THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Cáncer de mama hereditario: Riesgos y Diagnóstico

XXI CONGRESO CHILENO DE CANCEROLOGÍA
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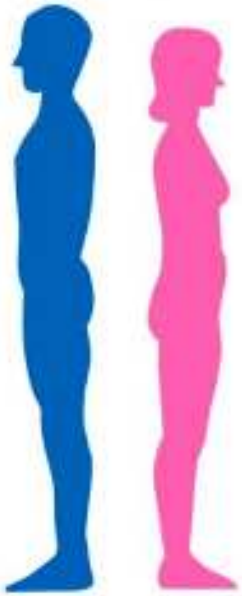
Epidemiology

Estimated New Cases

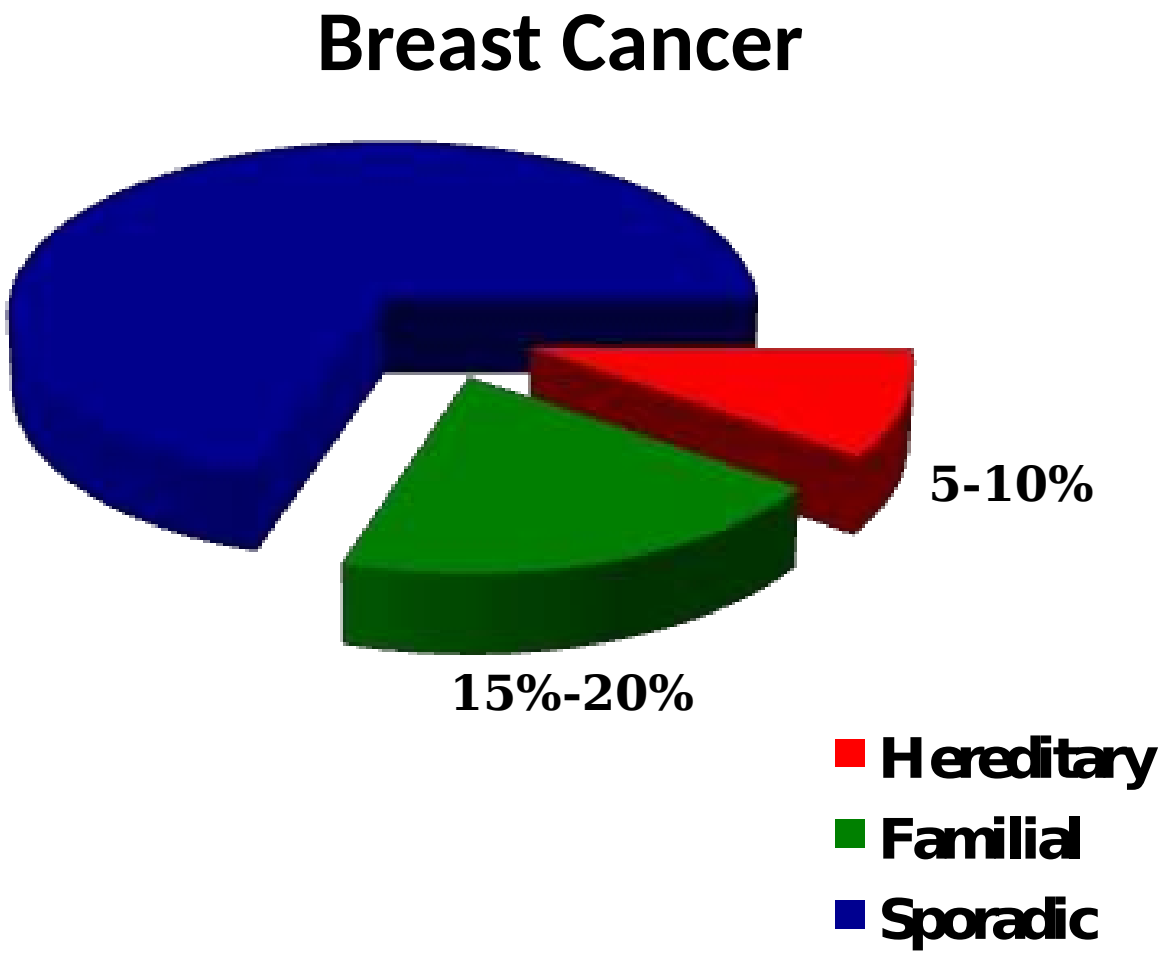
Males			Females		
Prostate	220,800	26%	Breast	231,840	29%
Lung & bronchus	115,610	14%	Lung & bronchus	105,590	13%
Colon & rectum	69,090	8%	Colon & rectum	63,610	8%
Urinary bladder	56,320	7%	Uterine corpus	54,870	7%
Melanoma of the skin	42,670	5%	Thyroid	47,230	6%
Non-Hodgkin lymphoma	39,850	5%	Non-Hodgkin lymphoma	32,000	4%
Kidney & renal pelvis	38,270	5%	Melanoma of the skin	31,200	4%
Oral cavity & pharynx	32,670	4%	Pancreas	24,120	3%
Leukemia	30,900	4%	Leukemia	23,370	3%
Liver & intrahepatic bile duct	25,510	3%	Kidney & renal pelvis	23,290	3%
All Sites	**848,200**	**100%**	**All Sites**	**810,170**	**100%**



