

# Genetics of Breast Cancer

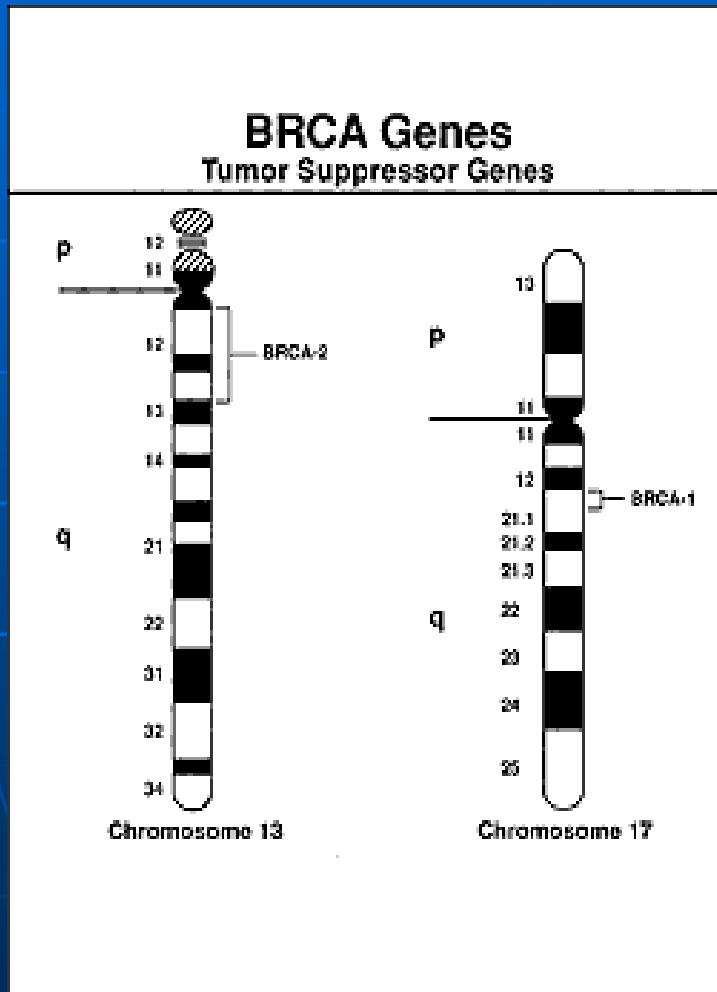


- Mutations in BRCA1 or BRCA2 predispose to breast cancer and ovarian cancer as well as prostate and other cancers.
- Prognosis for breast cancer survival depends upon the stage at which breast cancer is diagnosed.
- Prognosis for individuals with BRCA1 or BRCA2 cancer may not be different from that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

# Breast Cancer

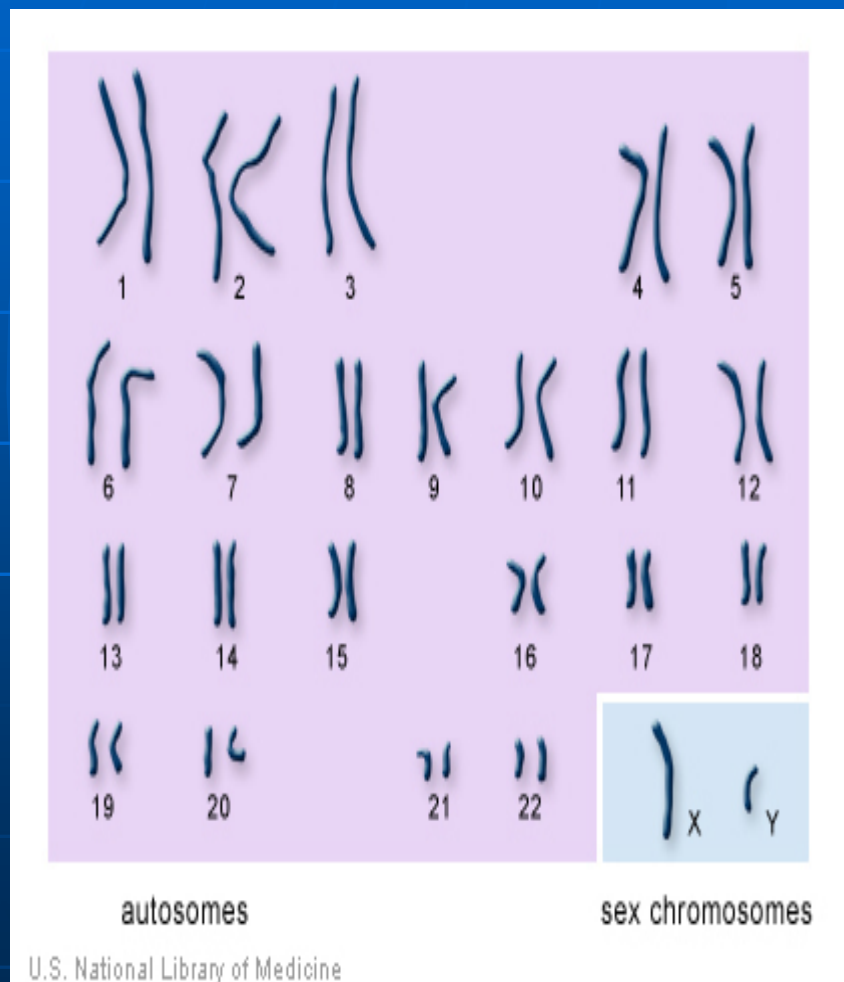
- Risk Factors:
- Null & late parity
- Breastfeeding
- Early menarche & late menopause
- Obesity
- Alcohol
- Oral contraceptives (24% for up to 10 y)
- HRT (5% per year of use for up to 5 Y post cessation)

