Genetic counseling and testing

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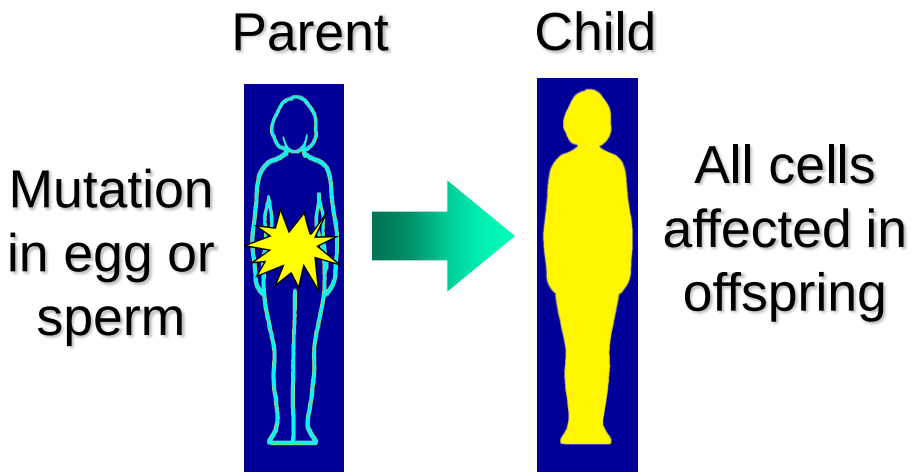
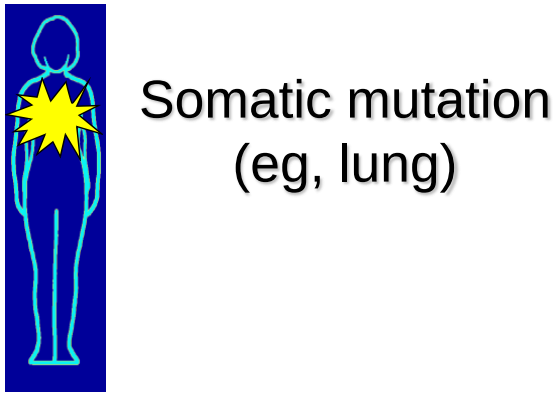
Cancer Arises From Gene Mutations

Germline mutations



- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Somatic mutations

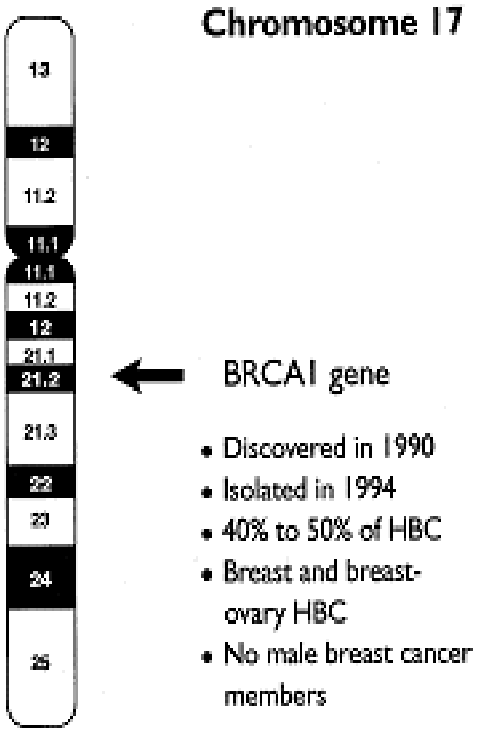


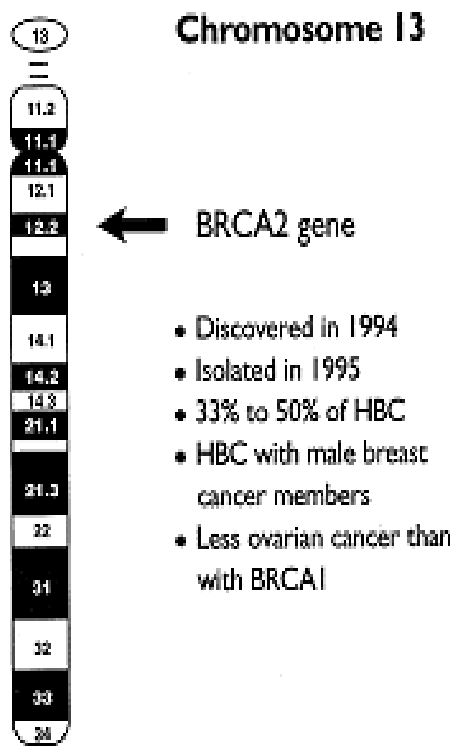
- Occur in nongermline tissues
- Are nonheritable