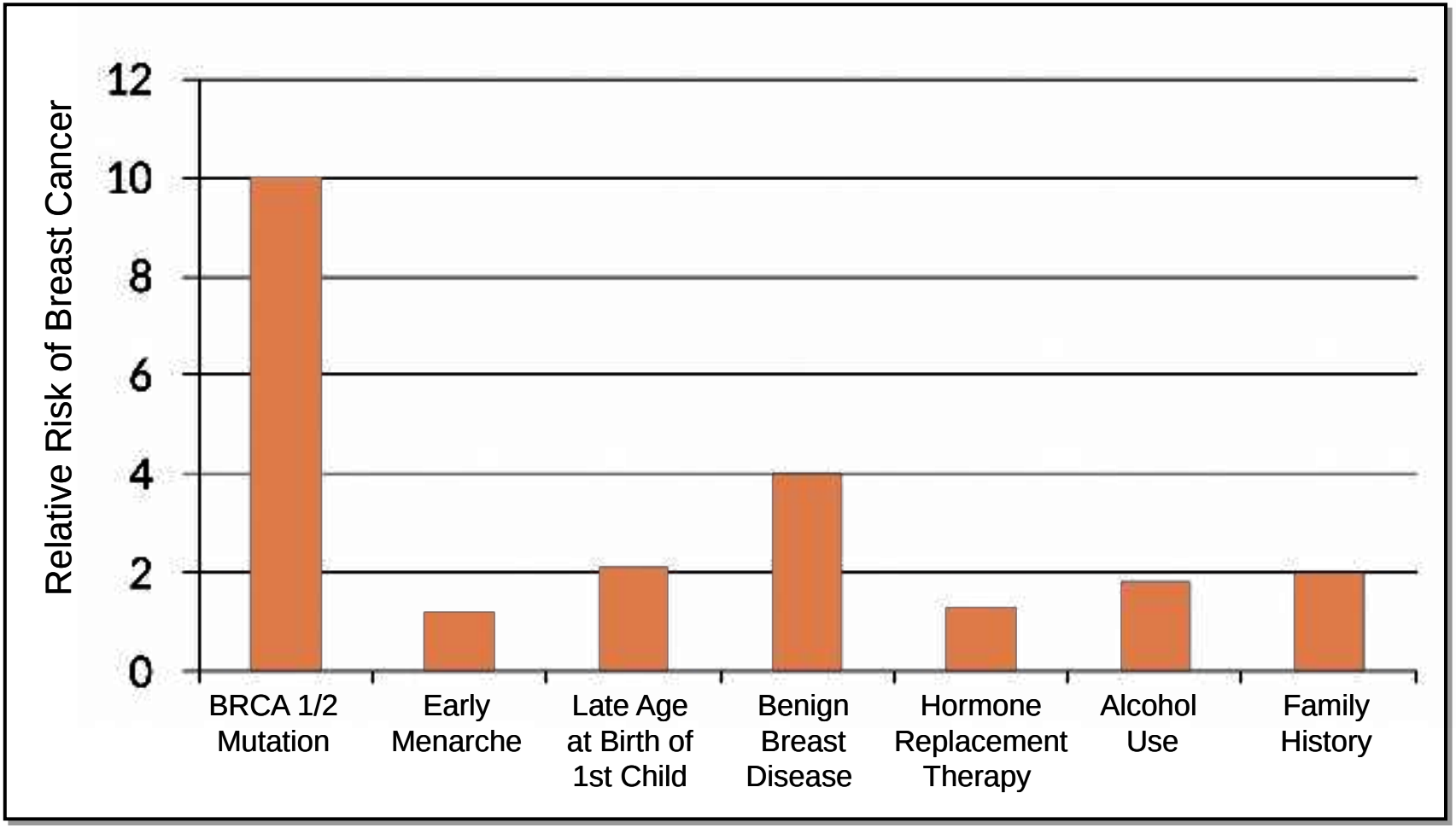
5-10% of all breast cancer cases: 23,000-11,500 cases

CA 2015

Genetic Basis of Breast Cancer



Breast Cancer Risk Factors



RED FLAGS for hereditary cancers

1 or more cancers diagnosed before the age of 50

2 or more generations affected

3 or more family members with the same or similar types of cancer

Hereditary Breast Cancer

Hereditary Breast and Ovarian Cancer Syndrome

- BRCA1 and BRCA2
- Increased risk for breast, ovarian, male breast, prostate, pancreatic, and melanoma

Li-Fraumeni Syndrome (multi-system hereditary cancer syndrome)

- TP53
- Pre-menopanusal, Her2Neu+ breast cancer
- Increased risk for bone and soft tissue sarcomas, brain cancer, ACC, leukemia, multiple cancers in the same individual

Cowden Syndrome (*PTEN* Hamartoma Tumor Syndrome)

