Hereditary Breast Cancer: Updates in Cancer Genetics

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Objectives

The presentation will help you understand genetic risk for breast cancer and the process for counseling and testing.

We will discuss:

- Hereditary breast cancer risk
- Benefits and limitations of genetic testing
- How test results can help you make informed decisions

Identifying Those at High Risk

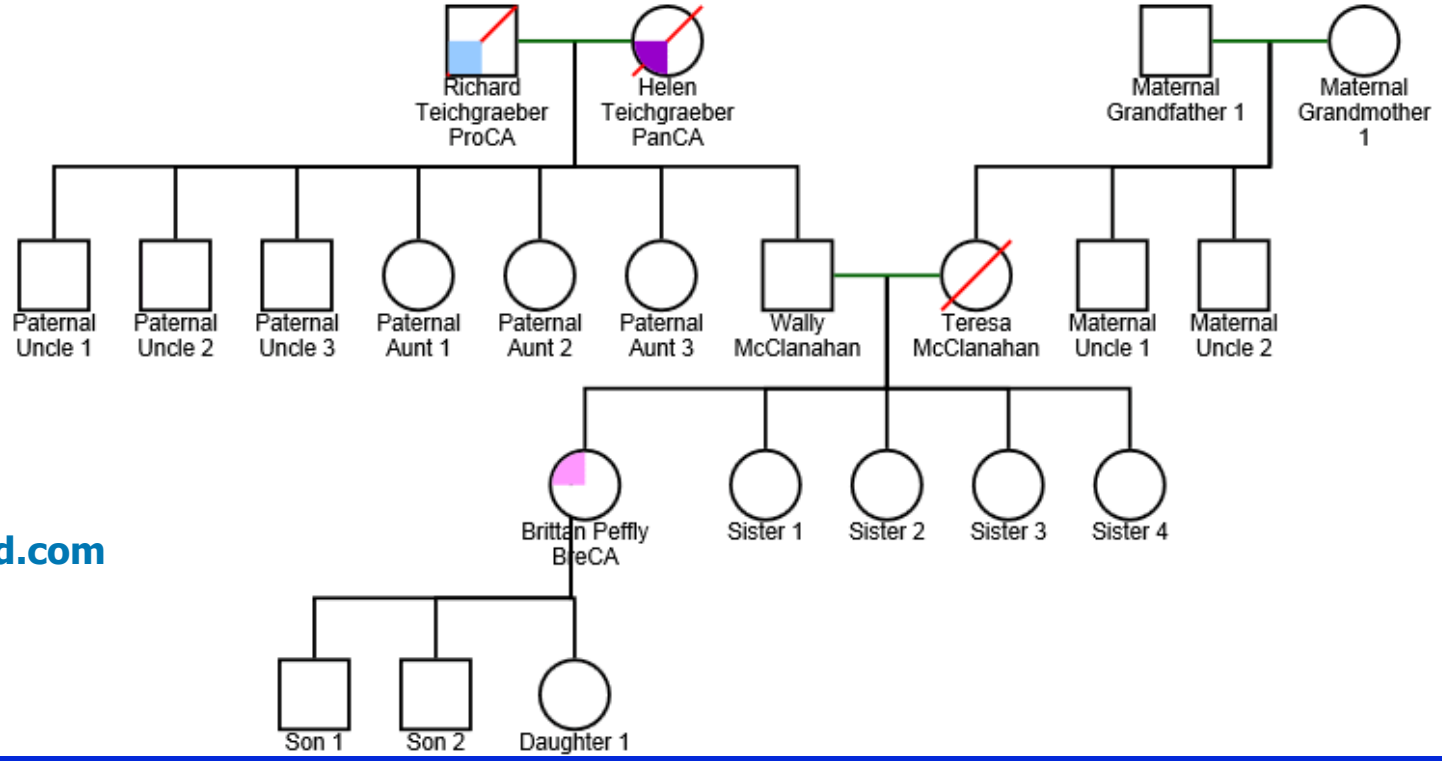
- Necessary for informed decision making
  - At diagnosis and survivorship care
- Part of National Accreditation Standards
- Important for risk stratification- patient & family

Assessing Risk

Patient Self-Report: Online

Your Family

Please add any cancer diagnoses by clicking on the appropriate family member.



https://fht.myriad.com

Red Flags

Based on your personal health information and the information from your family the following red flags have been identified.

Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

- You or a family member were diagnosed with breast cancer before age 50
- There are three or more HBOC-associated cancers at any age+^

Patient Self Report: In Clinic

CANCER FAMILY HISTORY QUESTIONNAIRE

Personal Information

Patient Name: _____ **Date of Birth:** _____ **Age:** _____

Gender (M/F):_____ **Today's Date(MM/DD/YY):**_____ **Health Care Provider:**_____

Instructions: This is a screening tool for cancers that run in families. Please mark (Y) for those that apply to YOU and/or YOUR FAMILY. Next to each statement, please list the relationship(s) to you and age of diagnosis for each cancer in your family.

You and the following close blood relatives should be considered: *You, Parents, Brothers, Sisters, Sons, Daughters, Grandparents, Grandchildren, Aunts, Uncles, Nephews, Nieces, Half-Siblings, First-Cousins, Great-Grandparents and Great Grandchildren*

YOU and YOUR FAMILY's Cancer History (Please be as thorough and accurate as possible)

	CANCER	YOU AGE OF Diagnosis	PARENTS / SIBLINGS / CHILDREN	AGE OF Diagnosis	RELATIVES on your MOTHER'S SIDE	AGE OF Diagnosis	RELATIVES on your FATHER'S SIDE	AGE OF Diagnosis
☒ Y ☐ N	*EXAMPLE: BREAST CANCER*	*45*	-------	---	*Aunt Cousin*	*45 61*	*Grandmother*	*53*
☐ Y ☐ N	BREAST CANCER							
☐ Y ☐ N	OVARIAN CANCER *(Peritoneal/Fallopian Tube)*							
☐ Y ☐ N	UTERINE/ENDOMETRIAL CANCER							
☐ Y ☐ N	COLON/RECTAL CANCER							

Red Flags: Hereditary Breast and Ovarian Cancer Syndrome

Age
- Under age 50

Pathology
- Triple Negative breast cancer

Personal History
- Ovarian cancer
- Male breast cancer
- Two primary breast cancers
- Ashkenazi Jewish ancestry
- Breast cancer with ≥2 relatives with HBOC associated cancers at any age

Family History
- An identified HBOC mutation in family
- Breast cancer diagnosed <50y
- Ovarian cancer
- Male breast cancer
- Two primary breast cancers
- Ashkenazi Jewish ancestry with an HBOC associate cancer
- Three or more HBOC associate cancers at any age

Hereditary Breast and Ovarian Cancer Syndrome

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Hereditary Breast and/or Ovarian Cancer Syndrome

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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

[a] Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. The probability of mutation detection associated with these criteria will vary based on family structure. Individuals with unknown or limited family history/structure, such as fewer than 2 first- or second-degree female relatives having lived beyond age 45 in either lineage, may have an underestimated probability of familial mutation detection. The likelihood of mutation detection may be very low in families with a large number of unaffected female relatives. Clinical judgment should be used to determine the appropriateness of genetic testing. The maternal and paternal sides should be considered independently.

[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.

[e] Close blood relatives include first-, second-, and third-degree relatives on same side of family. (See BR/OV-3)

[f] For the purposes of these guidelines, fallopian tube and primary peritoneal cancers are included. Ovarian/fallopian tube/primary peritoneal cancers are component tumors of Lynch syndrome/hereditary non-polyposis colorectal cancer; be attentive for clinical evidence of this syndrome. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

[g] Testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Full sequencing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria are met. Founder mutations exist in other populations.

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.