BRCA1/2 Mutations

BRCA1 and BRCA2

- Cloned in families with multiple cases of breast and/or ovarian cancer



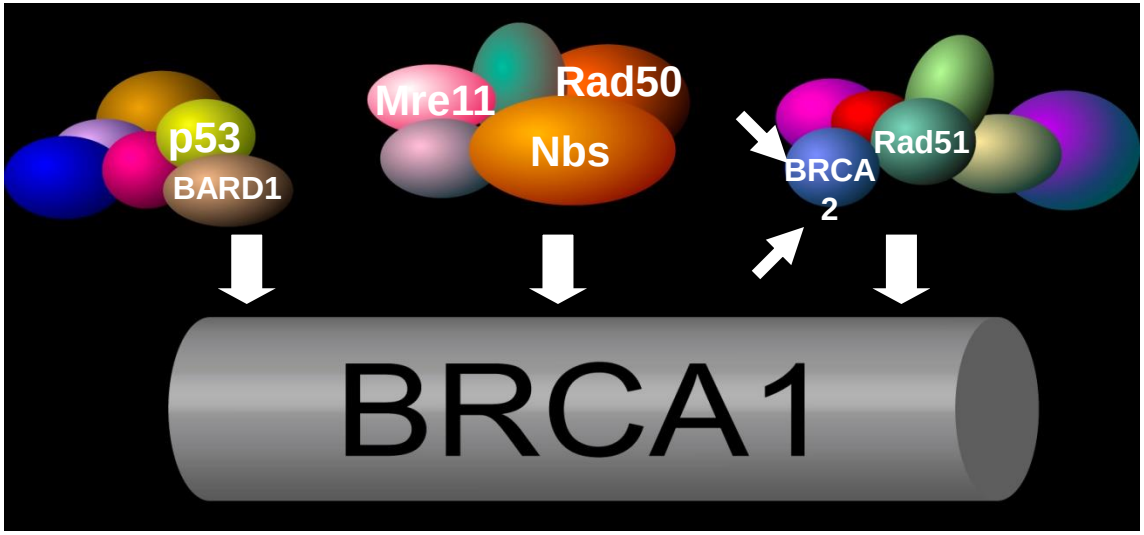


Mutations in different genes can cause the same disease

BRCA1- cloned 1994

BRCA2- cloned 1995

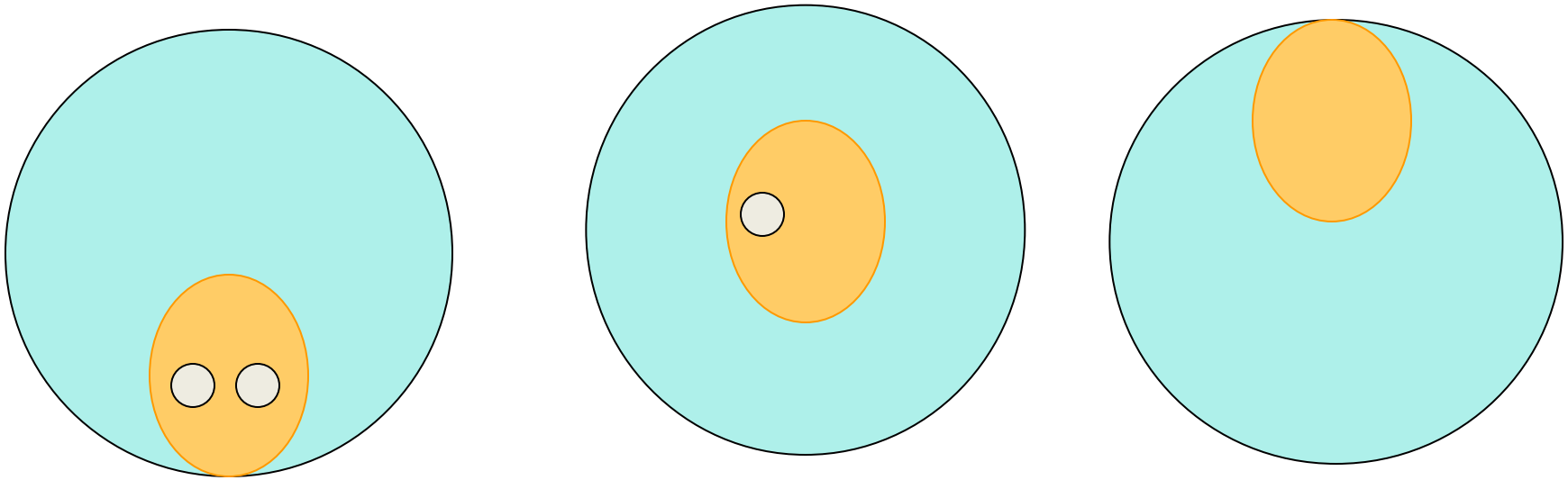
The BRCA1 Protein and Genomic Integrity



- Interacts with MANY proteins (including BRCA2) involved in maintaining genomic integrity
- Required for efficient repair of many types of DNA Damage, particularly homologous recombination
- Loss leads to cell line susceptibility to interstrand crosslinking agents such as cisplatin and mitomycin c
- Loss also causes dependency on other DNA repair systems, such as PARP

BRCA 1\2 Related Cancer

BRCA1\2 carriers only have one functional copy of gene, and cancer thought to arise from sporadic loss of the single functional copy



