

Genetics of Breast Cancer

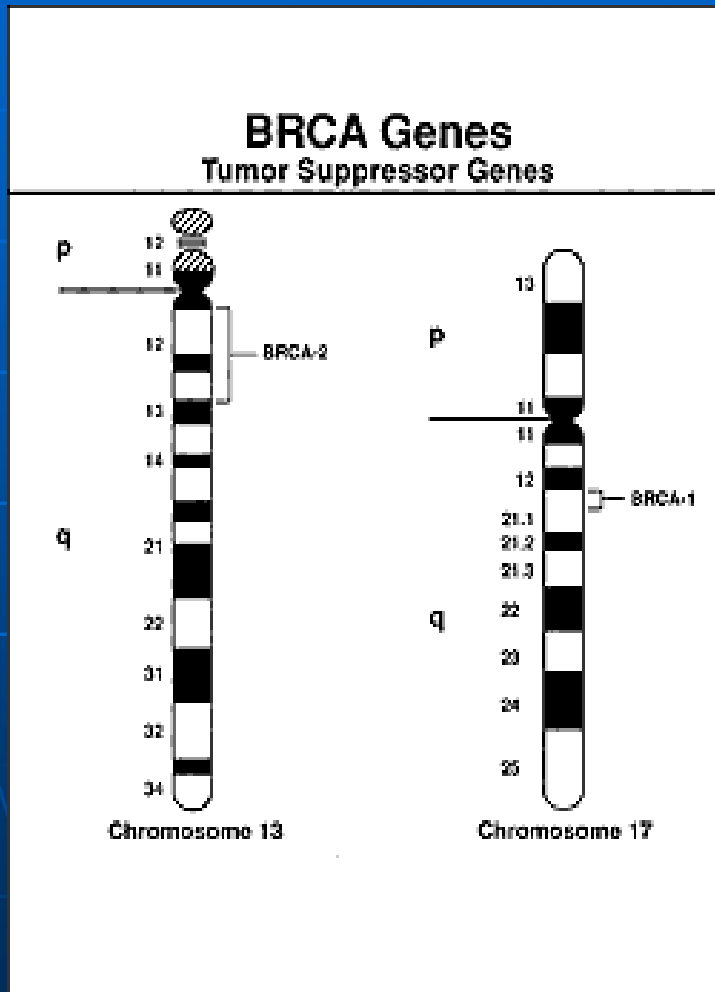


- Mutations in BRCA1 or BRCA2 predispose to breast cancer and ovarian cancer as well as prostate and other cancers.
- Prognosis for breast cancer survival depends upon the stage at which breast cancer is diagnosed.
- Prognosis for individuals with BRCA1 or BRCA2 cancer may not be different from that for controls.