What About DCIS?

- Ductal carcinoma in situ (DCIS; also known as *intraductal carcinoma*) is the most common type of non-invasive breast cancer
- About 1 in 5 new breast cancer cases will be DCIS
- NCCN and Medicare criteria
  - Both include DCIS as an equal cancer to invasive breast cancer when considering who should get testing for *BRCA1 or BRCA2*

Li-Fraumeni Syndrome

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Li-Fraumeni Syndrome

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LI-FRAUMENI SYNDROME TESTING CRITERIA

- Individual from a family with a known *TP53* mutation
- Classic Li-Fraumeni syndrome (LFS) criteria:[a]
  - Combination of an individual diagnosed age <45 y with a sarcoma[b]
    AND
    A first-degree relative diagnosed age <45 y with cancer
    AND
    An additional first- or second-degree relative in the same lineage with cancer diagnosed age <45 y, or a sarcoma at any age
- Chompret criteria:[c,d]
  - Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, brain tumor, breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age
    OR
  - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years
    OR
  - Individual with adrenocortical carcinoma or choroid plexus carcinoma[d,e] at any age of onset, regardless of the family history
- Early-age-onset breast cancer:
  - Individual with breast cancer ≤35 y, *TP53* testing can be ordered concurrently with *BRCA1/2* testing or as a follow-up test after negative *BRCA1/2* testing

FOLLOW-UP

LFS testing criteria met[f] → See Follow-up (LIFR-2)

LFS testing criteria not met → Individualized recommendations according to personal and family history

Cancers associated with LFS include but are not limited to:

- Premenopausal breast cancer
- Bone and soft tissue sarcomas
- Acute leukemia
- Brain tumor
- Adrenocortical carcinoma
- Choroid plexus carcinoma
- Colon cancer
- Early onset of other adenocarcinomas or other childhood cancers

Cowden Syndrome

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Cowden Syndrome/PHTS

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COWDEN SYNDROME/PTEN HAMARTOMA TUMOR SYNDROME TESTING CRITERIA[a,b]

- Individual from a family with a known *PTEN* mutation
- Individual meeting clinical diagnostic criteria[c] for CS/PHTS
- Individual with a personal history of:
  - Bannayan-Riley-Ruvalcaba syndrome (BRRS) or
  - Adult Lhermitte-Duclos disease (cerebellar tumors) or
  - Autism spectrum disorder and macrocephaly or
  - Two or more biopsy-proven trichilemmomas or
  - Two or more major criteria (one must be macrocephaly) or
  - Three major criteria, without macrocephaly or
  - One major and ≥3 minor criteria[d] or
  - ≥4 minor criteria

- At-risk individual[e] with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed
  - The at-risk individual must have the following:
    - Any one major criterion or
    - Two minor criteria

FOLLOW-UP

- CS/PHTS testing criteria met[f] → See Follow-up (COWD-2)
- CS/PHTS testing criteria not met → Individualized recommendations according to personal and family history

Major criteria:
- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas
- Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult women, 60 cm in adult men)[g]
- Macular pigmentation of glans penis
- Mucocutaneous lesions[h]
  - One biopsy proven trichilemmoma
  - Multiple palmoplantar keratoses
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucous)

Minor criteria:[i]
- Autism spectrum disorder
- Colon cancer
- ≥3 esophageal glycogenic acanthoses
- Lipomas
- Mental retardation (ie, IQ ≤75)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (eg, adenoma, nodule(s), goiter)
- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

[a] These are testing criteria, clinical diagnostic criteria on COWD-3.

[b] If two criteria involve the same structure/organ/tissue, both may be included as criteria.

[c] Pilarski R, Burt R, Kohlmann W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN Hamartoma Tumor Syndrome: Systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607-1616.

[d] If an individual has two or more major criteria, such as breast cancer and non-medullary thyroid cancer, but does not have macrocephaly, one of the major criteria may be included as one of the three minor criteria to meet testing criteria.

[e] An at-risk individual can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing.

[f] 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.

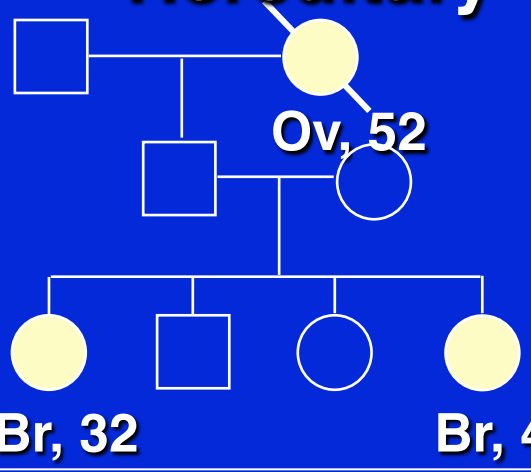
[g] Roche AF, Mukherjee D, Guo SM, Moore WM. Head circumference reference data: Birth to 18 years. Pediatrics 1987;79:706-712.

[h] The literature available on mucocutaneous lesions is not adequate to accurately specify the number or extent of mucocutaneous lesions required to be a major criterion for CS/PHTS. Clinical judgement should be used.

[i] Insufficient evidence exists in the literature to include fibrocystic disease of the breast, fibromas, and uterine fibroids as diagnostic criteria.

