status is helping to determine composition of breast and ovarian cancer treatment regimens

Why Family History Matters

Do You See How Cfhx Impacts All Patients?

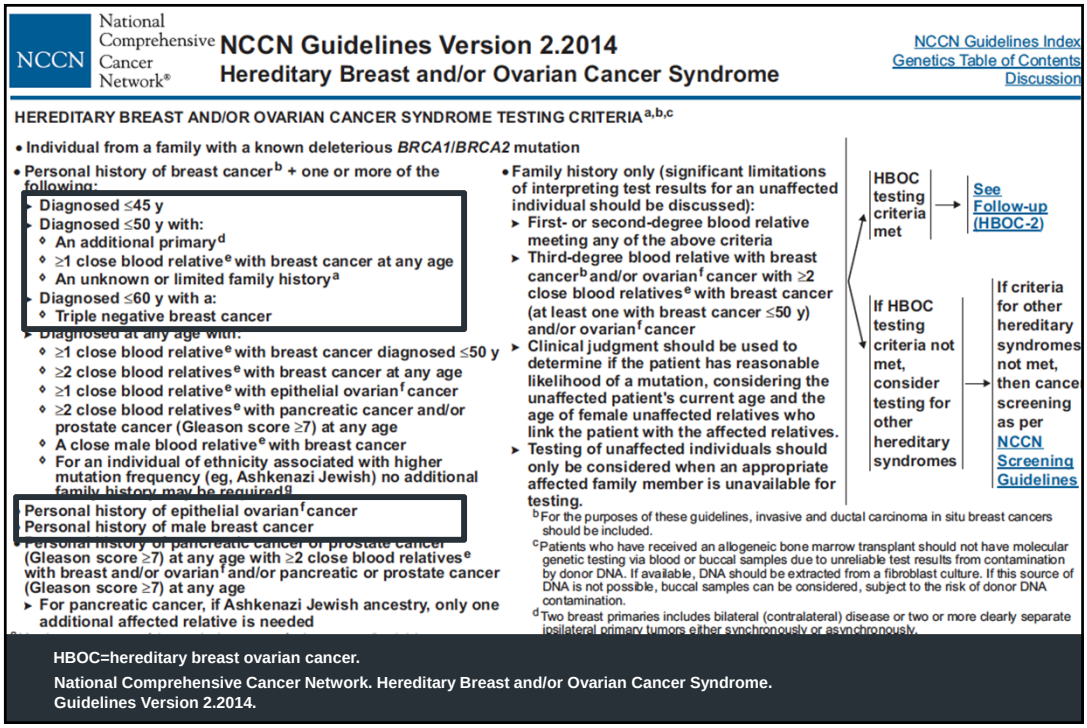


Cfhx=cancer family history.

"Normalizing" Hereditary Cancer Testing

The Follow-Up Visit

- Positive Results
- Negative Results
  - Barking up the family tree
  - Discussing Familial Risk
- Cancer Risk Reduction
  - Screening options
  - Medical management choices
  - Lifestyle choices



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Hereditary Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
Genetics Table of Contents
Discussion

HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA[a,b,c]

- Individual from a family with a known deleterious *BRCA1*/*BRCA2* mutation
- Personal history of breast cancer[b] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - An additional primary[d]
    - ≥1 close blood relative[e] with breast cancer at any age
    - An unknown or limited family history[a]
  - Diagnosed ≤60 y with a:
    - Triple negative breast cancer
  - Diagnosed at any age with:
    - ≥1 close blood relative[e] with breast cancer diagnosed ≤50 y
    - ≥2 close blood relatives[e] with breast cancer at any age
    - ≥1 close blood relative[e] with epithelial ovarian[f] cancer
    - ≥2 close blood relatives[e] with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age
    - A close male blood relative[e] with breast cancer
    - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[g]
- Personal history of epithelial ovarian[f] cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer or prostate cancer (Gleason score ≥7) at any age with ≥2 close blood relatives[e] with breast and/or ovarian[f] and/or pancreatic or prostate cancer (Gleason score ≥7) at any age
  - For pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional affected relative is needed

- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood relative meeting any of the above criteria
  - Third-degree blood relative with breast cancer[b] and/or ovarian[f] cancer with ≥2 close blood relatives[e] with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian[f] cancer
  - Clinical judgment should be used to determine if the patient has reasonable likelihood of a mutation, considering the unaffected patient's current age and the age of female unaffected relatives who link the patient with the affected relatives.
  - Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing.

HBOC testing criteria met → See Follow-up (HBOC-2)

If HBOC testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

[b] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

[c] Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to unreliable test results from contamination by donor DNA. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.

[d] Two breast primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.

HBOC=hereditary breast ovarian cancer.

National Comprehensive Cancer Network. Hereditary Breast and/or Ovarian Cancer Syndrome. Guidelines Version 2.2014.