Breast Cancer

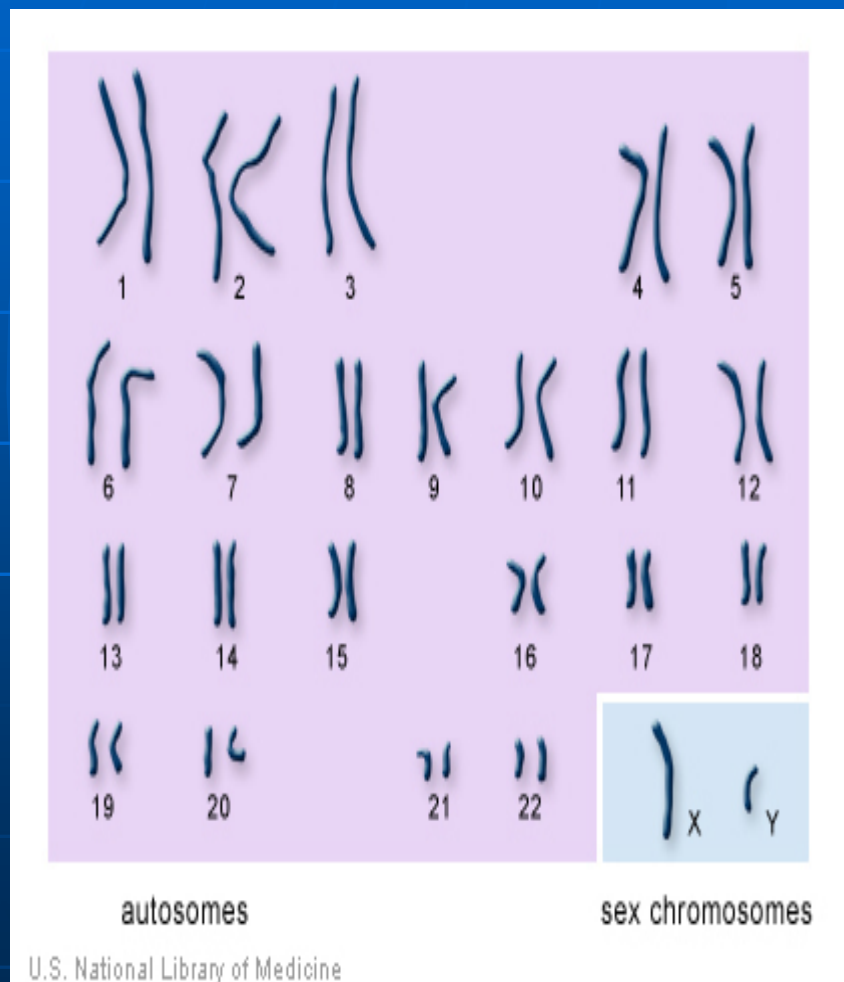
- Risk Factors:
- Null & late parity
- Breastfeeding
- Early menarche & late menopause
- Obesity
- Alcohol
- Oral contraceptives (24% for up to 10 y)
- HRT (5% per year of use for up to 5 Y post cessation)

Breast Cancer



- Most cancers are not inherited.
- About 5% of BR Ca & 5-10% of Ovarian Ca are due to inherited mutated genes.
- The prevalence of cancer-predisposing *BRCA1* mutations in the general population is between 1:500 and 1:1000.

Factors suggesting a familial breast cancer



- A few family members with BR, OV & Prostate Ca
- Multiple generations affected
- Young age at Dx (30% of BR Ca Dx <30 Y)
- Multiple primary Ca in one person
- BR Ca in a Male
- Both BR Ca & Ov Ca
- Bilateral BR Ca
- Ethnicity (Ashkenazi, Eastern Europeans, Dutch, Icelanders)

Pattern recognition
(Cancers associated with BRCA 1 & 2)

■ BRCA1

■ Breast (Average risk 60%)

■ Ovarian(40%)

■ Pancreatic

■ Prostate

■ Endometrial

■ Cervical

BRCA2

Breast(45%)

Ovarian(11%)

Prostate

Pancreatic

GB/Bile duct

Melanoma

Manchester Score

■ Diagnosis-Age	Combined score
■ F BR Ca < 30	11
■ F BR Ca 30-39	8
■ F BR Ca 40-49	6
■ F BR Ca 50-59	4
■ F BR Ca > 59	2
■ M BR Ca < 60	13
■ M BR CA > 60	10