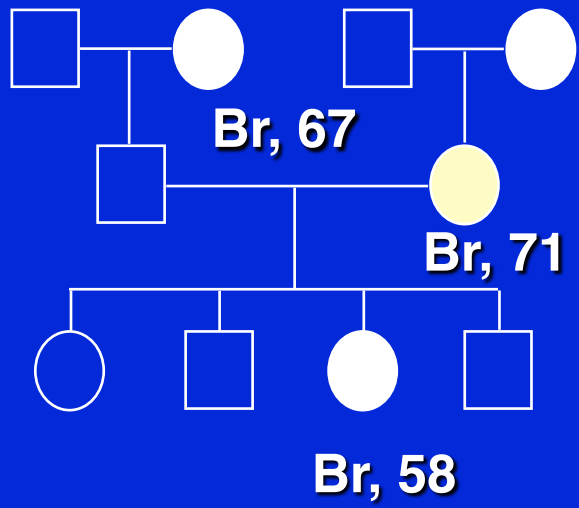
Hereditary vs Familial vs Sporadic

Hereditary

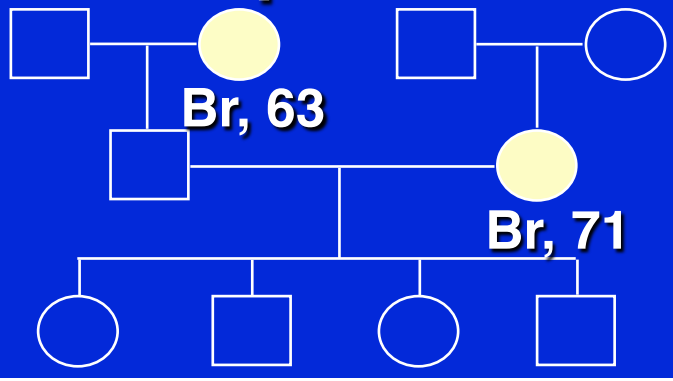


2 Breast cancers under 50 and ovarian cancer, Multiple generations, 50% women affected

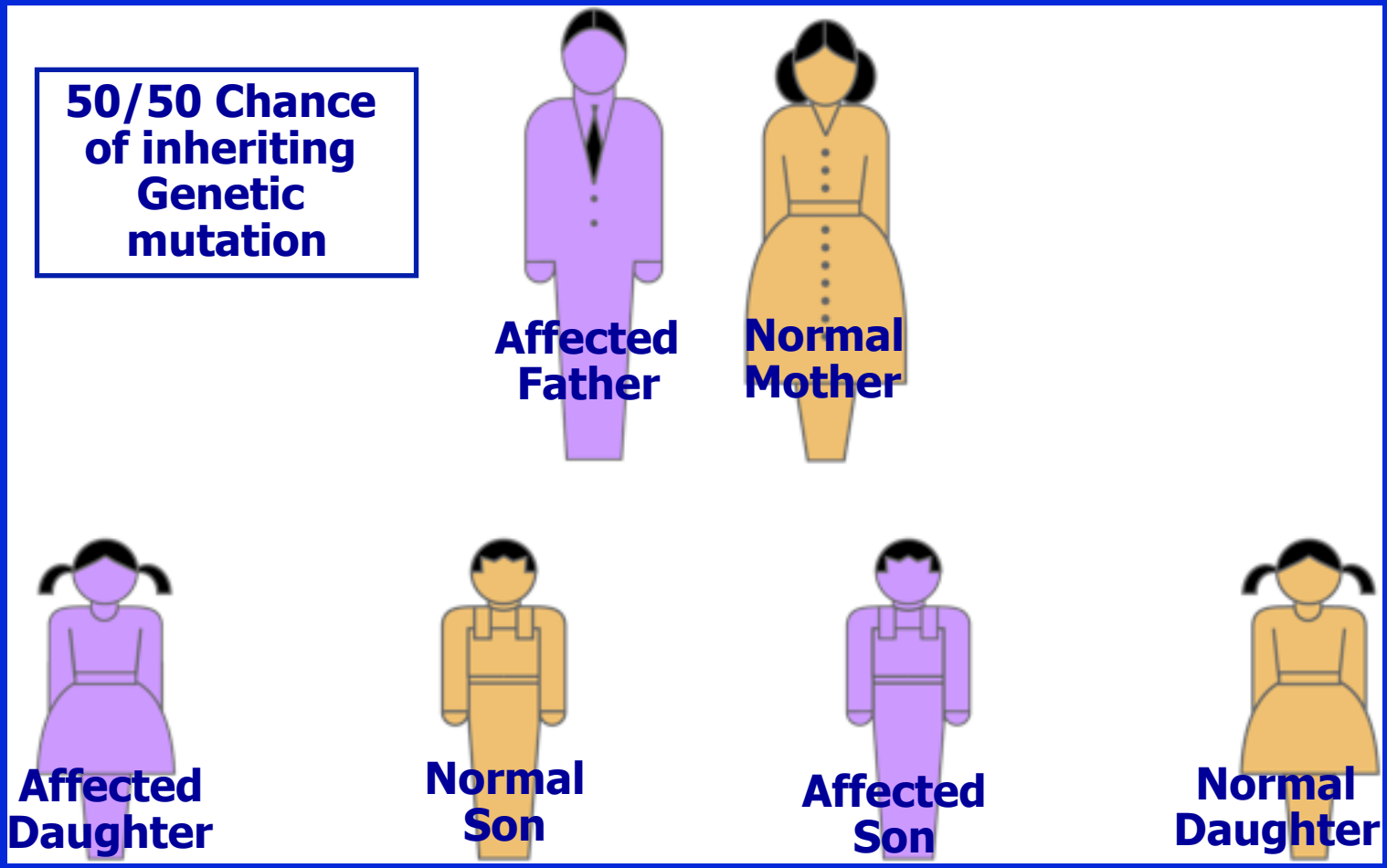
Familial Clustering



Sporadic



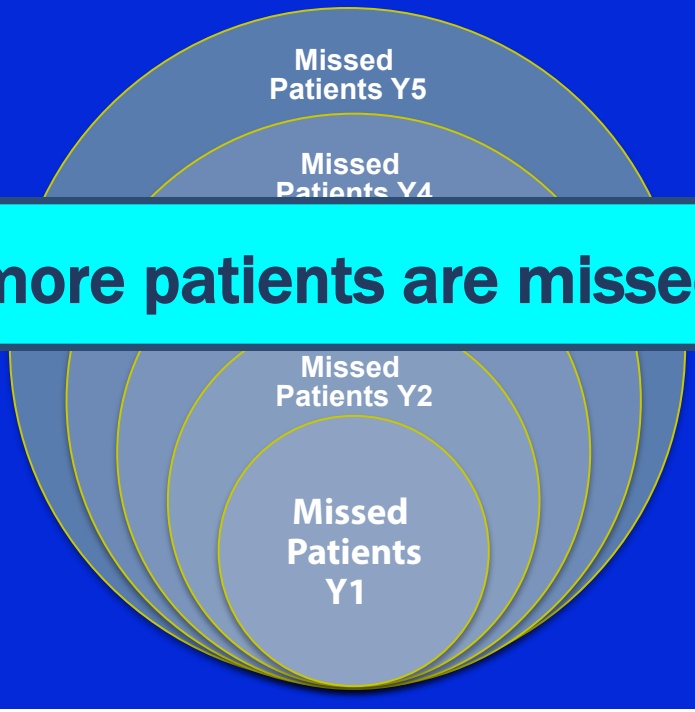
Autosomal Dominant Pattern of Inheritance



Newly Diagnosed Capture Rate: 34%

Leads to Survivor Patient Population AT RISK

Appropriate Patients	Breast Cancer	Ovarian Cancer	CRC/Endo	Total
Newly Diagnosed Patients[1]	289,534	22,240	192,480	504,254
Newly Diagnosed Patients Meeting NCCN[2,3,4]	116,976	20,016	48,095	185,087
Patients Tested[5]	53,041	4,827	4,376	62,244
% Captured	44.5%	24.1%	9.1%	34.0%