- PTEN
- Benign features: macrocephaly, papillomatous papules
- Increased risk for breast, thyroid, and endometrial cancer

Peutz-Jehgers (STK11) Breast cancer risk 44-50%, Ovarian 18-21%
Hereditary Diffuse Gastric Cancer (CDH1) Lobular breast cancer 39-52%, diffuse gastric cancer 67-83%

Other Genes To Consider…

- ***PALB2***
  - Breast cancer risk 33% - 58% based on family history
  - Possible increased risk for ovarian and pancreatic cancers
- ***CHEK2***
  - Breast cancer risk 20-25% (OR 1.5-3.0). Maybe higher with strong family Hx.
  - Possible increased risk for ovarian, prostate, and colon cancer – not well defined
- ***ATM***
  - Heterozygous carrier frequency 1-3% in general population
  - Proportion of familial breast cancer = 2%
  - Lifetime breast cancer risk in women (RR = 2.3) = 20%
- ***BARD1, BRIP1, MRE11A, MUTYH, NBN, RAD50, RAD51C, RAD51D***
  - Lifetime cancer risks are poorly defined
  - All thought to be associated with increased risk, albeit low risk, for breast cancer

Rich , Woodson Litton and Arun. J Surg Onc 2014
Antoniou et al. NEJM 2014

BRCA1 and BRCA2 Mutations

- Breast cancer risk up to 80%
- Increased risk of second breast cancer
  - 12% - 20% within 5 yrs
  - up to 64% by age 70
- Increased risk of ovarian cancer
  - 10-fold increase in risk
  - lifetime risk at least 16%
- Other cancers: Male breast cancer, prostate cancer, pancreas cancer, melanoma, GI cancers

JNCI 1999;15:1310-6
J Clin Oncol 1998;16:2417-25
Lancet 1998;351:316-21
J Clin Oncol 1999;17:3396-402
Lancet 1994;3343:692-5

BRCA1/2 Mutations Increase the Risk of Early-onset Breast Cancer

	By age 40	By age 50	By age 70
Population Risk	0.5%	2%	10%
Hereditary Risk	10%-20%	33%-50%	56%-

Ford D et al., Lancet 1994 343(8899):692
Struewing JP et al., N Engl J Med 1997 336(20):1401
Easton DF et al., Am J Hum Genet 1995 56(1):265

Guidelines for Genetic Testing

American Society of Clinical Oncology:

"Cancer predisposition testing should be offered only when…"

- There is a high likelihood of a positive test
- The test can be adequately interpreted
- The test result will influence medical management
  - affected patient: treatment decisions
  - unaffected individual: risk management options

Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, Adapted on February 20, 1996. J Clin Oncol 1996 14(5):1730

Candidates for Genetic Evaluation

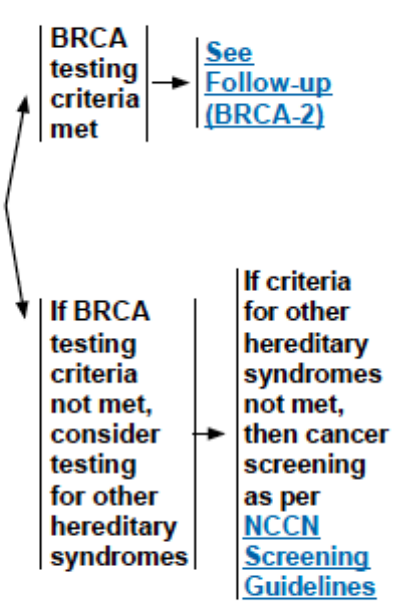
- Males
- Personal history of breast cancer ≤ 50 yo
- Personal history of breast cancer ≤ 60 yo for TNBC
- Any age and family history of multiple cases of early-onset breast cancer or ovarian cancer
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Family history of male breast cancer

BRCAPRO program, developed by Giovanni Parmigiani, Donald Berry, and Omar Aguilar at Duke University's Institute of Statistics and Decision Sciences

BRCA1/2 TESTING CRITERIA[a,b]

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious *BRCA1/BRCA2* gene mutation
- Personal history of breast cancer[b] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - An additional breast cancer primary[c]
    - ≥1 close blood relative[d] with breast cancer at any age
    - ≥1 close relative with pancreatic cancer
    - ≥1 relative with prostate cancer (Gleason score ≥7)
    - 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[d] with breast cancer diagnosed ≤50 y
    - ≥2 close blood relatives[d] with breast cancer at any age
    - ≥1 close blood relative[d] with ovarian[e] carcinoma
    - ≥2 close blood relatives[d] with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age
    - A close male blood relative[d] with breast cancer
    - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[f]
- Personal history of ovarian[e] carcinoma
- Personal history of male breast cancer
- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative[d] with breast cancer ≤50 y or two relatives with breast, pancreatic or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with ≥1 close blood relative[d] with breast cancer ≤50 y or two relatives with breast, pancreatic cancer or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood[d] relative meeting any of the above criteria
  - Third-degree blood[d] relative who has breast cancer[b] and/or ovarian[e] carcinoma and who has ≥2 close blood relatives[d] with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian[e] carcinoma



[a] For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

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

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

[d] Close blood relatives include first-, second-, and third-degree relatives on same side of family. (See BR/OV-B)

[e] Includes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated with epithelial non-mucinous histology. Lynch syndrome can be associated with both nonmucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

[f] Testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other *BRCA*-related criteria are met. Founder mutations exist in other populations.