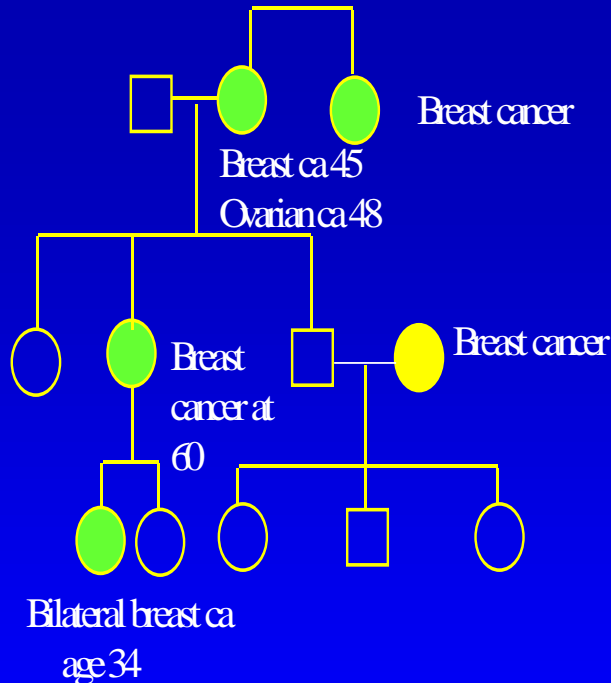
Manchester Score

■ Ov Ca < 60	13
■ Ov Ca > 60	10
■ Pancreatic Ca	1
■ Prostate Ca < 60	2
■ Prostate ca > 60	1

Manchester Score

- Scores are added for each cancer
- Bil BR Ca, score each separately & sum
- Cancer cases through 2 unaffected females aged >60 are discounted
- DCIS is included, doesn't take into account different types of breast cancer

Risk Calculation



- At or slightly above average risk:
- No FH
- One 1 degree relative Dx >50 Y
- One 2nd degree relative Dx at any age
- Two 2nd degree Dx at or > 50 Y
- Lifetime risk is no more than 1.5 general population.
- Reassurance & MMG q2y from 50 (women 40-49 also eligible)

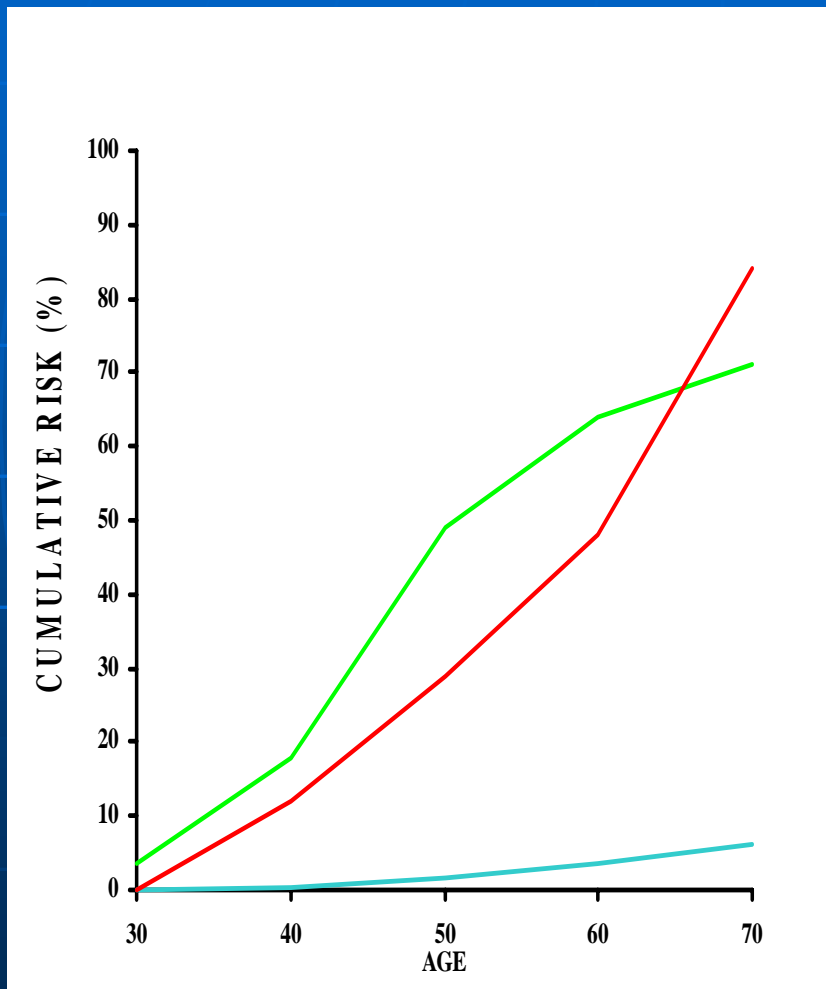
Risk Calculation

- Moderate risk:
- One 1 degree Dx < 50 Y
- Two 1 degree Dx with BR Ca
- Two 2nd degree Dx with BR Ca, one < 50 Y
- Lifetime risk is 1.5-3 times general population
- Advise as per category 1 & MMG from younger age or more frequently should be considered on individual basis