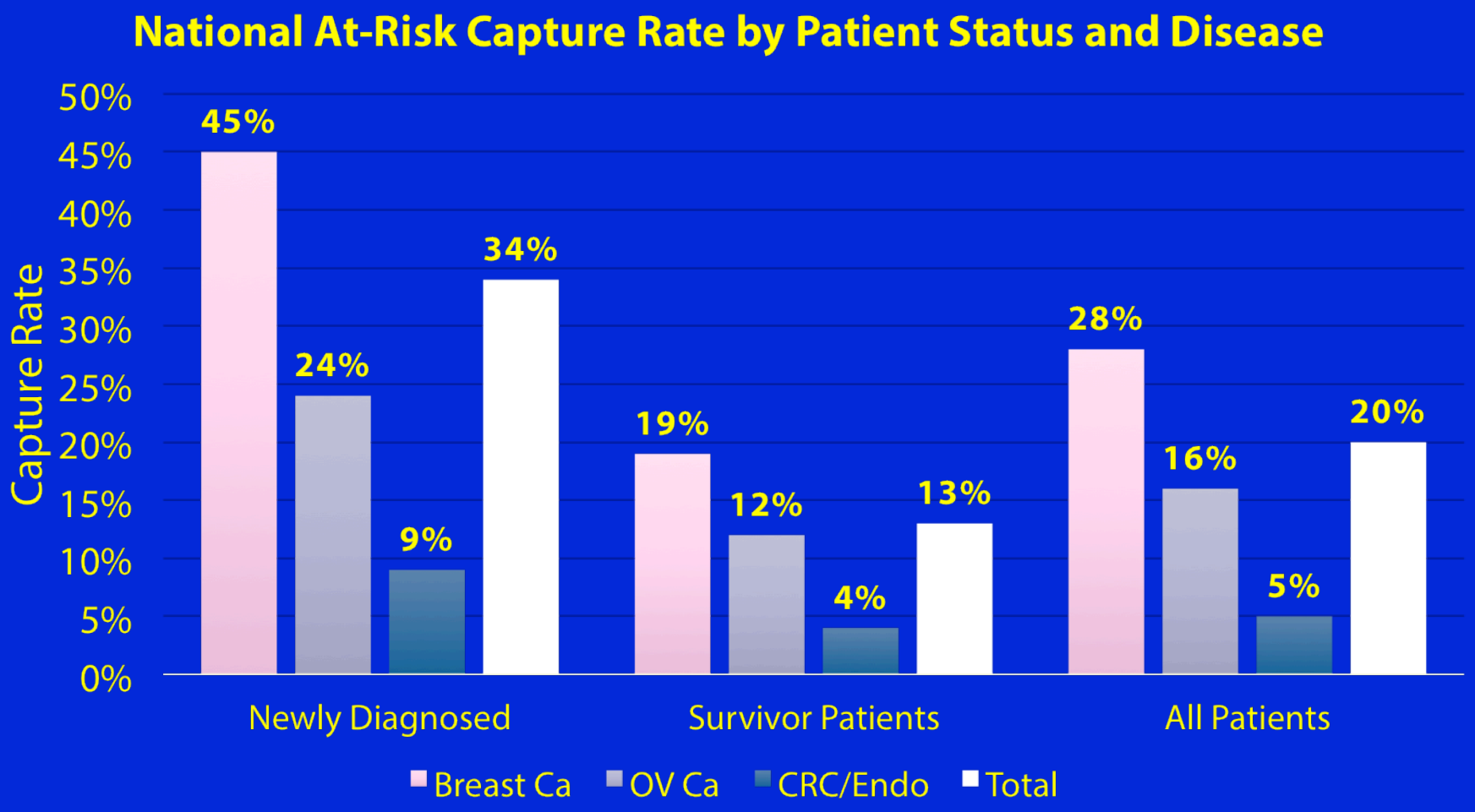


Every year, more patients are missed than tested

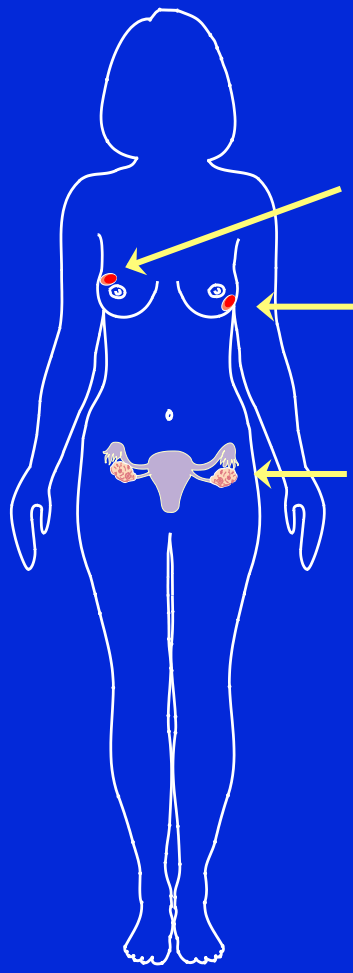
Large Survivor Patient Population

1. Surveillance, Epidemiology, and End Results (SEER), National Cancer Institute, 2012. http://seer.cancer.gov/statistics/
2. Eisenbraun et al. Hereditary Breast and Ovarian Cancer testing: integration and outcomes within community oncology practices. *Comm Oncol.* 2010;7:75-81.
3. NCCN Clinical Practice Guidelines in Oncology v. 4.2013 Genetic/Familial High-Risk Assessment: Breast and Ovarian. Accessed at www.nccn.org
4. Kerber RA, et al. Frequency of familial colon cancer and hereditary nonpolypsosis colorectal cancer (Lynch syndrome) in a large population database. *Familial Cancer* 2005;4:239-44.
5. Internal Myriad data