Incidence of deleterious germline BRCA mutations in patients with TNBC

Study	Patient Population	BRCA1	BRCA2	BRCA 1/2
Young, 2009	Age<41	9.0% (5/54)	2.0% (1/54)	11.0% (6/54)
Evans, 2011	Age<41	11.6% (5/43)	0%	11.6% (5/43)
Evans, 2011	Age<31	37.0% (11/30)	0%	37.0% (11/30)
Kwon, 2010	Age<40	-	-	23.5%
Kwon, 2010	Age<50	-	-	17.5%

Evans et al. J Med Genet. 2011 Aug;48(8):520-2.
Kwon et al. J Clin Onc. 2010 Sep 20;28(27):4214-20.
Young et al. BMC Cancer 2009;9

We ordered the genetic test, now what?

INTERPRETING THE RESULTS

Possible Genetic Test Results

- Positive

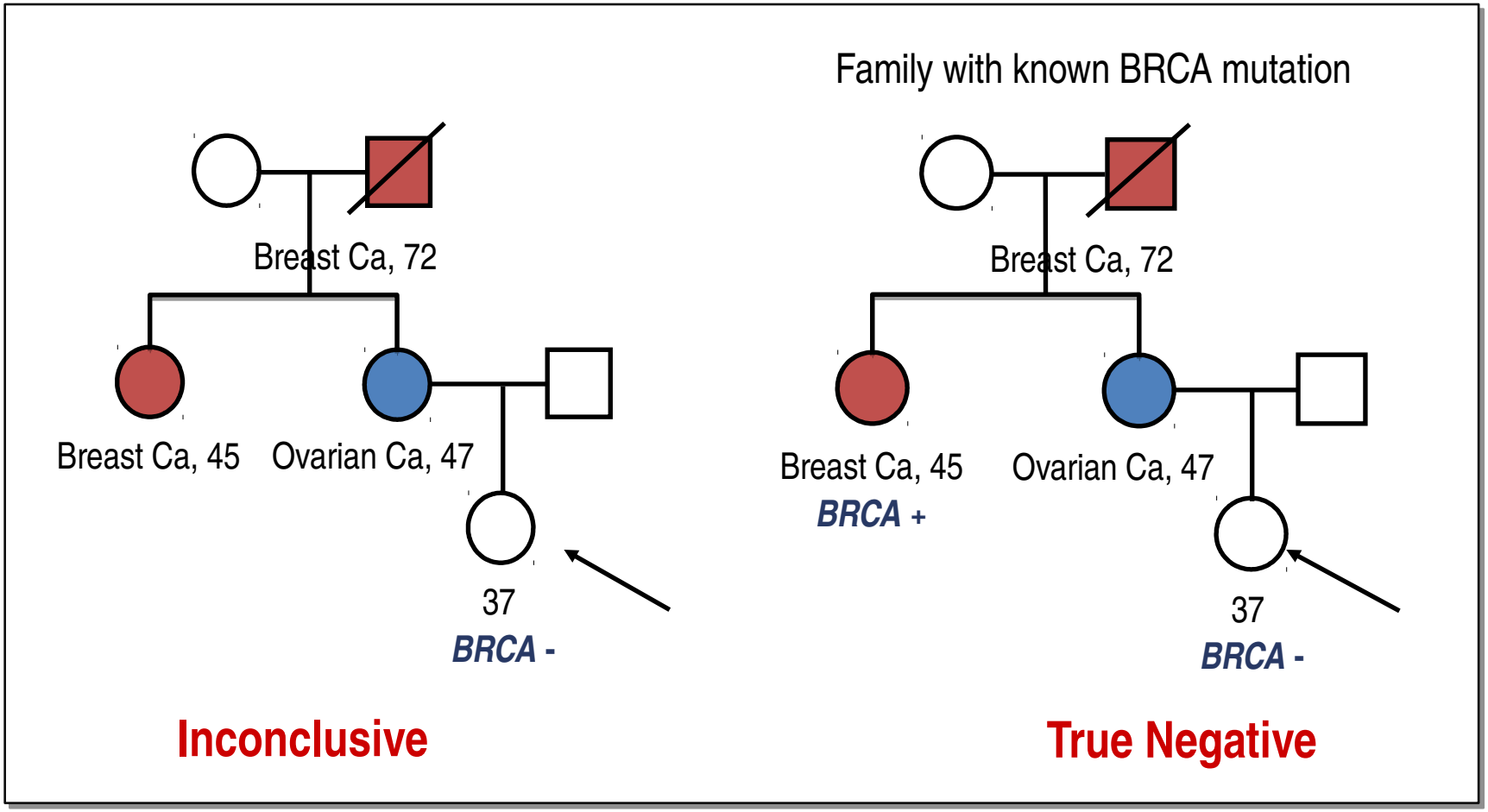
- Negative (true vs. inconclusive)