Risk Calculation

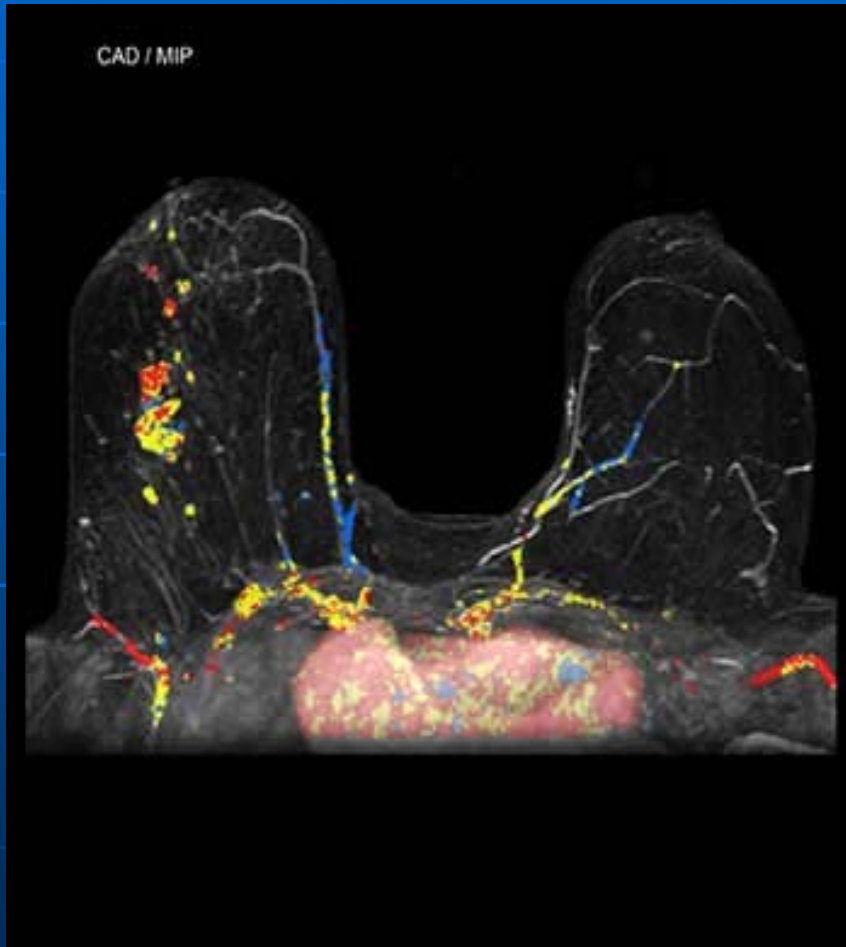
- High Risk:
- Two 1 or 2nd degree with BR or Ov Ca plus one of these features:
 - BR Ca Dx <40 Y
 - Bilateral BR Ca
 - Additional relatives with BR or Ov Ca
 - Br and Ov Ca in the same person
 - Ashkenazi ancestry
 - Male BR Ca
 - One relative with BR Ca <45 Y plus another relative with Sarcoma < 45 Y