# 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

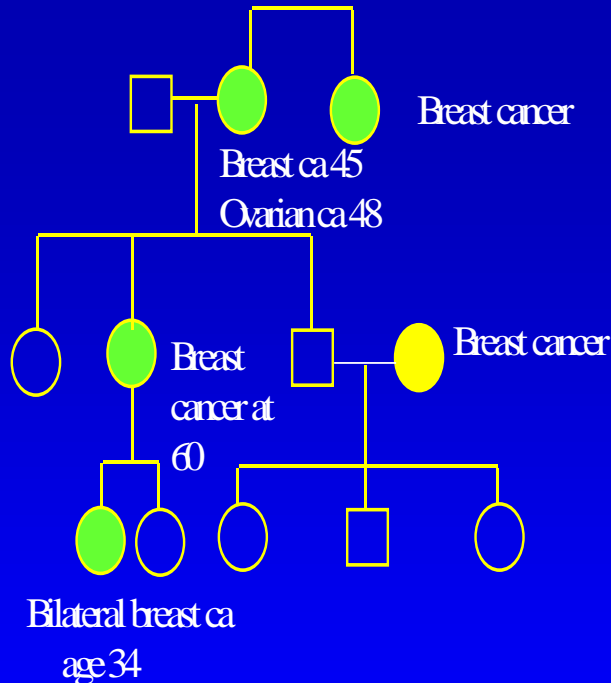
# Manchester Score

■ 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 2<sup>nd</sup> degree relative Dx at any age
- Two 2<sup>nd</sup> 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)