- Variant of uncertain clinical significance

Possible Genetic Test Results: Positive

- Explains cancer in the family
- Carrier at increased risk for breast, ovarian, and possibly other cancers
- Family members can be tested
  - 1st degree relatives at 50% risk
- Must work with patient to determine appropriate management plan

Possible Genetic Test Results: Inconclusive vs. True Negative



Possible Genetic Test Results: True Negative

- Only possible when the exact gene mutation in the family is known
- Individual's cancer risk is similar to that of the general population
- General population screening is recommended
- Individual's children are not at risk to inherit the mutation

Possible Genetic Test Results: Inconclusive Negative

- No mutation identified
- Interpretation is dependent upon:
  - Family history
  - Whether the most appropriate person was tested
  - What type of testing was performed
- If the result is not what you expected:
  - May need to do more testing, (i.e. consider comprehensive if only multisite done, or rearrangement studies)
  - DNA banking?
- Must work with patient to create individualized management plan based on personal and family history

Possible Genetic Test Results: Uncertain Variant

- Gene change found could be associated with an increased risk for cancer or could be a change that doesn't affect the gene at all
- Testing other **AFFECTED** family members or parents could be helpful
- Testing unaffected family members is not recommended
- Must work with patient to create individualized management plan based on personal and family history
- Should have annual follow up with patient to update status of variant

Management Options for BRCA mutation carriers who have Breast Cancer

Resources for BRCA positive patients

- Patient education materials
- Family letter and copies of results to inform at-risk family members
- Refer patients to high-risk cancer screening clinics
- Patient advocacy groups
  - FORCE: Facing Our Risk Cancer Empowered
    - www.facingourrisk.org
  - Be Bright Pink
    - www.bebrightpink.org

The REACH Registry

Research, Education and Awareness of Cancer family History

Clinical Cancer Genetics

Women's Moonshots Flagship Project: Making Cancer History for the Family

713-745-7050

Toll free: 1-855-217-6766

REACHregistry@mdanderson.org

Treatment Options for Affected Patients

Multidisciplinary approach

Treatment implications on affected patient:

- Breast surgery (segmental vs bilateral mastectomy)
- Clinical trials (Platinum salts)
- New targeted agents : PARP inhibitors
- Oophorectomy

    40 yo or after completion of parity

    Pre-implantation diagnosis

Risk Management Recommendations for Patient and Family Members

NCCN™ screening recommendation guidelines for individuals with a BRCA mutation and no Hx of breast cancer

Women

- Breast self exam (BSE) training and education starting at age 18
- Clinical breast exam, every 6-12 months, starting at age 25
- Annual breast MRI screening starting at age 25, or individualized based on earliest age of onset in family
- Annual mammogram and breast MRI from ages 30-75
- Discussion of risk reducing mastectomy

Men

- Breast self exam training and education starting at age 35
- Clinical breast exam, every 6-12 months, starting at age 35
- Consider baseline mammogram at age 40, annual mammogram if gynecomastia or parenchymal/glandular breast density on baseline study
- Adhere to screening guidelines for prostate cancer

www.NCCN.org; NCCN Guidelines™
Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 2.2014

Prophylactic Surgery

• • •

Tamoxifen-prevention

- No prospective randomized data published to date
- Several studies show decreased risk of contralateral breast cancer on tamoxifen therapy
- Overall efficacy may be affected by high rate of TNBC tumors in BRCA1 mutation carriers and comparison groups used

Next generation sequencing panels for hereditary cancer

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Panel Tests

- Use of nextgen sequencing technology allows for simultaneous analysis of many genes at a cost similar to current single gene tests
- Several well-established clinical genetic testing labs are now offering hereditary cancer-specific panel tests
- General – the kitchen sink approach
- Specific:
  - Geared to a particular cancer type

    AND/OR
  - Focused on high penetrant genes only

Example Panel - General

ATM
BARD1
BRIP1
MRE11A
NBN
RAD50
RAD51C
PALB2
CDH1
CHEK2
MUTYH
PTEN
STK11
TP53
EPCAM
MLH1
MSH2
MSH6
PMS2
APC
SMAD4
BRCA1
BRCA2
CDKN2A
NF1

Site Specific Panels - Breast

Multi-Gene Panel Testing

Benefits

- Efficient testing method
- Identify patients with atypical phenotypes or unknown family history
- Improved insurance coverage

Limitations

- Unknown level of cancer risk for many genes
- Lack of clear guidelines
- Variant rate
- Genetic counseling model
- Implications for family members

What genes would we like to see in a clinical hereditary cancer panel test?