Risk calculation / Breast Cancer Risk In BRCA1/2 Carriers



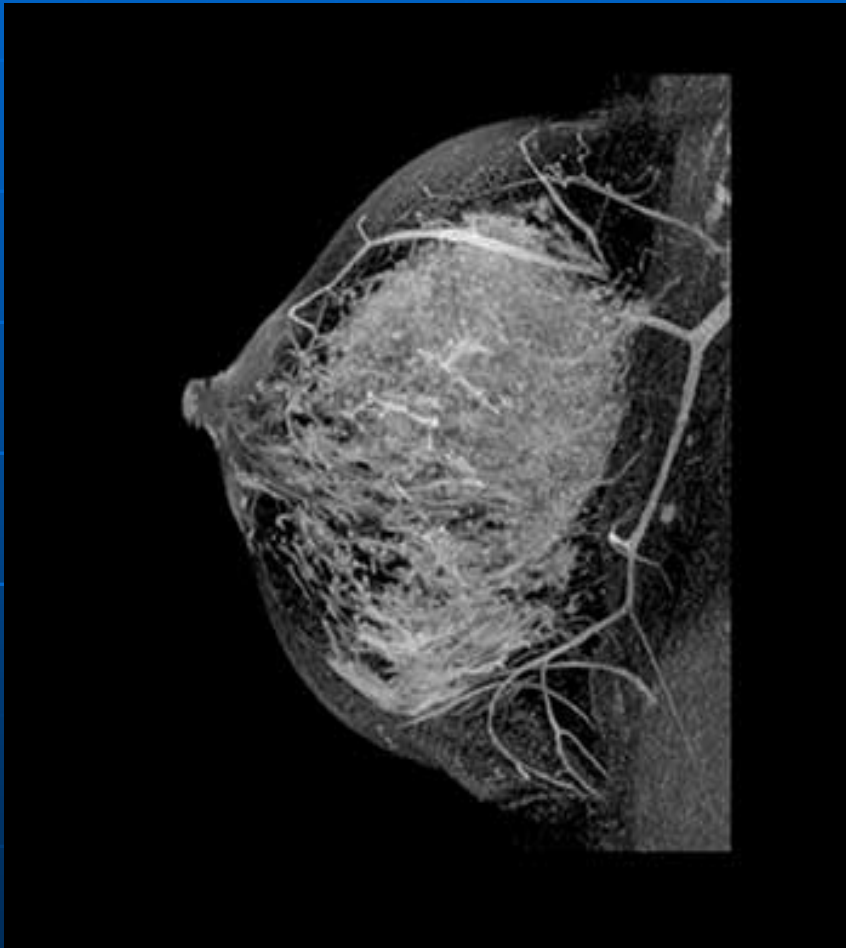
- Recommendations:
- Refer to a Cancer Genetics Clinic
- Individual surveillance program in consultation with a cancer specialist
- Surveillance for BR Ca
- Surveillance for Ovarian Ca
- Start screening 5 Y prior to age of Dx of the closest relative

Surveillance



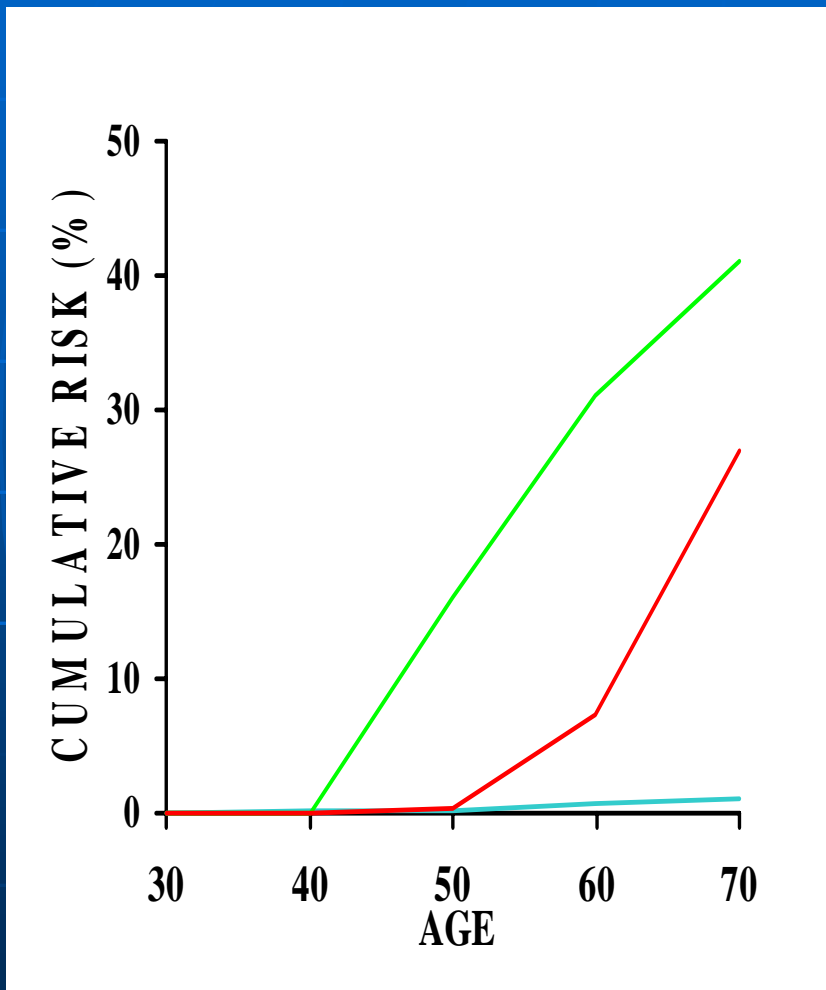
- Breast cancer screening: cancer risk begins in the late 20s or early 30s
- Monthly breast self-examination starting in early adulthood
- Annual or semiannual clinical breast examination beginning at age 25-35 years
- Annual mammography beginning at age 25-35 years
- Screening should be individualized based on the earliest age of onset in the family.