National Capture Rate by Patient Status and Disease



BRCA1-Associated Cancers: Risk by age 70



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

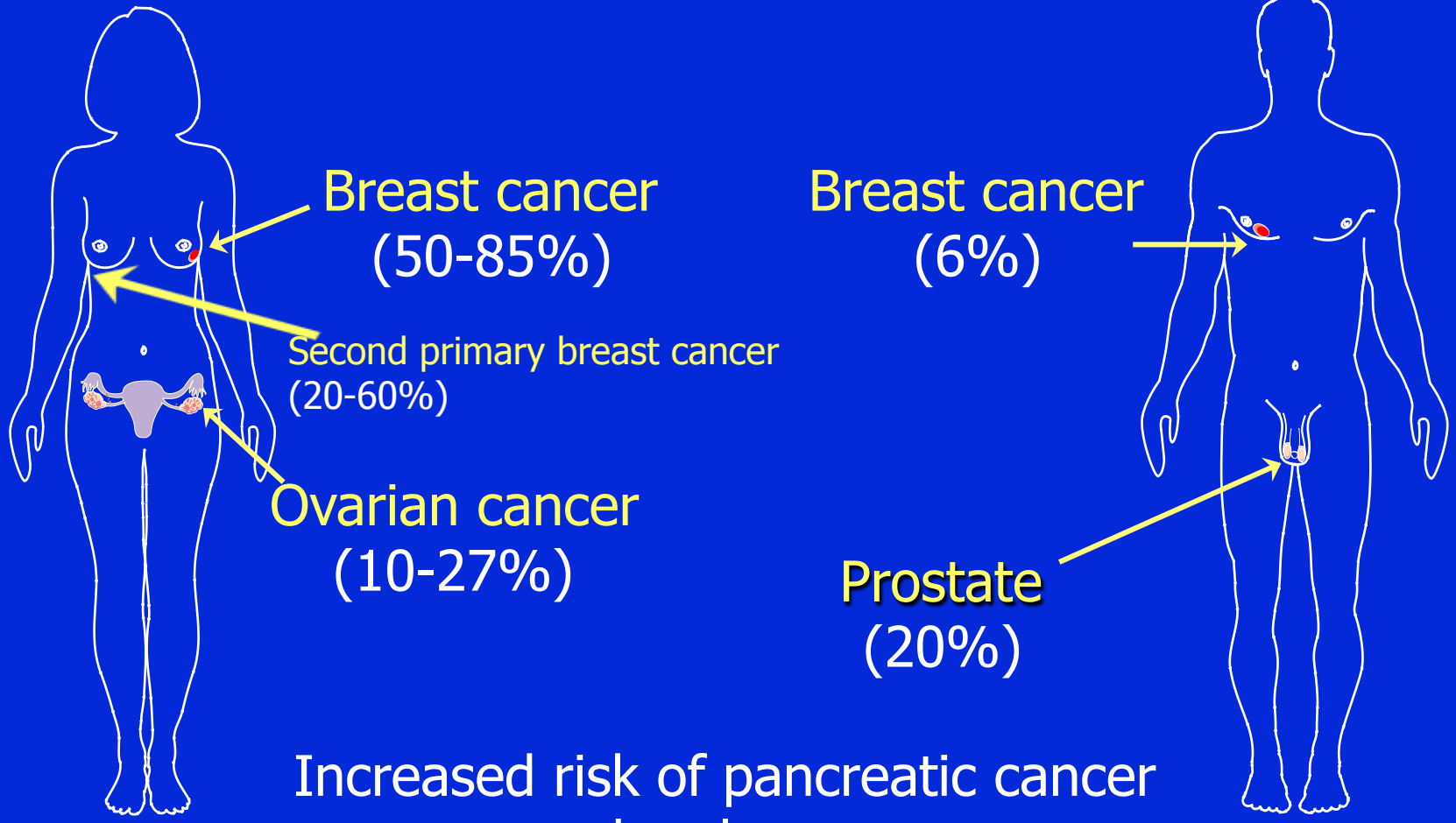
Second primary breast cancer 20%-60%

Ovarian cancer 15-45%

Possible increased risk of other cancers

JCO 2004;22: 735-42; NCI 2005

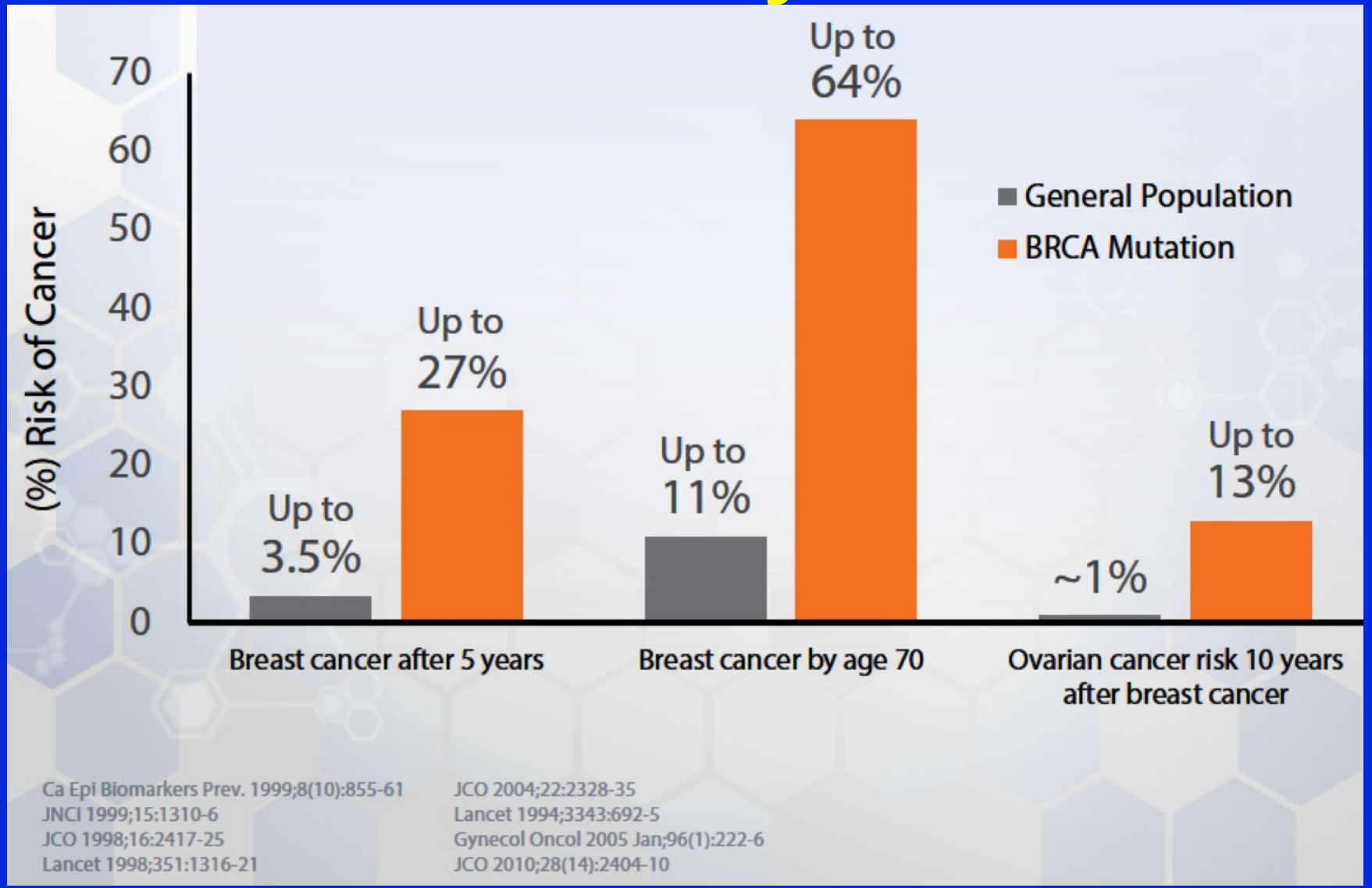
BRCA2-Associated Cancers: Risk by age 70



Increased risk of pancreatic cancer and melanoma

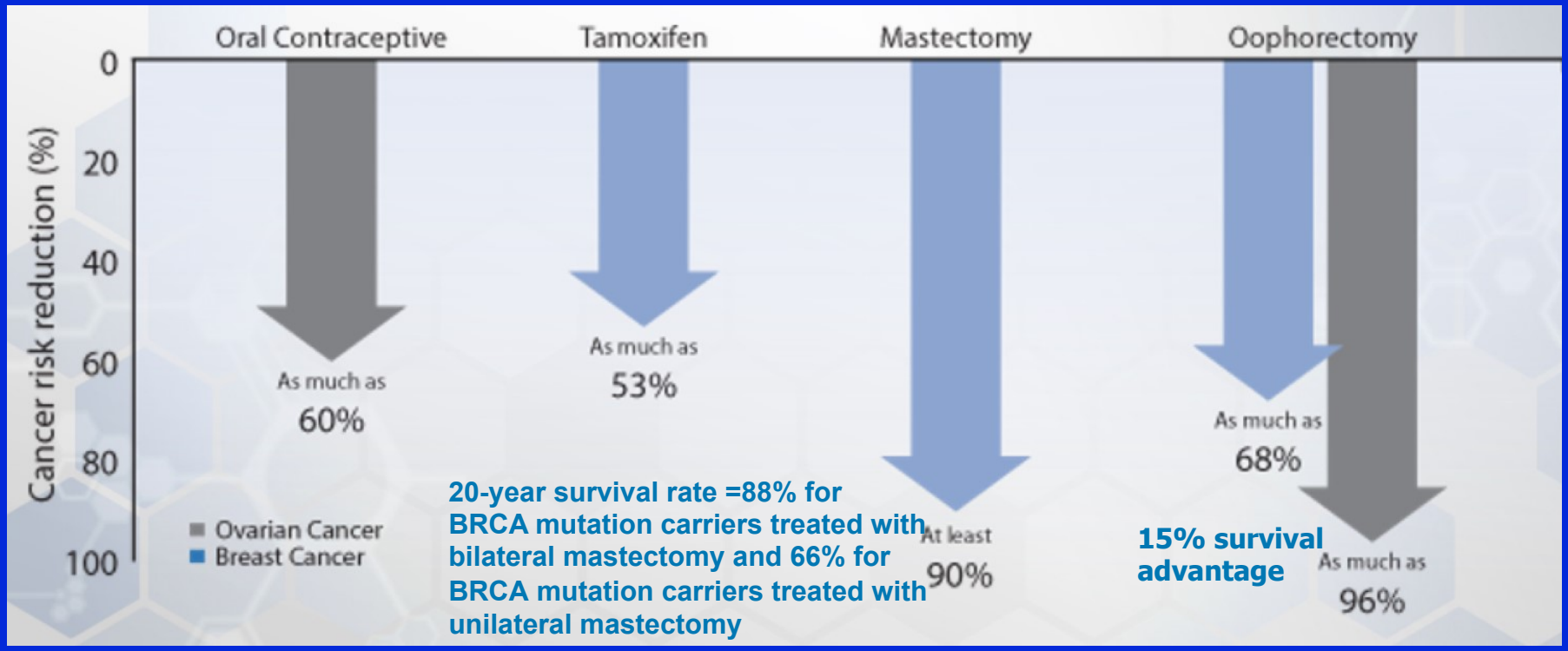
JCO 2004;22: 735-42; NCI 2005

BRCA Mutations Increase Risk of 2nd Primary Cancers



Ca Epi Biomarkers Prev. 1999;8(10):855-61
JNCI 1999;15:1310-6
JCO 1998;16:2417-25
Lancet 1998;351:1316-21
JCO 2004;22:2328-35
Lancet 1994;3343:692-5
Gynecol Oncol 2005 Jan;96(1):222-6
JCO 2010;28(14):2404-10

NCCN Recommended Management Reduces Cancer Risk



Metcalfe, K., Narod, S.A., *et al.*, "Contralateral Mastectomy and Survival After Breast Cancer in Carriers of BRCA1 and BRCA2 Mutations: Retrospective Analysis," British Medical Journal, published online February 11, 2014.