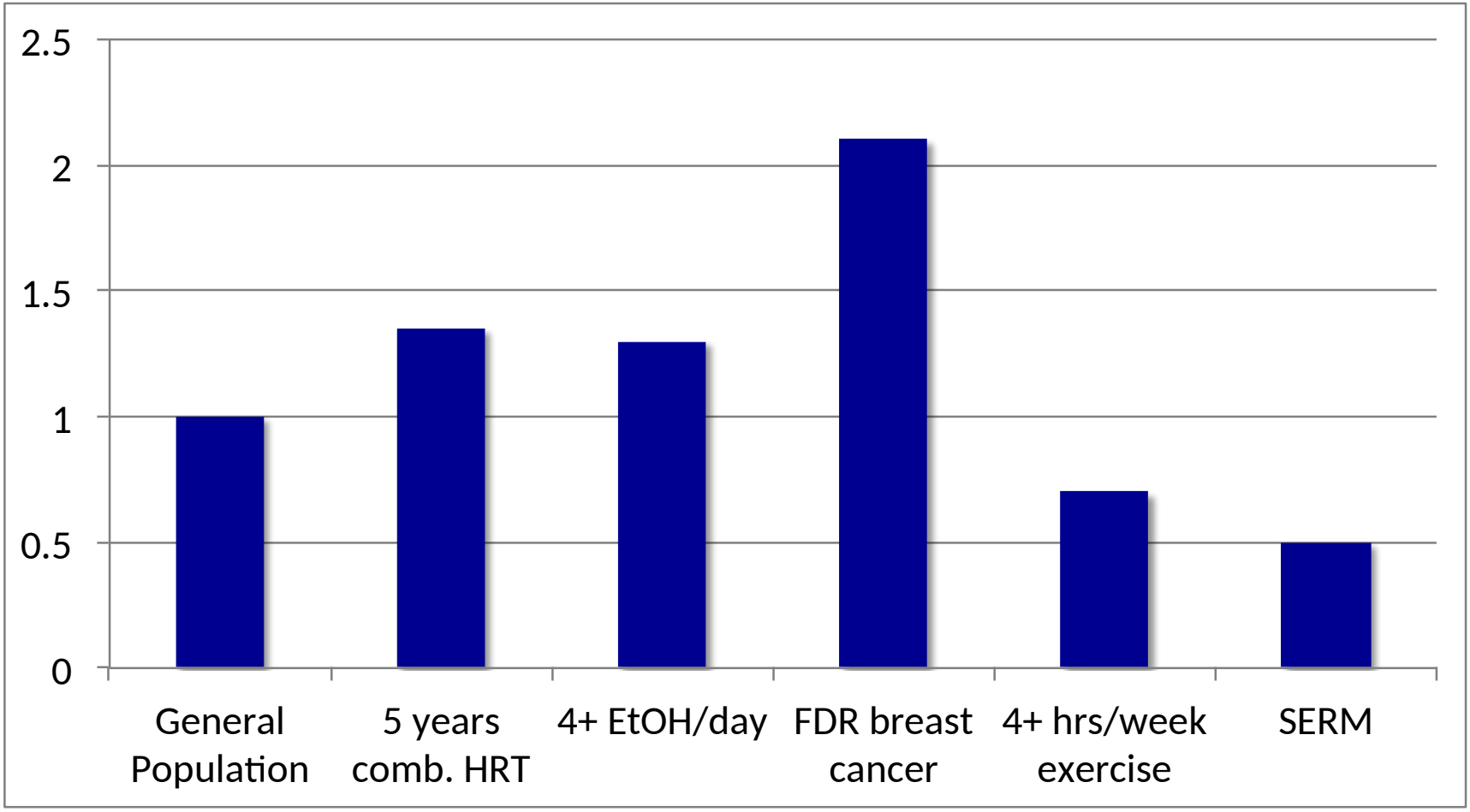
- High penetrant genes – of course

What about…

- Low penetrant genes?
- Genes of unknown clinical significance?