Evolving Models of Practice for Genetic Cancer Risk Assessment (GCRA)

Model	Benefits	Limitations
Academic Model		
Academic/medical center model: Patients referred to cancer genetics program, seen by interdisciplinary team (genetic counselor, nurse, physician). Pre- and post-genetic testing counseling and integrated risk assessment	1. Comprehensive state-of-the-art personalized GCRA delivery including genetics-focused physical exam and medical management 2. Level of care expected of a cancer center setting; billable patient visits 3. Critical research linkage	4. Through-put may be limited by physician availability, personnel costs and time intensity of providing comprehensive GCRA service 5. Possible community clinician barriers to referral
Community Models		
Collaborative model: Community center partners with academic center of excellence	• Advanced practice-based support from the academic center for community center clinicians. • Patients receive high level care • Access to the academic center clinical and research data forms and genetics research	• Possible fees for academic oversight • Time commitment for quality assurance activities
Medical practice model: Oncologist as genetic consultant or other trained/designated physician initiates genetic testing*; only refers patients with positive or ambiguous results to genetics provider (who may or may not be on-site)	• Immediate offering of genetic test may be effective means of GCRA delivery for carefully selected patients • Complicated cases referred to genetics provider for thorough counseling and risk assessment • Bill as usual fee-for-service • Potential downstream revenue generation	• Nuances of GCRA underestimated; possible errant test/testing approach; patient and family may be falsely reassured • Patient may not be given sufficient information to make informed decision for genetic testing/testing strategies
Genetic referral model (or Cancer risk referral model): Patient referred to community-based cancer risk counselor (GC^a/APN^b) for genetic counseling/testing, summary note sent to referring physician	• Meaningful counseling and risk assessment service provided by qualified personnel	• Patient given general vs. tailored risk reduction recommendations • No or limited billable GCRA service no or limited physical exam to help guide assessment • Cancer genetics research participation limited

CG/APN=genetic counselor/advanced practice nurse.

Adapted from Weitzel JN et al. *CA Cancer J Clin*. 2011;61(5):327-359.

Triage model*: APN performs initial personal/family history screening; triages to GC for further assessment; referring physician provides patient-recommendations	• Streamlined referral process • Patients requiring individual counseling identified and seen in a timely manner • Efficient use of limited genetics provider resources	• APN/GC may not have adequate cancer genetics knowledge to triage/assess appropriately • Referring physician may not be familiar with current risk level- based medical management • Cancer genetics research participation limited
Group model*: At-risk individuals attend a group-focused cancer genetics presentation, followed by individual counseling sessions as indicated based on risk and/or as desired by patient	• Efficient for providing overview of GCRA and pre-screening referred patients • Efficient use of limited genetics provider resources	• Ineffective for anxious patients, particularly if recent cancer diagnosis • Time constraints to address individual questions • Group session not a billable service • Patient confidentially/privacy may be compromised
Telemedicine model: Community center servicing a geographically or socioeconomically underserved population partnered with an academic center of excellence	• Patients gain access to academic center -level of clinical care, including opportunities for research participation • Efficient use of limited genetics provider resources	• Requires telemedicine set up and time commitment for quality assurance • consultation services may not be billable • may require funding to establish partnership
Remote open access model*: Educational materials and phone and/or internet counseling provided by for-profit company	• Counseling may be scheduled at the convenience of the patient (possibly from home) • May be cost savings	• Little quality outcomes data • Possible lack of local clinician communication or follow-up • No research opportunities

Adapted from Weitzel JN et al. *CA Cancer J Clin*. 2011;61(5):327-359.

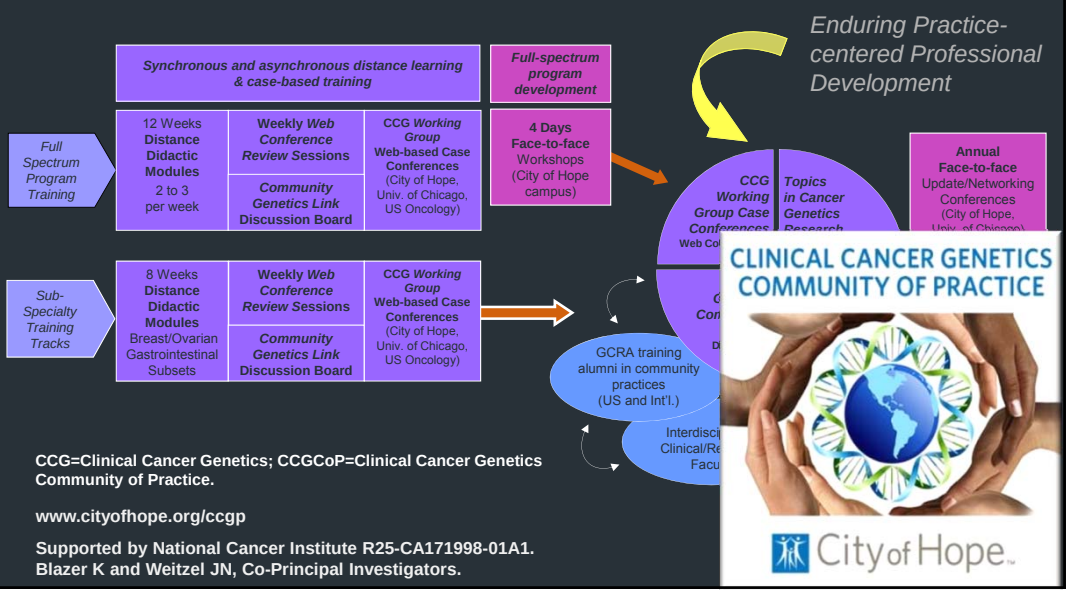
How Have We Learned Cancer Genetics Practice in the Past?