Surveillance



- *Breast MRI screening in women with BRCA1 and BRCA2.*
- *Studies compared the sensitivity and specificity of four methods of breast cancer screening (mammography, ultrasound, MRI, and clinical breast examination [CBE])*
- *The National Cancer Center Network has recommended the addition of breast MRI to standard mammography among women with a BRCA1 & 2*

OVARIAN CANCER RISKS IN BRCA1/2 CARRIERS & Surveillance



- Ovarian cancer screening. transvaginal U/S & serum CA-125 have limited sensitivity and specificity & not been shown to reduce ovarian cancer mortality. ? recommended in the absence of more effective means.
- Annual or semiannual pelvic examination beginning at age 25-35
- Annual or semiannual transvaginal U/S examination beginning at age 25-35 years
- Annual serum CA-125 beginning at age 25-35 years

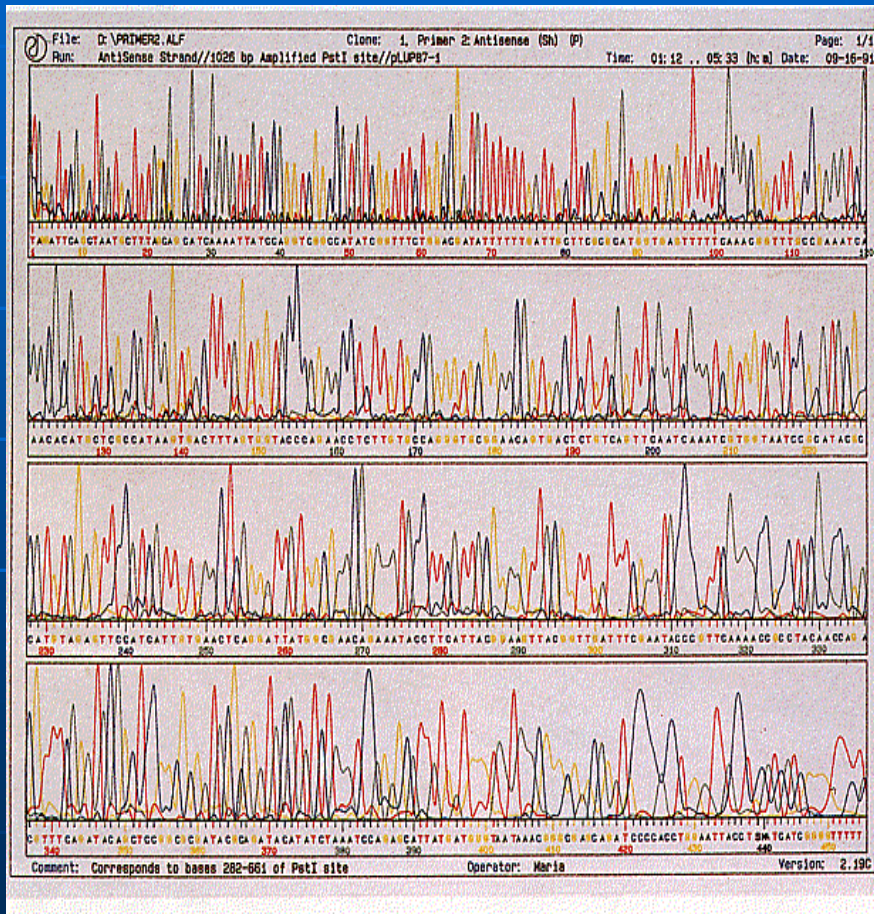
Surveillance