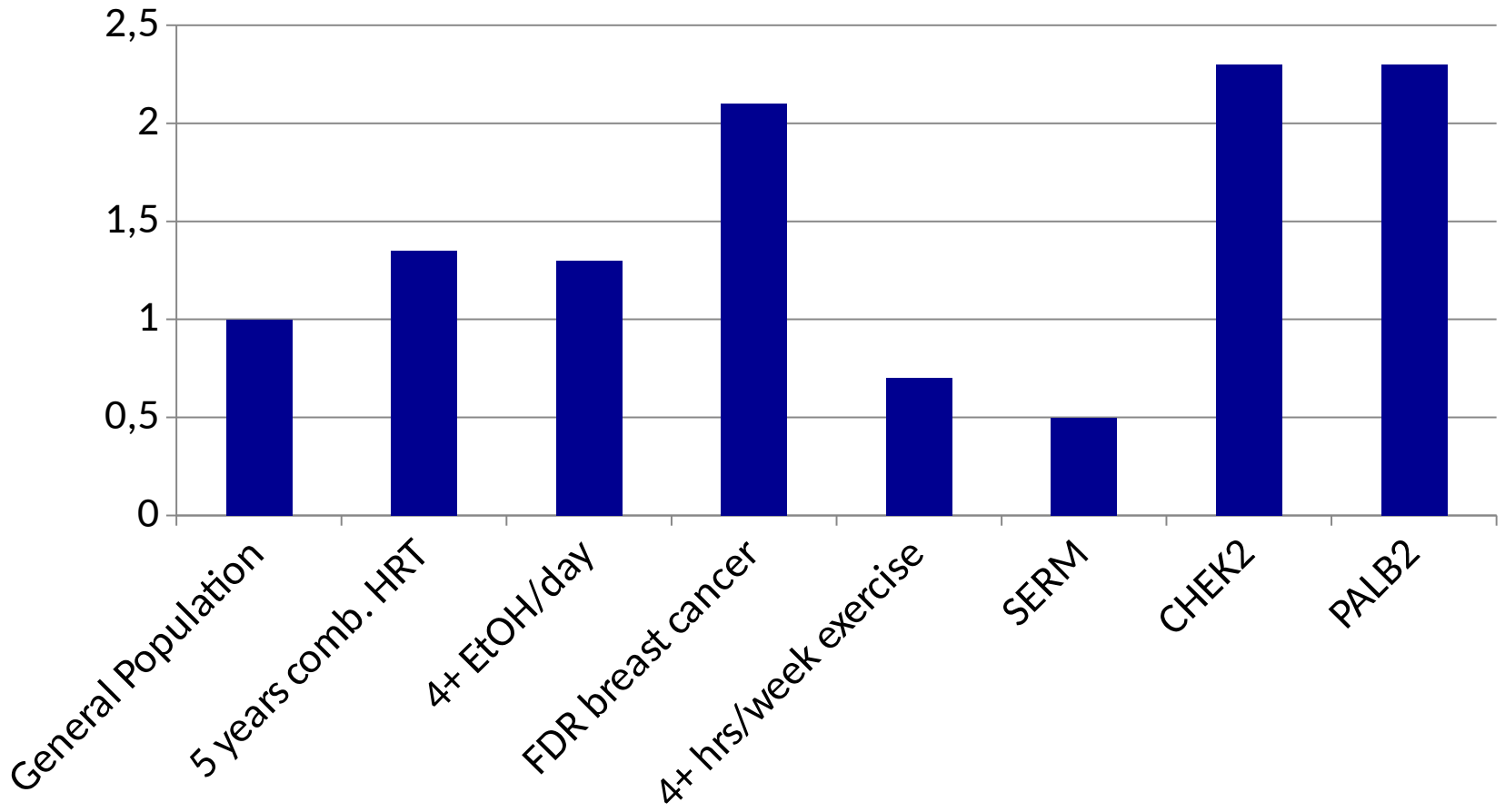
Pre-test counseling is fundamental

Breast Cancer General Population Risk Factors



Source: www.cancer.gov; "Breast Cancer Prevention", "Genetics of Breast and Ovarian Cancer"

CHEK2 and PALB2 compared to general population risk factors



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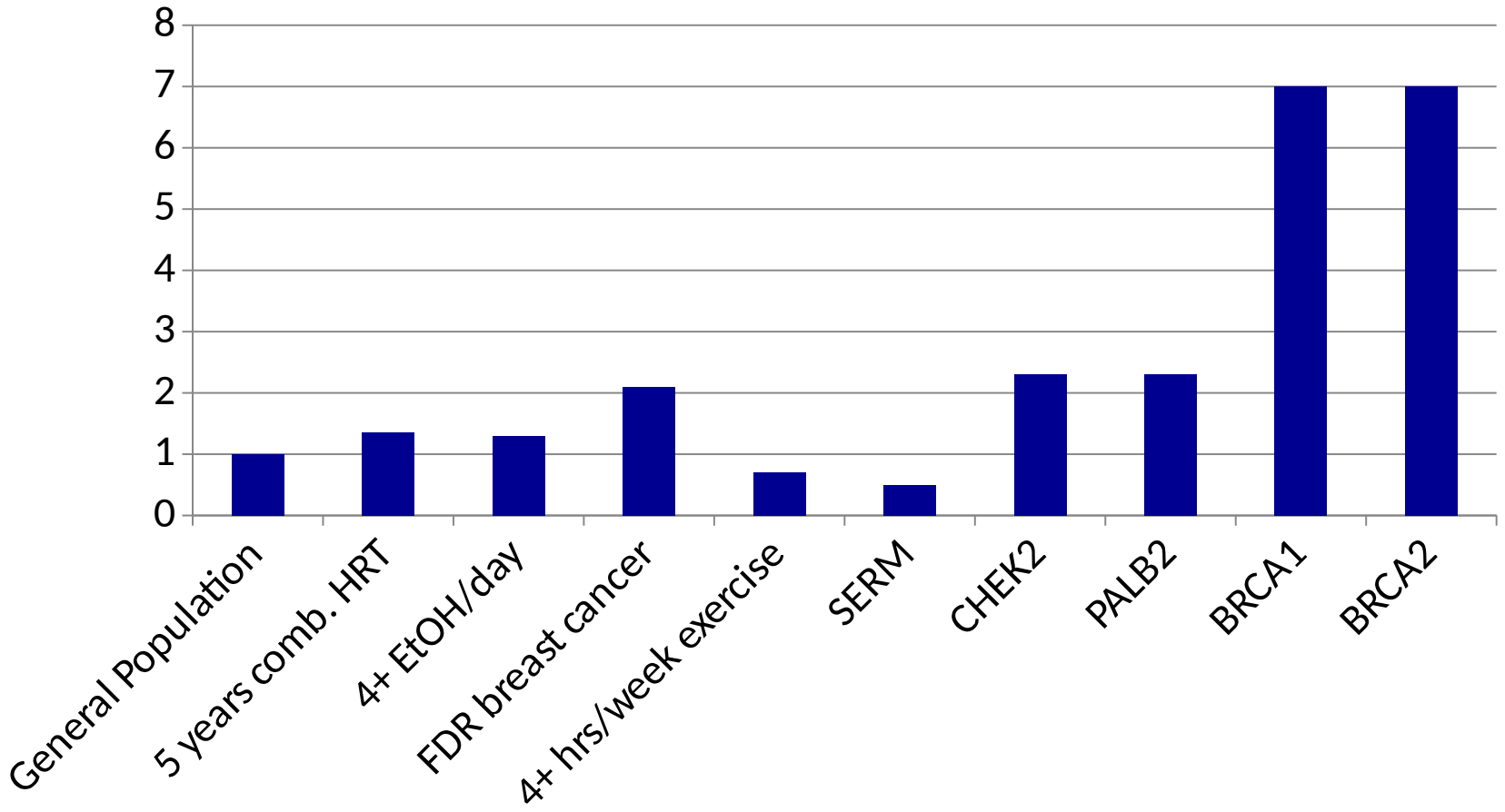
Low penetrant vs. High penetrant cancer susceptibility genes