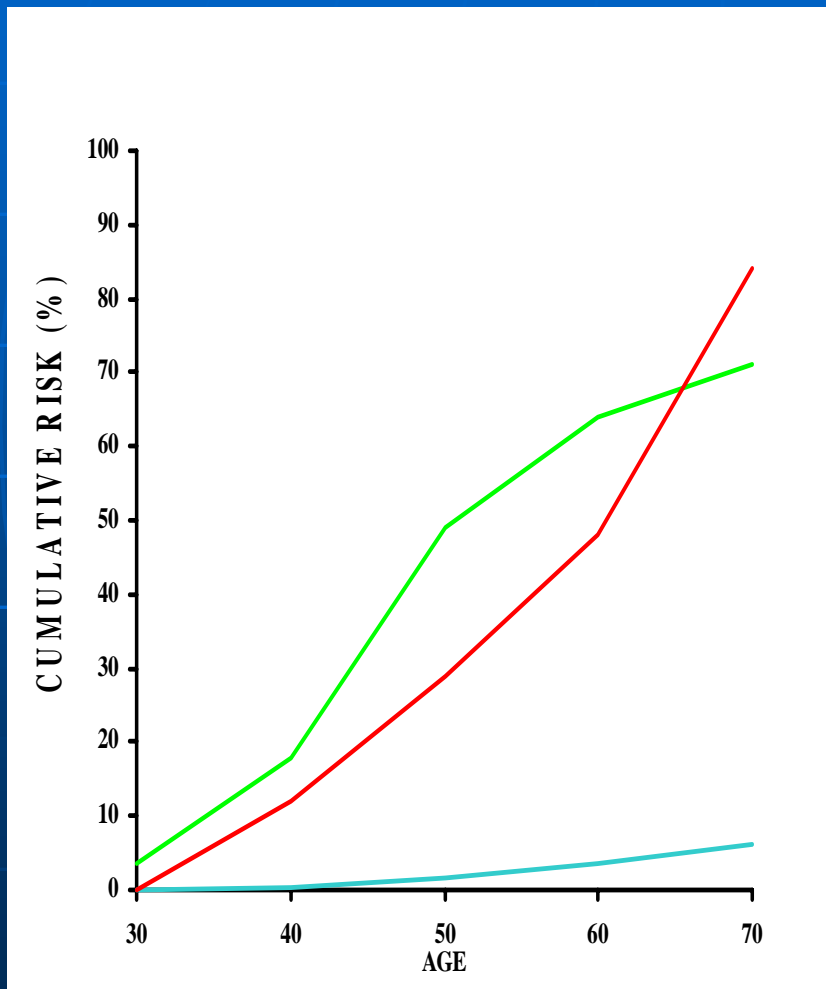
# Risk Calculation

- Moderate risk:
- One 1 degree Dx < 50 Y
- Two 1 degree Dx with BR Ca
- Two 2<sup>nd</sup> 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

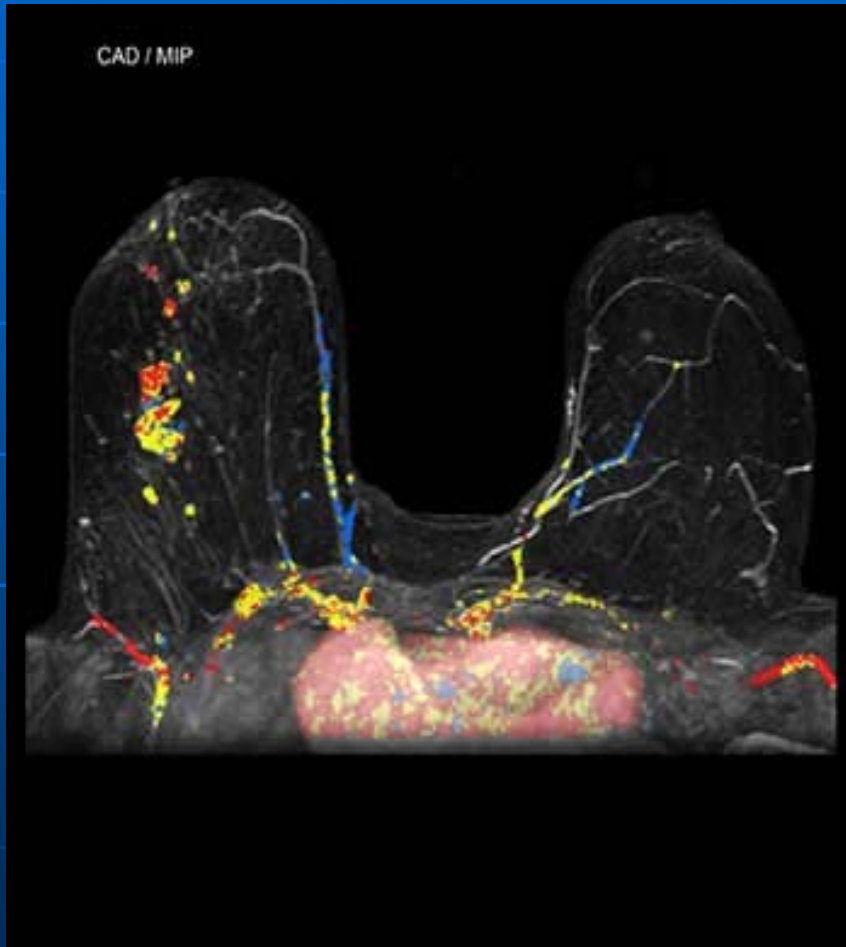
- High Risk:
- Two 1 or 2<sup>nd</sup> degree with BR or Ov Ca plus one of these features:
  - BR Ca Dx <40 Y
  - Bilateral BR Ca
  - Additional relatives with BR or Ov Ca
  - Br and Ov Ca in the same person
  - Ashkenazi ancestry
  - Male BR Ca
  - One relative with BR Ca <45 Y plus another relative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