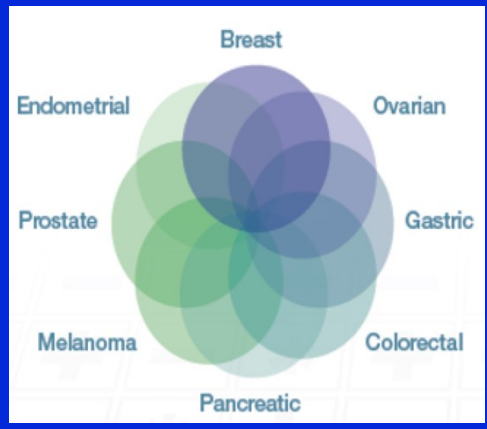
Next Generation Sequencing:
Multiplex Genetic Testing for Inherited Cancer--The Future is Now

1. **Many patients with suggestive family histories test negative on standard testing**
   a. **Need for additional/expanded screening**

2. **Patients do not meet classic guidelines for hereditary cancer syndromes**
   a. **Variable expressivity and reduced penetrance**

3. **Many genes implicated in cancer**
   a. **Testing multiple genes simultaneously can be more time and cost effective**

4. **Overlapping phenotypes of different hereditary cancer syndromes**



NextGen Testing: Who to test??

Cast the net widely, test nearly anyone

- Pro
  - —No sure approach for excluding anyone
  - —Find more mutation carriers
- Con
  - —Difficult to interpret and develop management recommendations

Test Selectively

- Pro
  - —Higher penetrance families
  - —Easier to interpret and recommend management
- Con
  - —Missed mutations

Always test the relative with the highest mutation probability in the family
Reduce non-informative negative results

High Penetrance Genes vs. Moderate/Low Penetrance Genes

Multigene panels include high-penetrance genes, such as *TP53*, *PTEN*, *PALB2*, *STK11*, and *CDH1*, for which guidelines exist for management of breast cancer risk. However, the larger panels also include Moderate/Low Penetrance genes that may have guidelines in other cancers, but not necessarily breast cancer, and genes for which no guidelines exist and the cancer risks are variably understood. (ASCO, 2014)

Rare changes in other genes associated with breast cancer

GENE	DESCRIPTION
PTEN	Helps regulate cell growth. Causes Cowden syndrome leading to higher risk of both benign and cancerous tumors in the breast, digestive tract, thyroid, uterus, and ovaries.
TP53	Provides instructions for making a protein to stop tumor growth. Causes Li-Fraumeni syndrome and increases soft tissue cancer at young ages and higher risk of BrCa, leukemia, brain tumors, and sarcomas.
CHEK2	Provides instructions for making a protein to stop tumor growth. Causes Li-Fraumeni syndrome and can double breast cancer risk.
CHD1	Supports protein growth that helps cell adherence and tissue formation. Increased risk of lobular BrCa and rare, early onset stomach cancer.
PALB2	Supports protein growth that works with the BRCA2 protein to repair damaged DNA and stop tumor growth. Doubles BrCa Risk. Inheriting 2 abnormal PALB2 genes causes Fanconi anemia, higher risk of cancer, including kidney cancer and brain cancer
ATM	Helps repair damaged DNA. Linked to increased risk of BrCa

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

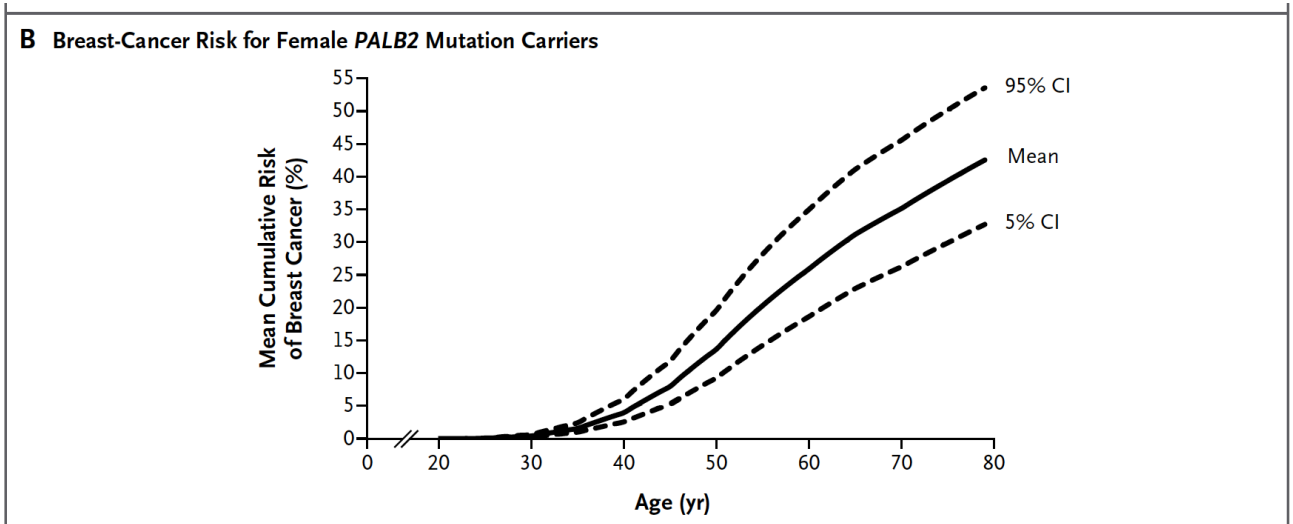
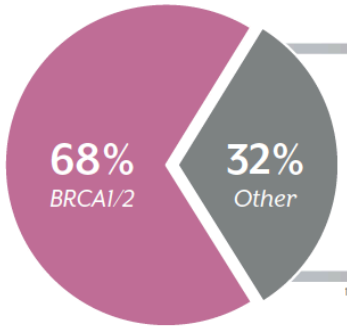


Figure 1. Loss-of-Function *PALB2* Germline Mutations in Relation to Functional Domains and Structural Motifs of the PALB2 Protein, and Cumulative Breast-Cancer Risk for Female Mutation Carriers.

Panel A is a schematic representation of the *PALB2* gene together with all deleterious variants reported in this study, superimposed on the exonic structure of the gene, with functional domains and structural motifs indicated. The number of families with a certain allele is shown in parentheses after the mutation; no such number is given for mutations present only in single families. Numbers in square brackets after functional domains and structural motifs denote amino acid positions. Note that the KEAP1 interaction functional domain is an extended ETGE motif. Panel B shows the mean cumulative risk of breast cancer for female *PALB2* mutation carriers and associated confidence intervals.