"The hard way"

- Self-directed studies
- Hands-on experience
- Gleaning the literature
- Formal fellowship training

(Medical Oncology, Clinical Genetics, ? Both)

Evolving Model for Academic Health Center-mediated Communities of Practice



CCG=Clinical Cancer Genetics; CCGCoP=Clinical Cancer Genetics Community of Practice.

www.cityofhope.org/ccgp

Supported by National Cancer Institute R25-CA171998-01A1. Blazer K and Weitzel JN, Co-Principal Investigators.

Educational Resources

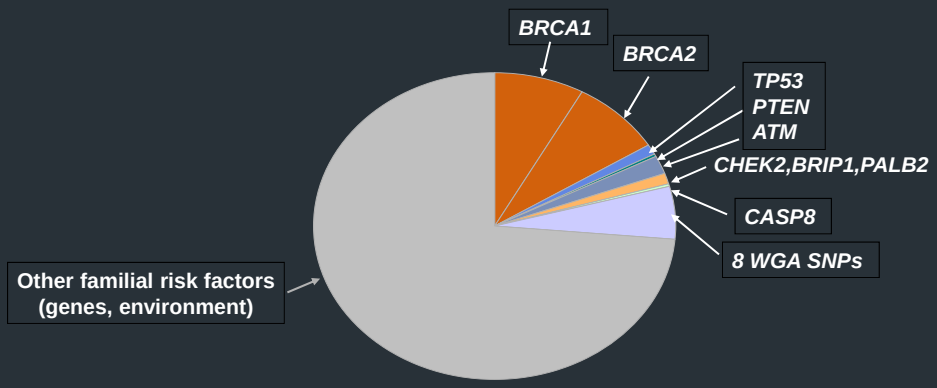
- More robust literature dealing with all the domains
- ASCO University Curriculum and Courses
- NSGC Short Courses, Starter Packs, Flip Charts, Cancer SIG Listserv for members
- ONS Curriculum – courses, scope and practice guidelines, Cancer SIG
- ISONG – scope and practice guidelines
- National Coalition for Health Professional Education in Genetics (NCHPEG)
- City of Hope Intensive Course

ASCO=American Society of Clinical Oncology; ISONG=International Society of Nurses in Genetics; NSGC=National Society of Genetic Counselors; ONS=Oncology Nursing Society; SIG=Scientific Interest Group.

The Follow-Up Visit

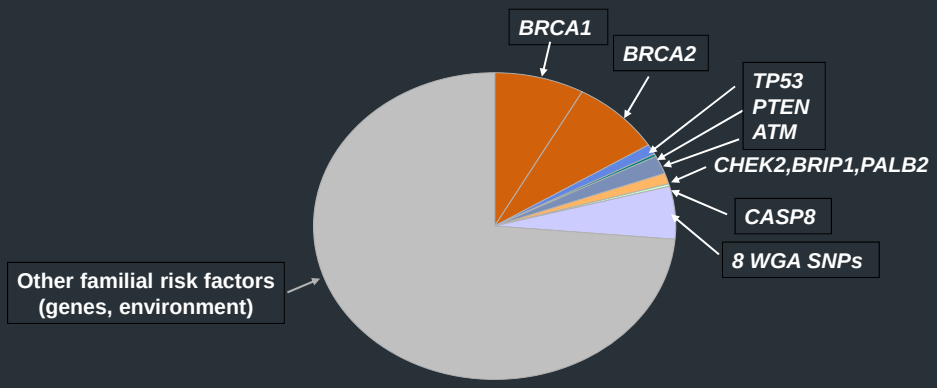
- Positive Results
- Negative Results
  - Barking up the family tree
  - Discussing Familial Risk
- Cancer Risk Reduction
  - Screening options
  - Medical management choices
  - Lifestyle choices