# Risk calculation / Breast Cancer Risk In BRCA1/2 Carriers



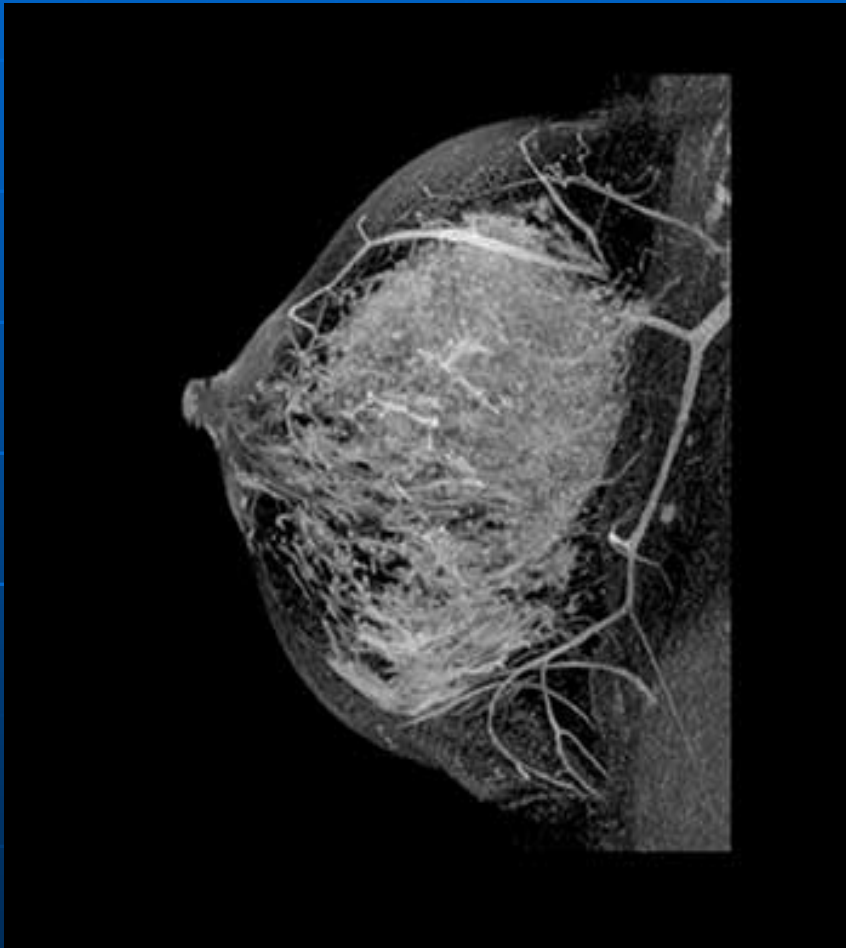
- Recommendations:
- Refer to a Cancer Genetics Clinic
- Individual surveillance program in consultation with a cancer specialist
- Surveillance for BR Ca
- Surveillance for Ovarian Ca
- Start screening 5 Y prior to age of Dx of the closest relative