Emerging Data Confirms This Dilemma Across Multiple Patient Presentations

In 1,781 Patients with Breast Cancer

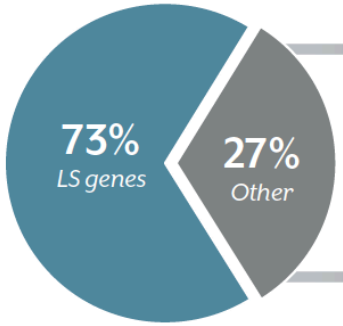


32% of pathogenic mutations identified with Myriad myRisk™ were outside of *BRCA1* and *BRCA2*[1]

244 mutations

[1]Prevalence of Gene Mutations Among Hereditary Breast and Ovarian Cancer Patients Using a 25-gene Panel, Nadine Tung et. al. Presented at ACMG in March 2014

In 1,260 Patients Suspicious for Lynch Syndrome (LS)

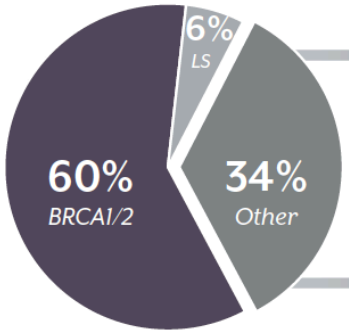


27% of pathogenic mutations identified with Myriad myRisk™ were outside of the genes associated with Lynch syndrome[2]

157 mutations

[2]Multi-gene panel testing in patients suspected to have Lynch syndrome, Matthew B. Yurgelun et. al. Presented at ASCO June 2014

In 648 Patients with Ovarian Cancer

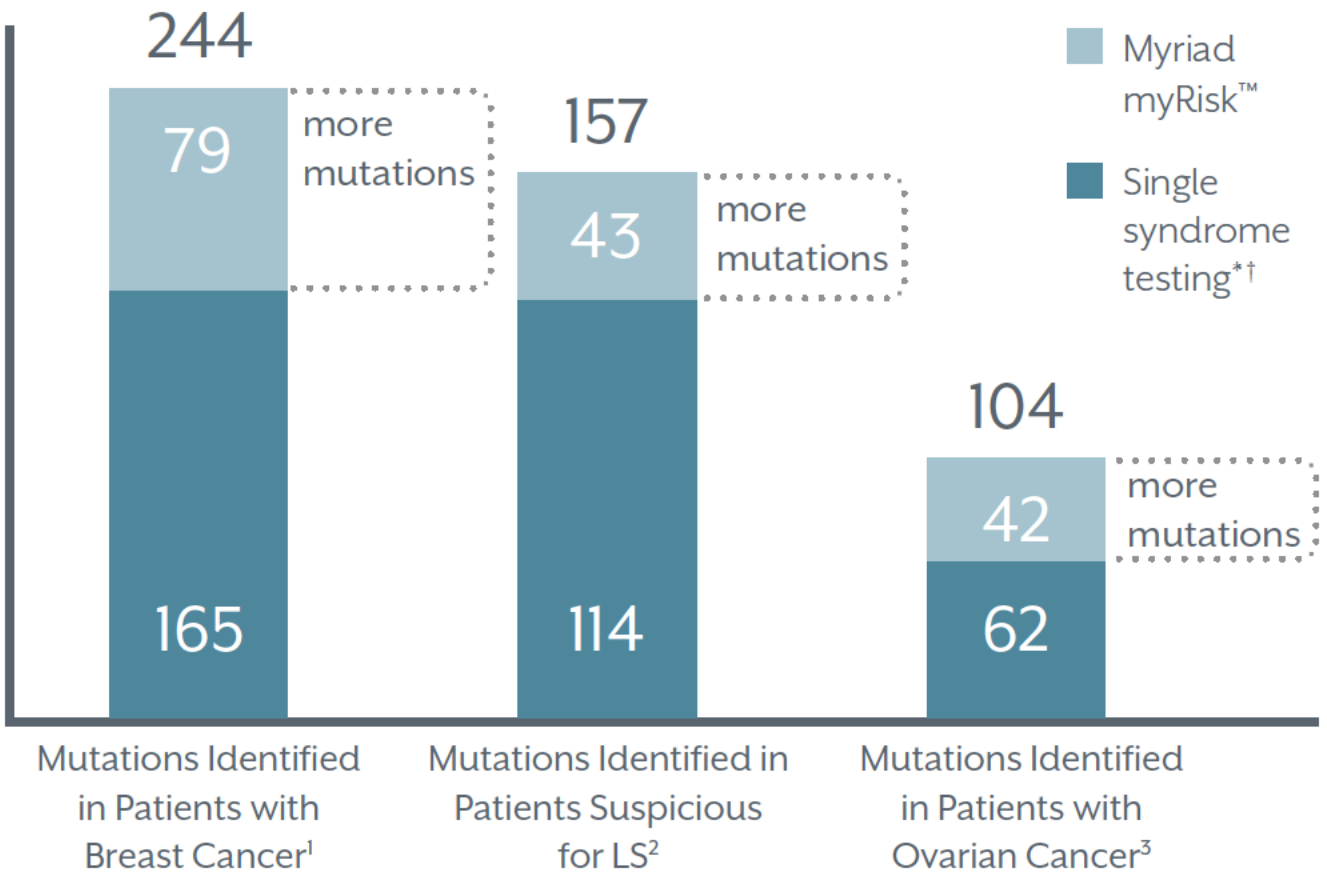


34% of pathogenic mutations identified with Myriad myRisk™ were outside of *BRCA1/2* and the genes associated with LS[3]

104 mutations

[3]A Study of Ovarian Cancer Patients Tested With a 25-gene Panel of Hereditary Cancer Genes, Lucy R. Langer et. al. Presented at ASCO June 2014

~40-50% Relative Increase in Mutation Detection Over Current Approach[1,2]



*BRCA1/2

†Lynch syndrome

[1]Prevalence of Gene Mutations Among Hereditary Breast and Ovarian Cancer Patients Using a 25 Gene Panel, Nadine Tung et. al. Presented at ACMG in March 2014

[2]Multi-gene panel testing in patients suspected to have Lynch syndrome, Matthew B. Yurgelun et. al. Presented at ASCO June 2014

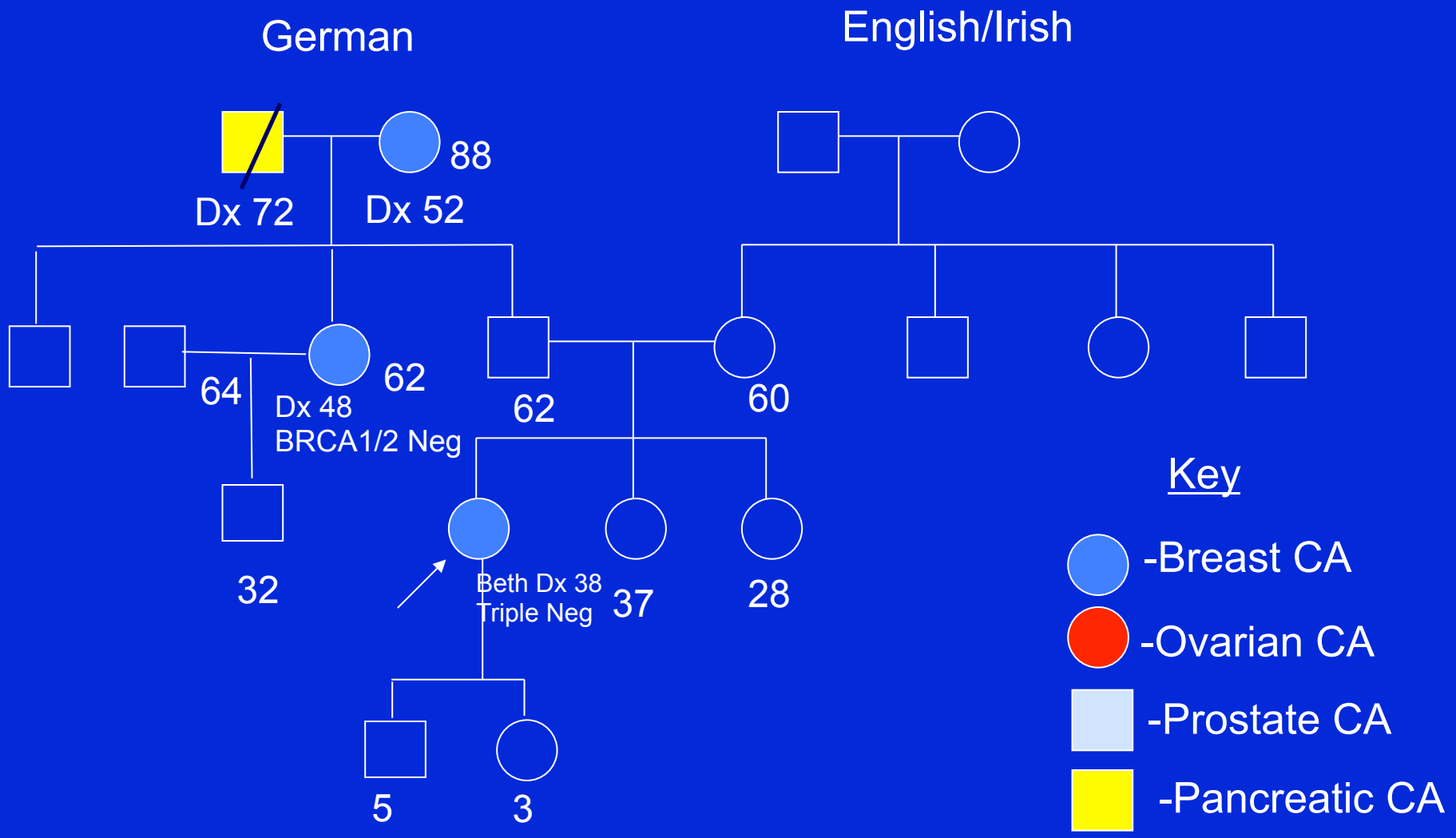
[3]A Study of Ovarian Cancer Patients Tested With a 25-gene Panel of Hereditary Cancer Genes, Lucy R. Langer et. al. Presented at ASCO June 2014