Contribution of Known Genes to Explaining Familial Aggregation of Breast Cancer

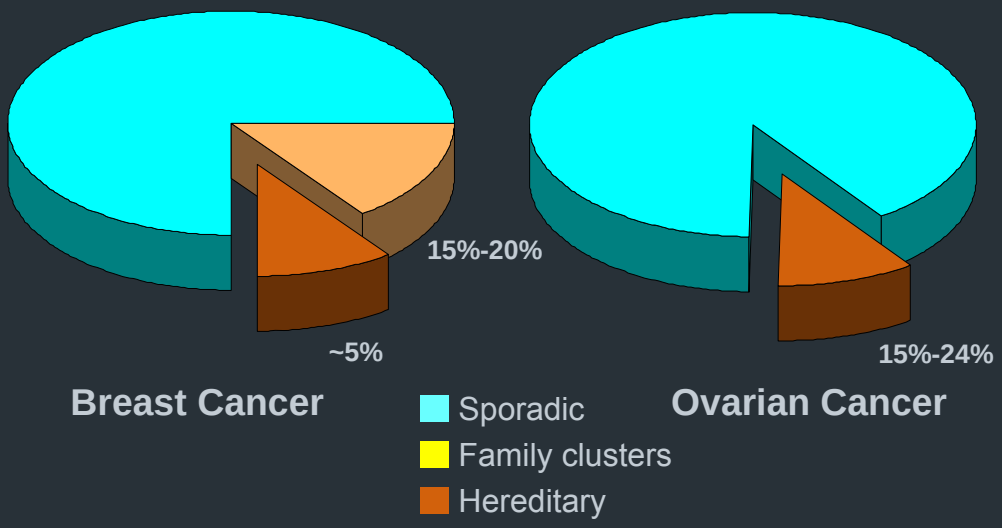


Why Family History Matters

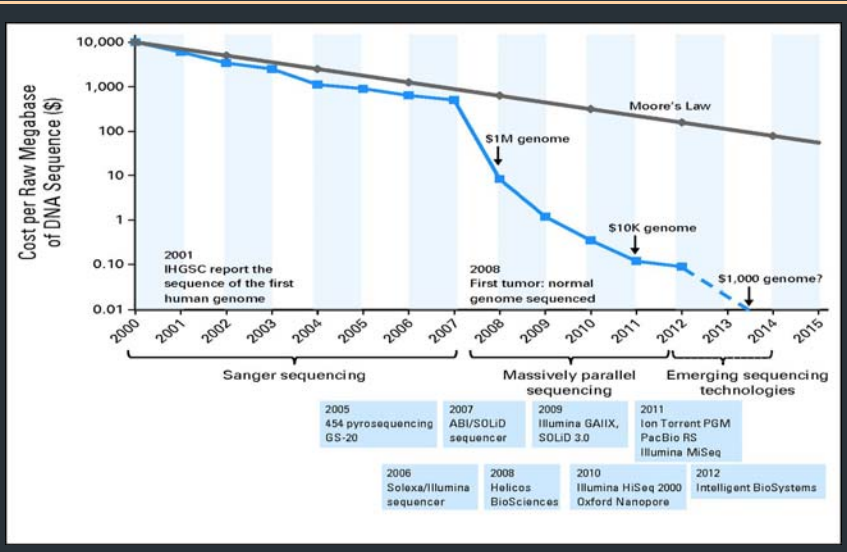
Contribution of Known Genes to Explaining Familial Aggregation of Breast Cancer



How Much Breast and Ovarian Cancer Is Hereditary? It is a different answer with multiplex testing



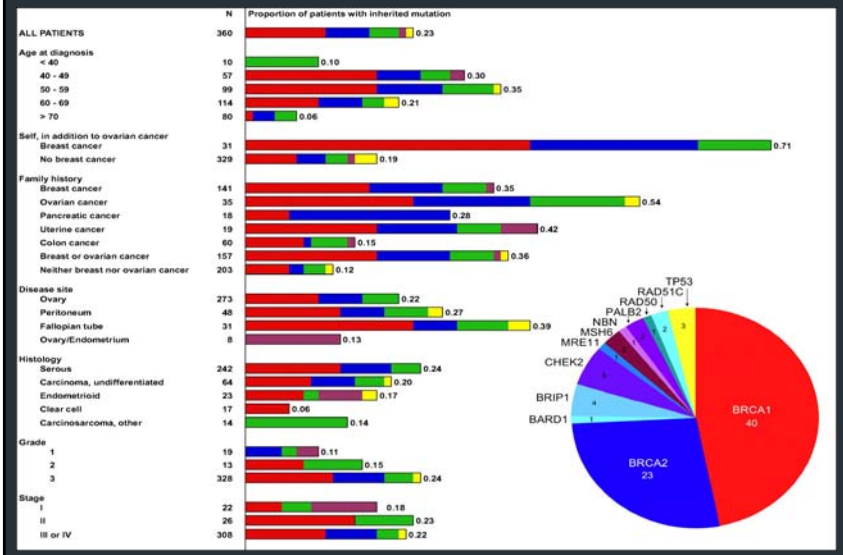
Advances in Massively Parallel Technologies Have Dramatically Reduced the Cost of Sequencing



IHGSC=International Human Genome Sequencing Consortium.

MacConaill LE. *J Clin Oncol*. 2013;31(15):1815-1824.

Proportion of 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%

Walsh T et al. *Proc Natl Acad Sci U S A*. 2011;108(44):18032-18037

Breast-Cancer Risk in Families With Mutations in *PALB2*

Results of a combined analysis of 154 families:

- Good estimate of BC risk (greater with + family Hx)
- Inadequate data to determine magnitude of increased OC risk

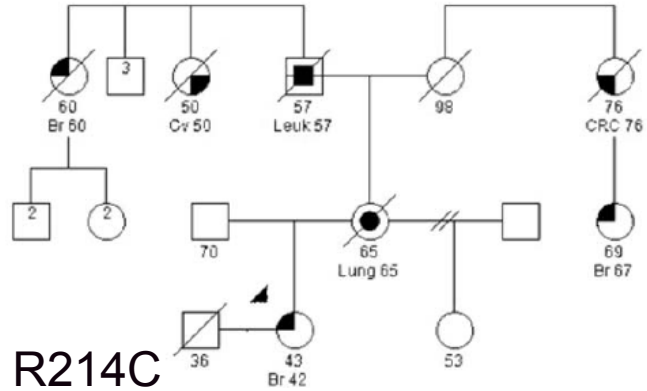
OC=ovarian cancer.

Antoniou AC et al. *N Engl J Med*. 2014;371(6):497-506.