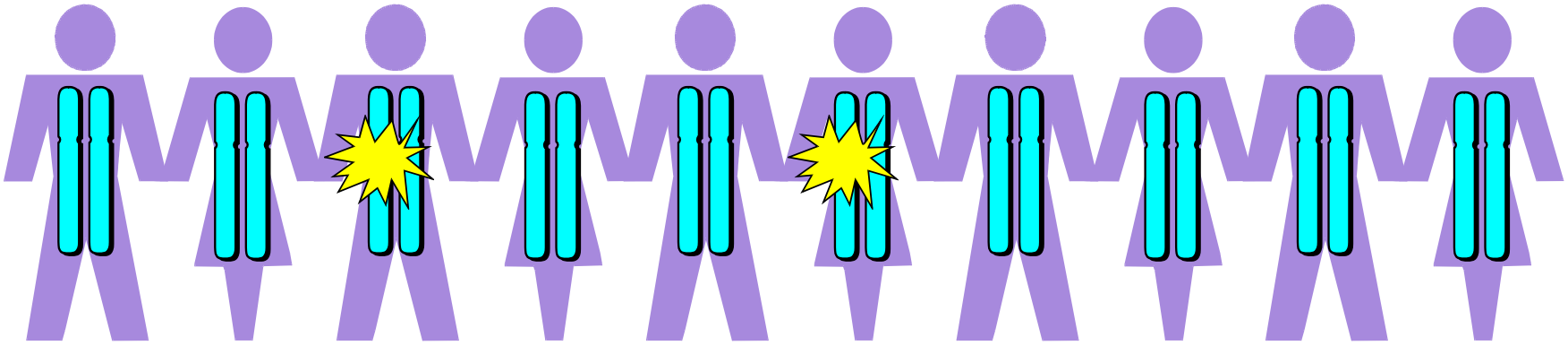
Normal cell with two copies of gene

LOH
Only one functional copy present

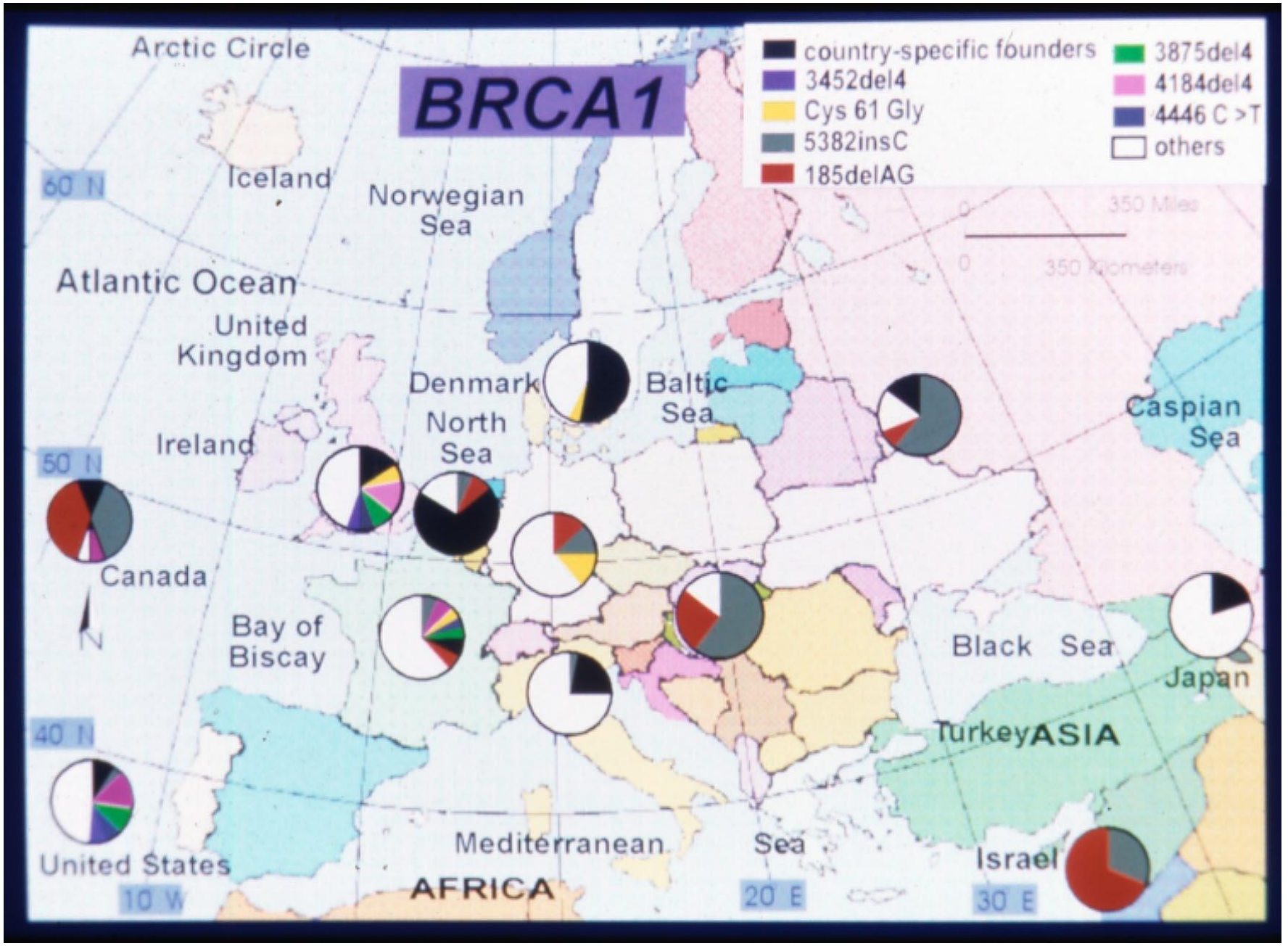
Sporadic loss of single copy… >> cancer

Carrier Frequency

Prevalence of an altered disease gene in a given population



•Approximately 1/300 to 1/800 women in the US carry a BRCA1/2 mutation
•In different ethnic groups certain inherited diseases are more common, (founder mutations)


BRCA1
country-specific founders
3452del4
Cys 61 Gly
5382insC
185delAG
3875del4
4184del4
4446 C >T
others
Arctic Circle
Iceland
Norwegian Sea
Atlantic Ocean
United Kingdom
Denmark
Baltic Sea
North Sea
Ireland
Caspian Sea
Canada
Bay of Biscay
Black Sea
Japan
Turkey
ASIA
Mediterranean Sea
AFRICA
United States
Israel
60 N
50 N
40 N
10 W
20 E
30 E
350 Miles
350 Kilometers

Common BRCA1 and BRCA2 mutations in Ashkenazi Jews

- BRCA1 - 185del AG 1%

  5382insC 0.1%
- BRCA2 - 6174delT 1.4%

  2.5% (1/40)

Epidemiological estimates in other populations - 1/300-1/800.

Iceland - BRCA2 999del5 - 0.6% (~1/170)

The prevalence of BRCA1/BRCA2 mutations: Contribution to cancer - **in non-selected population**

- Breast cancer ~ 2.5%-5%
- Ovarian cancer ~ 10-15%
- Pancreatic cancer ?
- Prostate cancer ?

The prevalence of BRCA1/BRCA2 mutations: Contribution to cancer - **in Ashkenazi Jews**.

- Breast cancer ~11% of cases are carriers
- Ovarian cancer ~40% of cases are carriers
- Pancreatic cancer ~8% of cases are carriers
- Prostate cancer ~ 5% of cases are carriers

When to refer for onco-genetic counseling & testing?