Case Study: Beth

Beth is a 38 year old woman recently diagnosed with triple negative breast cancer and is trying to determine her course of treatment. She has two young children (5 & 3 y/o), but also two female siblings. Beth reports the following family history:

- Maternal family history is negative for cancer
- Paternal family history is significant for:
  - Her father has one brother & one sister
    - Limited Family Structure
  - Paternal grandmother diagnosed with breast cancer age 52, but she thinks she was pre-menopausal

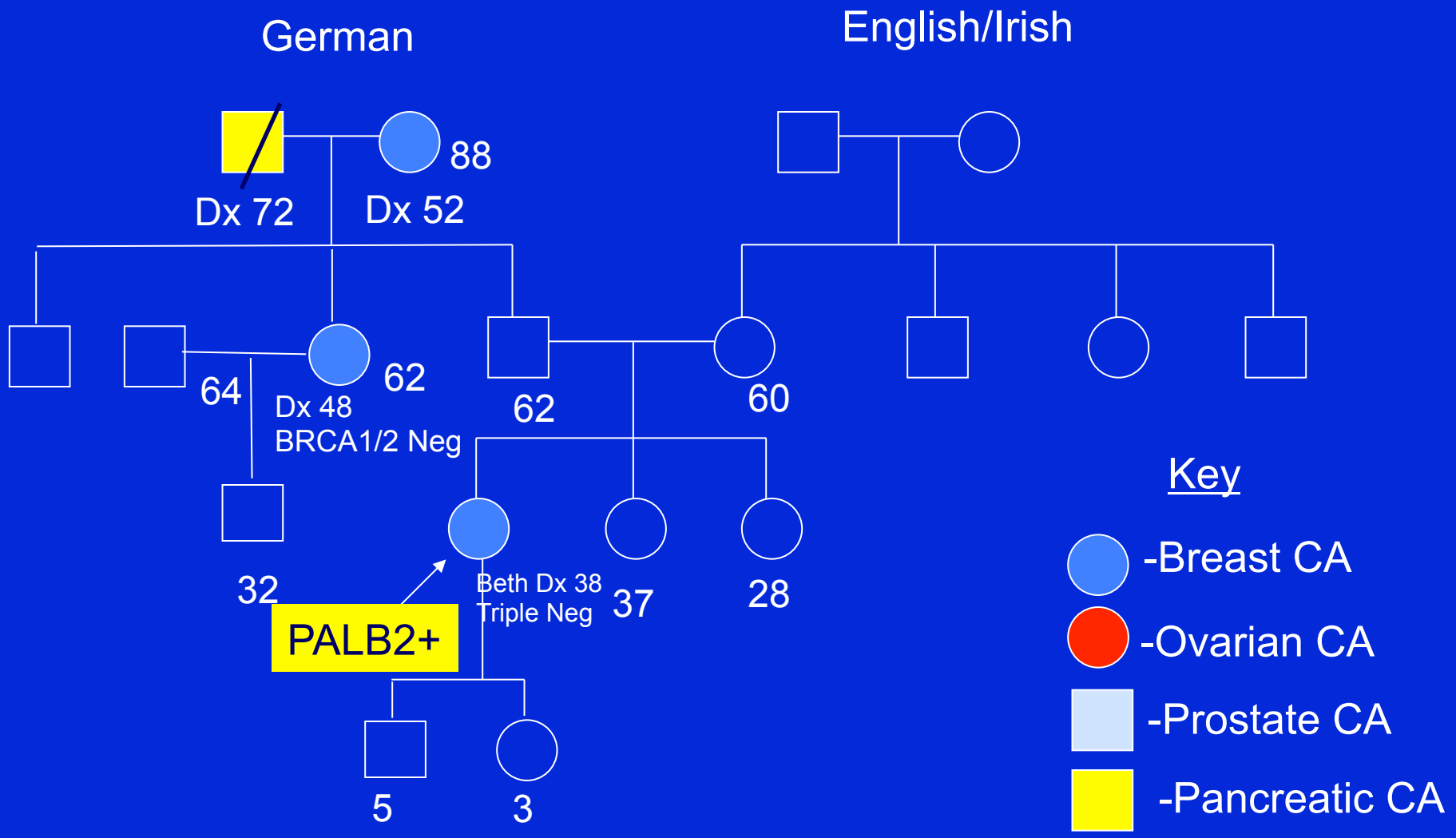
Case Study: Triple Negative BrCa



Case Study: BRCA1/2 Risks

- Rational for Testing:
  - Testing will assist with informed treatment decision making (ASCO Guidelines)
  - Early age of Onset and Triple negative BrCa (NCCN guidelines)
- Limited family structure
- Paternal Aunt tested Negative for BRCA1/2
  - Genetic counseling & testing prior to definitive surgery and for treatment planning.

Case Study: Updated Pedigree



Case Study: Impact of results – medical management

- Beth
  - PALB2+: High BrCa risk (20-40% by age 80)
  - Discuss surgical management including:
    - Breast conservation
    - Therapeutic and Preventive Mastectomy
  - Discuss whether she has completed child-bearing
    - Options for fertility preservation
  - Risks for other cancers

Case Study: Impact of results – medical management

- Beth's 1st degree relatives: sisters & father
  - Discuss results (duty to warn) and encourage genetic counseling and testing
  - If negative, General population risk for breast cancer –follow standard screening (ACS) guidelines
    - Cannot pass this on to their children
  - If positive, elevated risk for breast cancer- follow NCCN guidelines
- Beth's children:
  - Genetic counseling and testing at the appropriate time/age

Case Study: Take Home Messages

- Risk assessment and genetic testing gives information to patient AND family members
  - Some family members may want this information and some may not
- Genetic testing, when informative, can help individuals make decisions about early detection and risk-reduction
- Can also relieve anxiety about cancer risk (if negative)
- Informed decision-making imperative
- Additional follow-up support and/or counseling sometimes necessary

Thank You!!

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