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NCCN Guidelines – low penetrant genes and gene panels

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2013
Genetic/Familial High-Risk Assessment: Breast and Ovarian

NCCN Guidelines Index
Genetics Table of Contents
Discussion

ADDITIONAL GENETIC MUTATIONS ASSOCIATED WITH BREAST/OVARIAN CANCER RISK

Syndromes

- Hereditary Diffuse Gastric Cancer Syndrome
  - *CDH1* gene
  - Diffuse gastric cancer – 67%-83% risk
  - Lobular cancer of the breast – 39%-52% risk
- Peutz-Jeghers Syndrome (See NCCN Guidelines for Colorectal Cancer Screening for more information)
  - *STK11/LKB1* gene
  - Breast cancer – 44%-50% risk
  - Ovarian cancer – 18%-21% risk (ovarian sex cord tumors are the most common)
- Lynch Syndrome (See NCCN Guidelines for Colorectal Cancer Screening for more information)
  - Mismatch Repair (MMR) genes – *MLH1*, *MSH2*, *MSH6*, *PMS2*
  - *EPCAM* gene deletion
  - Ovarian cancer – 9% risk
  - Breast cancer – conflicting data regarding increased risks

Gene Panels

- New genetic testing panels using next-generation sequencing for hereditary breast, ovarian, and other cancers have recently been introduced.
- These panels are intended for individuals who have tested negative for high penetrance genes (eg, *BRCA1/2*) and for those whose family history is suggestive of more than one syndrome.
- The genetic testing laboratories include somewhat different, but often overlapping, genes. Examples of currently available genes within these panels include:

ATM	*MRE11A*
BARD1	*NBN*
BRIP	*PALB2*
CDH1	*PMS2*
CHEK1	*PTEN*
CHEK2	*RAD50*
MLH1	*RAD51B*
MSH2	*RAD51C*
MSH6	*RAD51D*
MUTYH	*STK11*
	TP53

- Limitations of these panels include an unknown percentage of variants of unknown significance, uncertainty of level of risk associated with most of these genes, and lack of clear guidelines on risk management of carriers of some of these mutations.
- Because of the complexity and limited data regarding their clinical utility, hereditary multigene cancer panels should only be ordered in consultation with a cancer genetics professional.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

GENE 1

Summary

- Ask detailed family history questions including structure
- Refer appropriate patients for genetic counseling and testing
- Guidelines and available testing are changing
- Follow up and interpretation of genetic results is important for risk assessment and further recommendations for your patients
  - Complex discussions regarding risk, and risk reduction strategies
- Next generation sequencing is promising – but we have a lot to learn about the lower-penetrant genes

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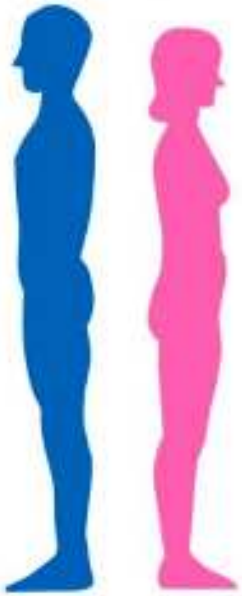

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Gracias

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