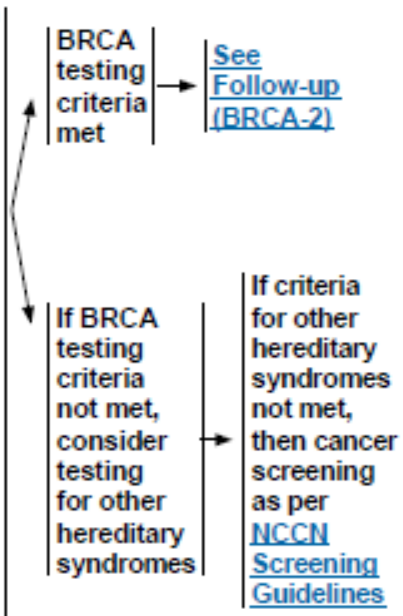
NCCN Guidelines Version 2.2016
BRCA-Related Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
Genetics Table of Contents
Discussion

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 ovarian carcinoma at any age or 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 ovarian carcinoma at any age or 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.

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.

NICE Guidelines (UK) June 2013

- **Carrier probability at which genetic testing should be offered**
- **Breast/ovarian cancer cases** with combined *BRCA1/BRCA2 mutation carrier probability of ≥10% (based on acceptable methods)*

Consider genetic counseling & testing when:

- **Bilateral breast cancer**
- **Early onset breast cancer (≤40-45)**
- **Histo-pathologic features including : triple negative subtype**
  (Medullary carcinoma, lymphocytic infiltration)
- **Personal or family history of – breast (incl. male breast cancer), ovarian, pancreatic or prostate cancer**
- **Certain ethnic groups (eg Ashkenazi Jewish ancestry)**

Genetic counseling

Genetic counseling for inherited cancer predisposition

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease*

******Journal of Genetic Counseling, Vol. 15, April 2006***.**

Who *can* give genetic counseling?

- USA – Physicians and genetic counselors **(relatively new profession, MSc to PhD; ABGC)**

- Europe **–also "genetic nurses"**

- Israel **– Genetic Information Law (2001):**

Physicians within their specialty and genetic counselors.

Genetic counseling for inherited cancer predisposition

Affected vs. Healthy

Common issues:

- **Risk assessment** for specific cancers.
- **Cancer surveillance and prevention**.
- **Familial implications**: mode of inheritance, relatives at risk, reproduction.
- **Genetic testing**: sensitivity, clinical utility, method, result interpretation.

Issues for affected women:

- **Therapeutic implications** –Surgical & Medical.
- Recently diagnosed – time pressure & information overload
- **Reproductive**

Genetic counseling for inherited cancer predisposition

The traditional model:

- Pretest counseling (30-45 min, and more)
  - Drawing a family pedigree
  - Discussion – inheritance, risk assessment , etc.
  - Reaching an informed decision about testing.
- Genetic testing
- Post-test counseling (variable length)
  - Discussion of results
  - Recommendations for patient and relatives

Genetic Counseling - Issues

- Different national requirements and institutional policies
- Could be a bottleneck to timely testing
- New studies suggesting that written information or post-testing counseling as acceptable alternative

How BRCA testing may change with the introduction of specific BRCA therapies

- More patients referred for testing
- Quicker results needed
- Testing may take place earlier – at diagnosis or during early treatment phase
- Role/timing of counselling may change

Hereditary breast cancer syndrome & multi-gene panel testing

Other HBOC Syndromes

- **Li Fraumeni Syndrome**
- ***p53* mutation**
- ***PTEN*/Cowden Syndrome**
- ***ATM* mutation**
- **Lynch Syndrome**
- ***MLH1, MSH2,MSH6, EPCAM* and *PMS2* mutations**
- ***RAD51* mutation**
- ***BRIP1* mutation**
- ***PALB2* mutation**
- ***CHEK2* mutation**
- ***STK11* mutation**
- **(Peutz-Jeghers Syndrome)**
- ***CDH1* mutation**

Clinical implications for prevention and screening not well understood for all these mutations…..

Future directions

- Population screening
- Further understanding of genetic and non-genetic risk modifiers to personalise risk assessment and tailor recommendations for screening and risk-reducing measures

  For example: ovarian-cancer-cluster-regions and breast-cancer-cluster-regions that modify risk of OC or BC
- whole exome/genome studies may bring further insights into risk modification

Thank you