RAD51C Germline Mutations in Breast and Ovarian Cancer Cases from High-Risk Families

Jessica Clague[1☯], Greg Wilhoite[2☯], Aaron Adamson[2], Adam Bailis[3], Jeffrey N. Weitzel[1], Susan L. Neuhausen[2*]

1 Division of Clinical Cancer Genetics, Beckman Research Institute at the City of Hope National Medical Center, Duarte, California, United States of America, **2** Department of Population Sciences, Beckman Research Institute at the City of Hope National Medical Center, Duarte, California, United States of America, **3** Department of Molecular and Cellular Biology, Beckman Research Institute at the City of Hope National Medical Center, Duarte, California, United States of America



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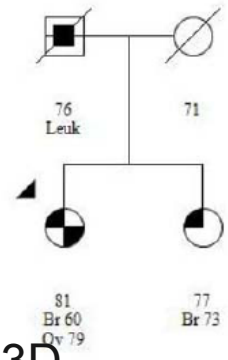

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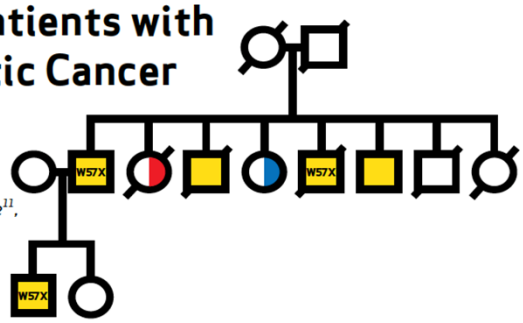
Clague J et al. *PloS One*. 2011;6(9):e25632.

Hereditary Pancreatic Cancer Risk

ATM Mutations in Patients with Hereditary Pancreatic Cancer

Nicholas J. Roberts[1], Yuchen Jiao[1], Jun Yu[2,3], Levy Kopelovich[7], Gloria M. Petersen[8], Melissa L. Bondy[9], Steven Gallinger[10], Ann G. Schwartz[11], Sapna Syngal[12], Michele L. Cote[11], Jennifer Axilbund[3], Richard Schulick[4], Syed Z. Ali[3], James R. Eshleman[3], Victor E. Velculescu[1], Michael Goggins[2,3,5], Bert Vogelstein[1], Nickolas Papadopoulos[1], Ralph H. Hruban[3,5], Kenneth W. Kinzler[1], and Alison P. Klein[3,5,6]



2.4% (4/166) of familial pancreatic cancer probands carried deleterious *ATM* mutations

The list: *ATM*; *BRCA2*; *PALB2*; *CDKN2A*; *STK11*; *TP53*; *MMR*; Hereditary pancreatitis (*PRSS1*, *PRSS2*)

Adapted from Roberts NJ et al. *Cancer Discov*. 2012;2(1):41-46.

Cancer-Specific Panel Rationale

- Multiple genes often considered in suspected hereditary cancers
- Family structure may limit the opportunity to "see" a syndromic pattern
- Current testing is stepwise, at high cost to the patient
  - Cost of testing + cost of multiple visits
- Concurrent testing of multiple genes is potentially cost-effective using available NGS technologies

NGS=next-generation sequencing.

Commercial Multigene Panels Available in the United States

	BRCAPlus	BreastNext	OvaNext	CancerNext	myRisk	ColoNext	Coloseq	BROCA	MDL 30	GeneDx
APC				x	x	x	x	x	x	x
ATM		x	x	x	x			x	x	x
ATR								x		
AXIN2									x	x
BAP1								x	x	
BARD1		x	x	x	x			x	x	x
BIP1									x	
BLM										x
BMPR1A				x	x	x	x	x	x	x
BRCA1	x	x	x	x	x			x		x
BRCA2	x	x	x	x	x			x		x
BRIP1		x	x	x	x			x	x	x
CDH1	x	x	x	x	x	x	x	x	x	x
CDK4					x			x		x
CDKN2A					x			x		x
CHEK1								x		
CHEK2		x	x	x	x	x		x	x	
DCC									x	
EPCAM			x	x	x	x	x	x	x	x
ExOx									x	
FAM175A/Abraxas								x		x
FANCC										
GALNT12								x		
GEN1								x		
GREM1								x		
HOXB13								x		x

Commercial Multigene Panels… (cont'd)

	BRCAPlus	BreastNext	OvaNext	CancerNext	myRisk	ColoNext	Coloseq	BROCA	MDL 30	GeneDx
MLH1			x	x	x	x	x	x	x	x
MRE11A		x	x	x				x	x	x
MSH2			x	x	x	x	x	x	x	x
MSH6			x	x	x	x	x	x	x	x
MUTYH		x	x	x	x	x	x	x	x	
NBN		x	x	x	x			x	x	x
PALB2	X	x	x	x	x			x	x	x
PDGFRA									x	
PMS1									x	
PMS2			x	x	x	x	x	x	x	x
PRSS1								x		
PTEN	x	x	x	x	x	x	x	x	x	x
RAD50		x	x	x				x	x	
RAD51								x		
RAD51C		x	x	x	x			x	x	x
RAD51D					x			x	x	
RBBP8								x		
RET								x		
SMAD4				x	x	x	x	x	x	
STK11	x	x	x	x	x	x	x	x	x	x
TP53	x	x	x	x	x	x	x	x	x	x
TP53BP1								x		
VHL1								x		
XRCC2								x	x	x
XRCC3								x		