- Prostate cancer screening relies on annual digital rectal examination and prostate-specific antigen (PSA) testing.
- *Testing of relatives at risk*

Management

- Treatment of breast and ovarian cancer in individuals with *BRCA1* & *2* tumors is similar to sporadic forms
- Prophylactic Mastectomy (90% risk reduction)
- Prophylactic salpingo-oophorectomy (96% RR)
- Chemoprevention using tamoxifen been used, but not been assessed by randomized trials
- Physical exercise & avoidance of obesity

Molecular Testing



Mutation screening
whole gene
sequencing

Targeted analysis for
Ashkenazi Jewish

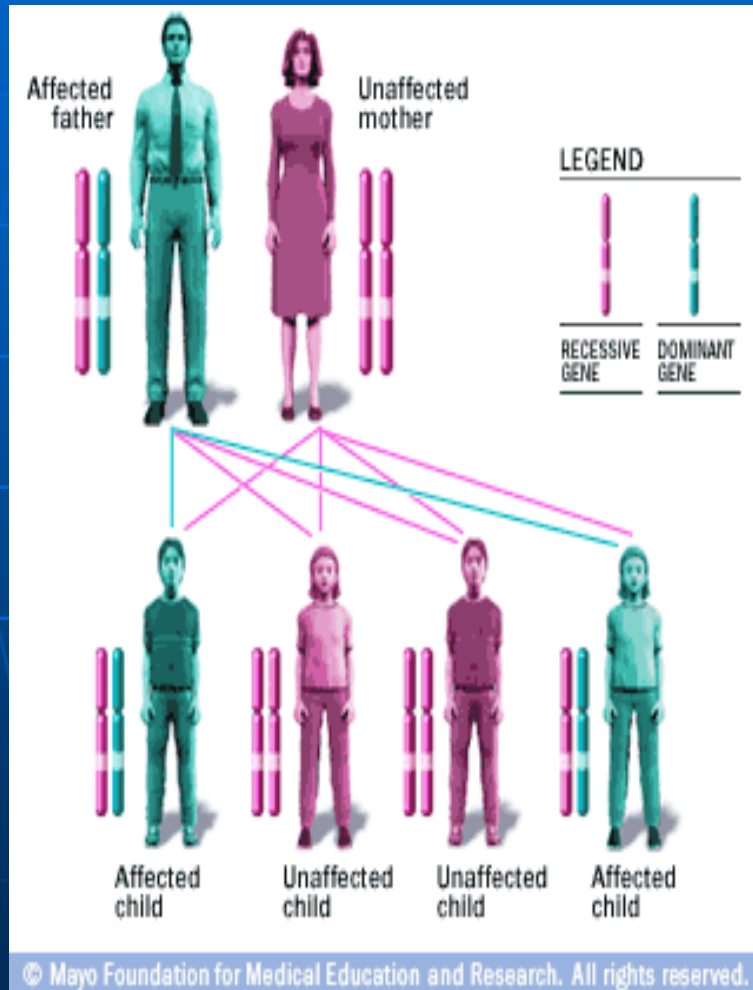
Testing Strategy

- Probands of Ashkenazi ancestry: three founder mutations are observed: 187delAG (BRCA1), 5385insC (BRCA1), and 6174delT (BRCA2).
- As many as one in 40 Ashkenazi has one of these three founder mutations. Targeted analysis is an effective way to assess rather than sequencing as recommended for all other populations.