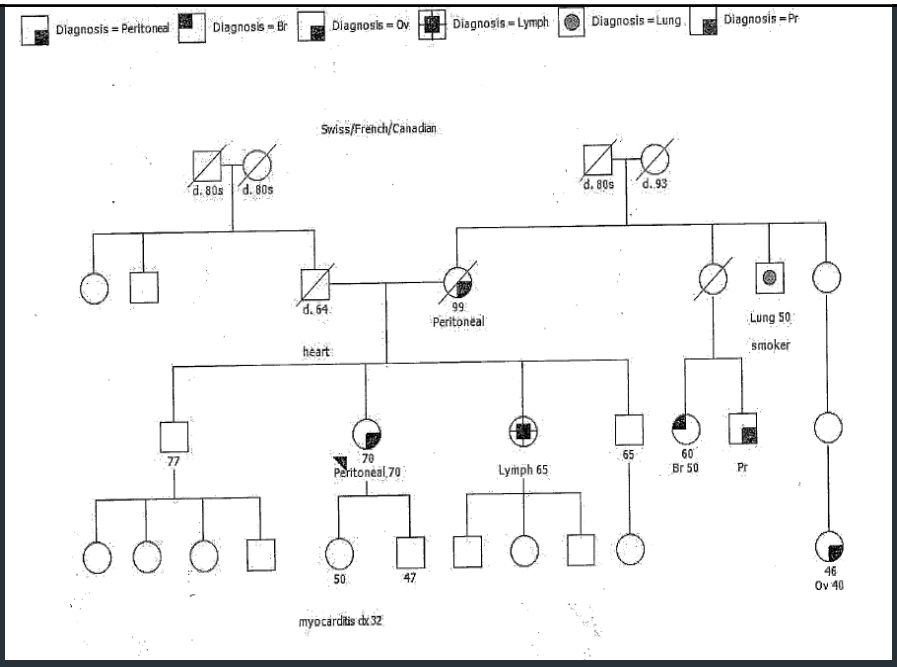


Image Courtesy of Jeffrey N. Weitzel, MD

SUMMARY

POSITIVE: MUTATION DETECTED

INTERPRETATION

- This individual is heterozygous for the **c.1082delA** mutation in the *BRIP1* gene.
- **Risk estimate:** up to a 3 fold increased risk for breast cancer (females only)++
- The expression and severity for this individual cannot be predicted.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

No mutations, variants of unknown significance, or gross deletions or duplications were detected in the other genes analyzed. In total, 19 genes were analyzed as part of this panel: ***ATM, BARD1, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, STK11,*** and ***TP53***.

The **c.1082delA** mutation, located in exon 8 (coding exon 7) of the *BRIP1* gene, results from a deletion of one nucleotide at position 1082, causing a translational frameshift with a predicted alternate stop codon. Since frameshifts are typically deleterious in nature, this alteration is interpreted as a disease-causing mutation (ACMG Recommendations for Standards for Interpretation and Reporting of Sequence Variations. Revision 2007. *Genet Med* 2008;10:294).

++The *BRIP1* gene is involved in the Fanconi anemia (FA)–BRCA pathway, which is critical for DNA repair by homologous recombination, and interacts *in vivo* with *BRCA1*. Mutations in *BRIP1* are estimated to confer up to a 2-3 fold increased in breast cancer risk (Pennington KP et al. *Gynecol Oncol.* 2012 Feb;124(2):347-53) compared to the general population; however this risk may be higher for female carriers under the age of 50

Image Courtesy of Jeffrey N. Weitzel, MD

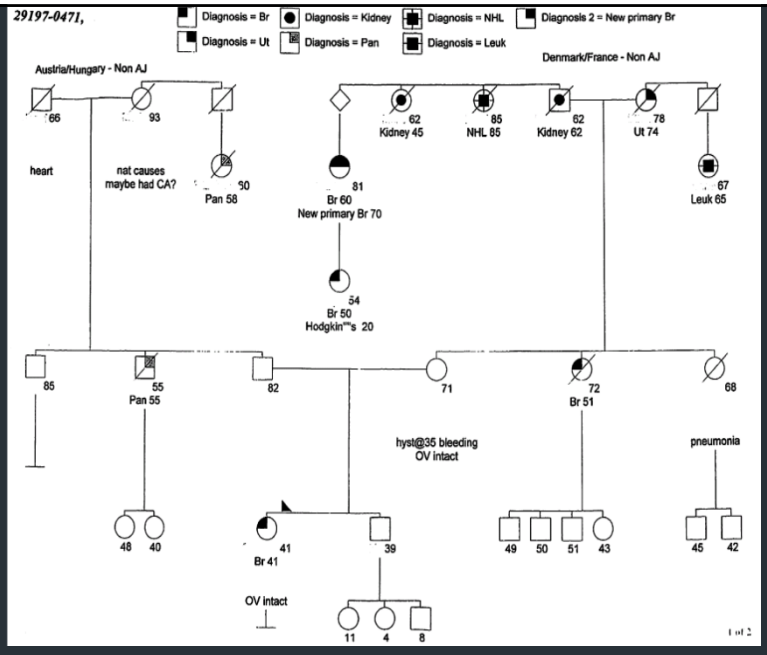
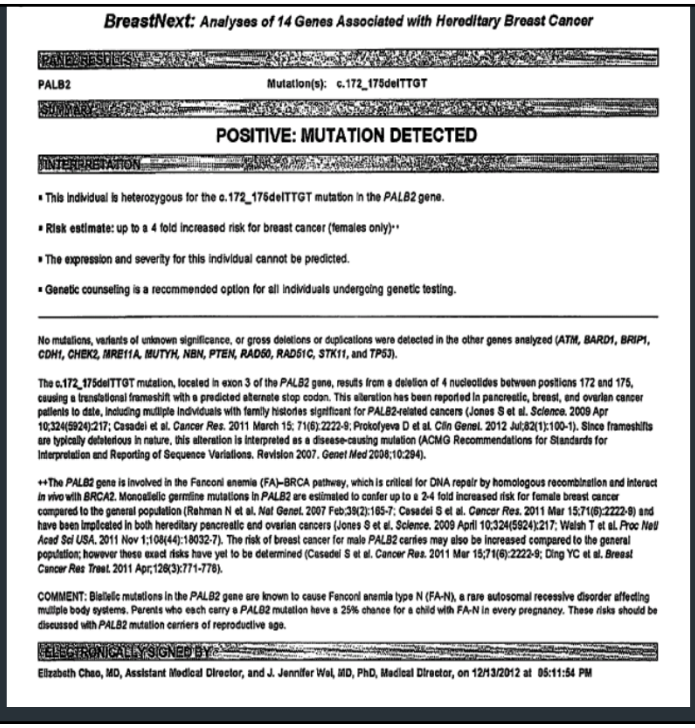


Image Courtesy of Jeffrey N. Weitzel, MD

NHL=non-Hodgkin lymphoma.



BreastNext: ***Analyses of 14 Genes Associated with Hereditary Breast Cancer***

PANEL RESULTS

PALB2 **Mutation(s): c.172_175delTTGT**

SUMMARY

POSITIVE: MUTATION DETECTED

INTERPRETATION

- This individual is heterozygous for the c.172_175delTTGT mutation in the *PALB2* gene.
- **Risk estimate:** up to a 4 fold increased risk for breast cancer (females only)++
- The expression and severity for this individual cannot be predicted.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

No mutations, variants of unknown significance, or gross deletions or duplications were detected in the other genes analyzed (*ATM, BARD1, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, PTEN, RAD50, RAD51C, STK11,* and *TP53*).

The c.172_175delTTGT mutation, located in exon 3 of the *PALB2* gene, results from a deletion of 4 nucleotides between positions 172 and 175, causing a translational frameshift with a predicted alternate stop codon. This alteration has been reported in pancreatic, breast, and ovarian cancer patients to date, including multiple individuals with family histories significant for *PALB2*-related cancers (Jones S et al. *Science.* 2009 Apr 10;324(5924):217; Casadei et al. *Cancer Res.* 2011 March 15; 71(6):2222-9; Prokofyeva D et al. *Clin Genet.* 2012 Jul;82(1):100-1). Since frameshifts are typically deleterious in nature, this alteration is interpreted as a disease-causing mutation (ACMG Recommendations for Standards for Interpretation and Reporting of Sequence Variations. Revision 2007. *Genet Med* 2008;10:294).

++The *PALB2* gene is involved in the Fanconi anemia (FA)–BRCA pathway, which is critical for DNA repair by homologous recombination and interact *in vivo* with *BRCA2*. Monoallelic germline mutations in *PALB2* are estimated to confer up to a 2-4 fold increased risk for female breast cancer compared to the general population (Rahman N et al. *Nat Genet.* 2007 Feb;39(2):165-7; Casadei S et al. *Cancer Res.* 2011 Mar 15;71(6):2222-9) and have been implicated in both hereditary pancreatic and ovarian cancers (Jones S et al. *Science.* 2009 April 10;324(5924):217; Walsh T et al. *Proc Natl Acad Sci USA.* 2011 Nov 1;108(44):18032-7). The risk of breast cancer for male *PALB2* carries may also be increased compared to the general population; however these exact risks have yet to be determined (Casadei S et al. *Cancer Res.* 2011 Mar 15;71(6):2222-9; Ding YC et al. *Breast Cancer Res Treat.* 2011 Apr;128(3):771-778).

COMMENT: Biallelic mutations in the *PALB2* gene are known to cause Fanconi anemia type N (FA-N), a rare autosomal recessive disorder affecting multiple body systems. Parents who each carry a *PALB2* mutation have a 25% chance for a child with *FA-N* in every pregnancy. These risks should be discussed with *PALB2* mutation carriers of reproductive age.

ELECTRONICALLY SIGNED BY

Elizabeth Chao, MD, Assistant Medical Director, and J. Jennifer Wei, MD, PhD, Medical Director, on 12/13/2012 at 05:11:54 PM

- Could be either parental lineage
- Need to think about pancreatic cancer risk, too

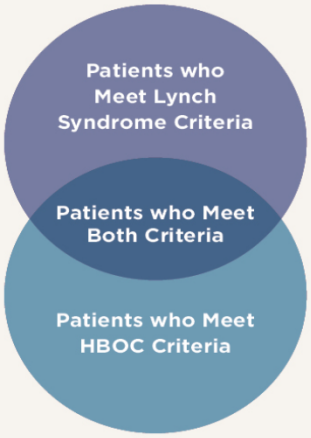
Image Courtesy of Jeffrey N. Weitzel, MD

Significant Syndromic Overlap

Many patients have personal and family history associated with multiple syndromes

Retrospective analysis of patients recorded at Myriad (2006-2013)

- **6.9%** of patients appropriate for HBOC testing also meet Lynch criteria
- **30%** of patients appropriate for Lynch testing also meet HBOC criteria