Testing Strategy

- Family not known to have a BRCA1 or BRCA2 mutation: molecular genetic testing should be performed on the individual in the family who is most likely to have a BRCA1 or BRCA2.
- Family known to have a BRCA1 or BRCA2 mutation: Once a deleterious mutation has been identified within a family, adult relatives may then be tested for the same mutation with great accuracy.

Genetic Consultation



- What would you like to discuss today? people often are interested in knowing...
 - ...is this genetic?
 - ...can our family have a genetic test?
 - ...what might it mean for us, my children?
 - ...what are the pros and cons of testing?
 - ...what can we do about our risks?

Genetic Consultation

- Explain
- That testing may not always answer the question...we can't find every mutation
- That it takes several months for the lab
- That not everyone chooses to have a test

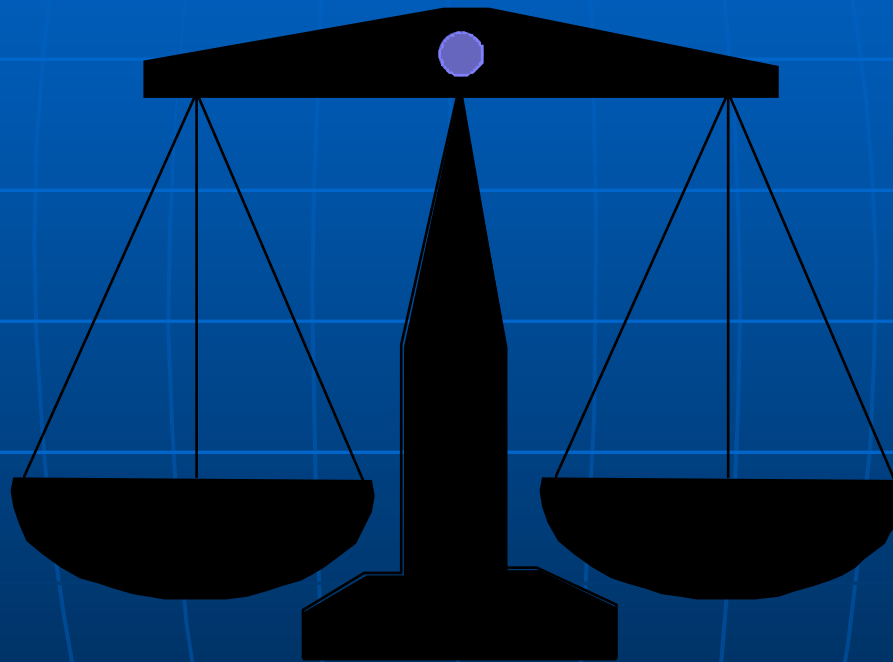
Pros & Cons of Genetic Testing

Potential Benefits:

**tailor
screening
advice**

**sense of
control**

**alleviate
anxiety in
some**



Potential Harms:

anxiety

guilt

**insurance
issues**

Interpretation of results

- Possible results in a proband:
- Mutation is absent: Failure to detect a mutation must be interpreted with caution since the underlying cause of the cancer in the family has not been established. The possibility remains that the cancer is either associated with a mutation not detectable by the method of genetic testing used, is caused by a change in a different cancer gene, or is the result of non-hereditary factors.
- Failure to detect a mutation does not eliminate the possibility of a hereditary factor.

Interpretation of results

- Mutation is present: confers an increased risk for BRCA1- or BRCA2- associated cancers.
- Result is inconclusive: Sequence analysis may reveal a novel BRCA1 or BRCA2 variation of uncertain clinical significance. Generally, this is a change in a single DNA nucleotide (missense mutation) that may or may not disrupt protein function.
- To further evaluate, laboratory may test additional members of the family (usually affected individuals and/or parents) to determine if the variant co-segregates with the cancer in the family. Such studies could reveal that the variant is either a pathogenic mutation or a polymorphism of no clinical significance.

THANK YOU