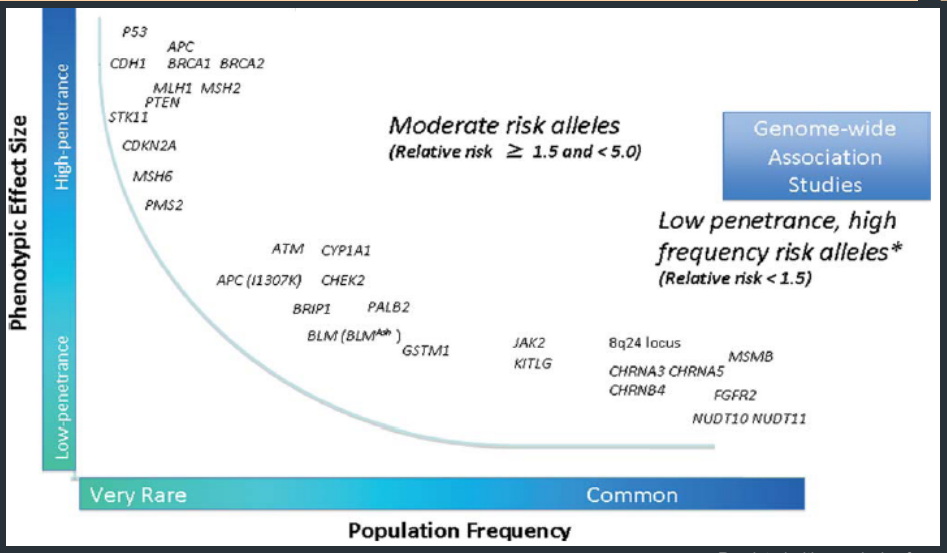
Saam J et al. Overlap between Lynch syndrome and hereditary breast and ovarian cancer syndrome among family histories in patients tested for hereditary cancer syndromes. Presented at: 17th Annual Meeting of the Collaborative Group of the Americas on Inherited Colorectal Cancer; October 7-8, 2013; Anaheim, CA.

Human Genetic Variation

- We find more genes with deleterious mutations
  - We also find more VUS
- There can be more than 1 attributable genetic variation in a given case
- The phenotype and the test result may be discordant
  - Or are they?

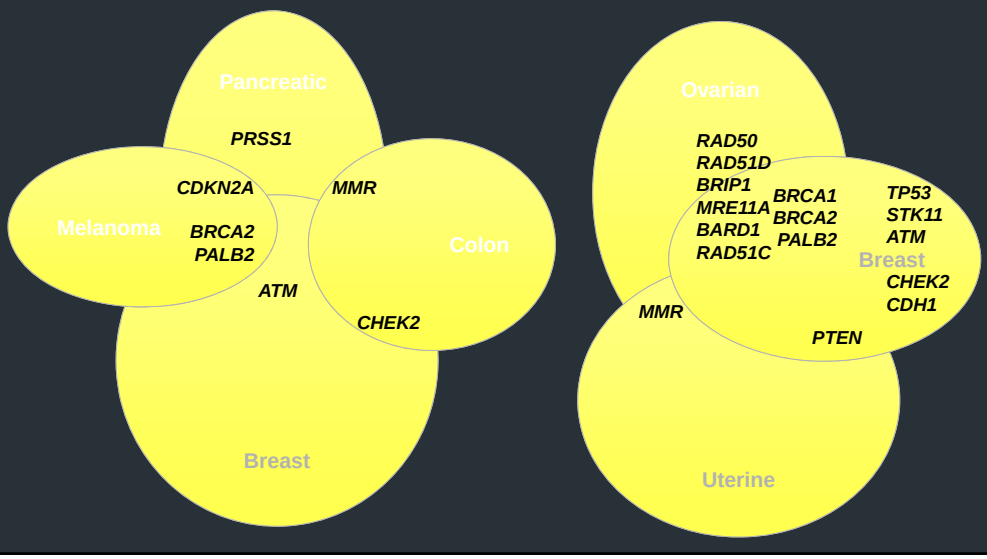
VUS=variant of undetermined significance.

High-penetrance, Rare Cancer Predisposition Genes (Relative Risk ≥ 5)



Weitzel JN et al. *CA Cancer J Clin*. 2011;61(5):327-359.

Genetic Heterogeneity and Overlapping Phenotypes = Expanded Differential Diagnoses



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

ENIGMA: Rare Gene/Variants Working Group

ENIGMA
(Evidence-based Network for the Interpretation of Germline Mutant Alleles)

Great need to understand:

- clinical implications of rare variants
- potentially broader phenotypes of "known" high penetrance genes
- define penetrance for the genes in hand

Multiple approaches to collaborative family studies, collection of pedigrees and multiplex test results will be considered

- established research networks, new industry relationships, direct to family recruitment such as the **PROMPT** study

PROMPT=Prospective Registry of Multiplex Testing.

ENIGMA. http://enigmaconsortium.org. Accessed May 6, 2015.

Cancer Screening & Prevention Program
Hereditary Cancer Risk Assessment and Management

- There is clearly a potential to benefit carefully selected and counseled families, with ever broader arrays of genetic tools
- *PALB2* is among the first rare variant genes to acquire adequate data for absolute risk estimation
- Genetic technologic advances are changing diagnostic approaches
- Surveillance and prevention can improve survival in at-risk individuals
- Protocols will need to be adapted to lower risk

Conclusions

- Training in genetic/genomic cancer risk assessment and counseling is important for clinical implementation of NGS analyses, and should be disseminated
- Participation in cancer genetics research registries is a critical contribution to the knowledge base necessary to develop the evidence for advice
- The remarkable advances in NGS technologies should be brought to bear to enhance access globally

“He is a better physician that keeps diseases off us, than he that cures them being on us; prevention is so much better than healing because it saves the labour of being sick.”

Thomas Adams,1618

Thank you!