# Surveillance



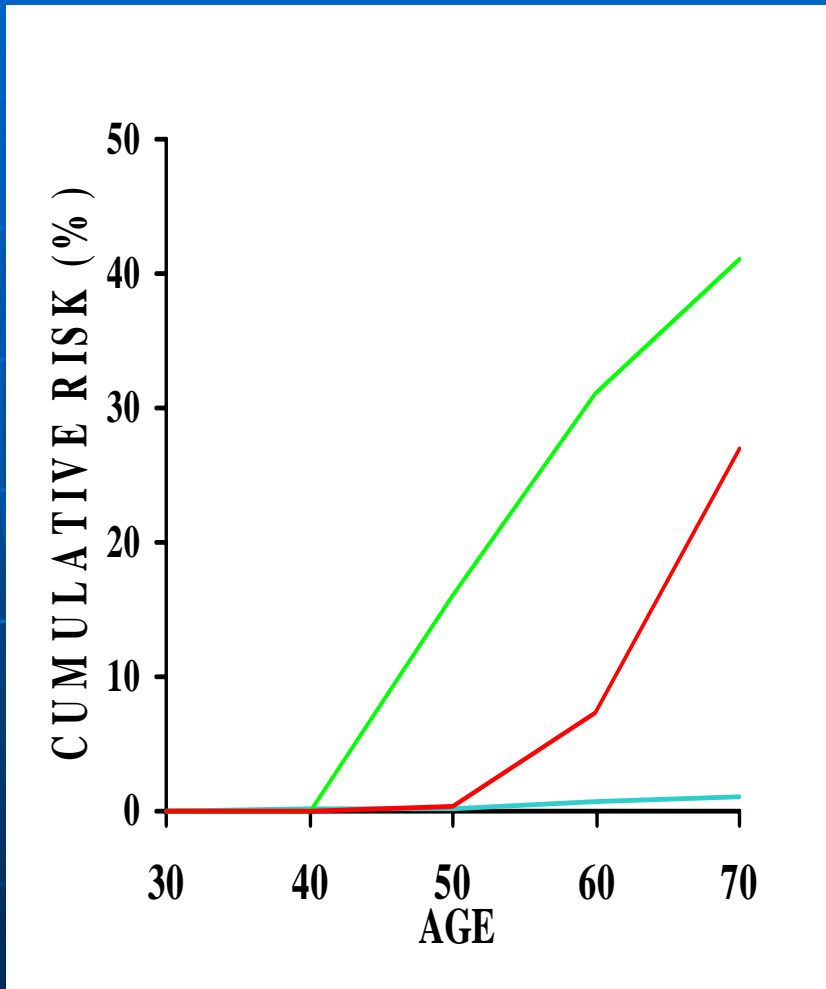
- Breast cancer screening: cancer risk begins in the late 20s or early 30s
- Monthly breast self-examination starting in early adulthood
- Annual or semiannual clinical breast examination beginning at age 25-35 years
- Annual mammography beginning at age 25-35 years
- Screening should be individualized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

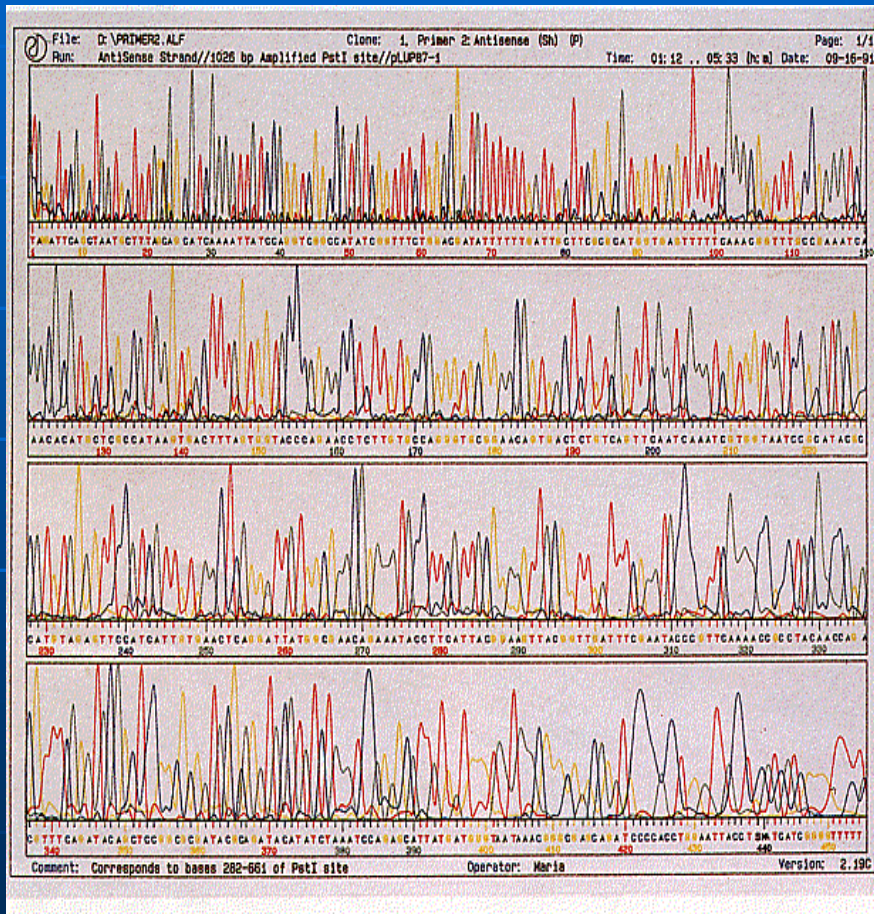
# Surveillance

- 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

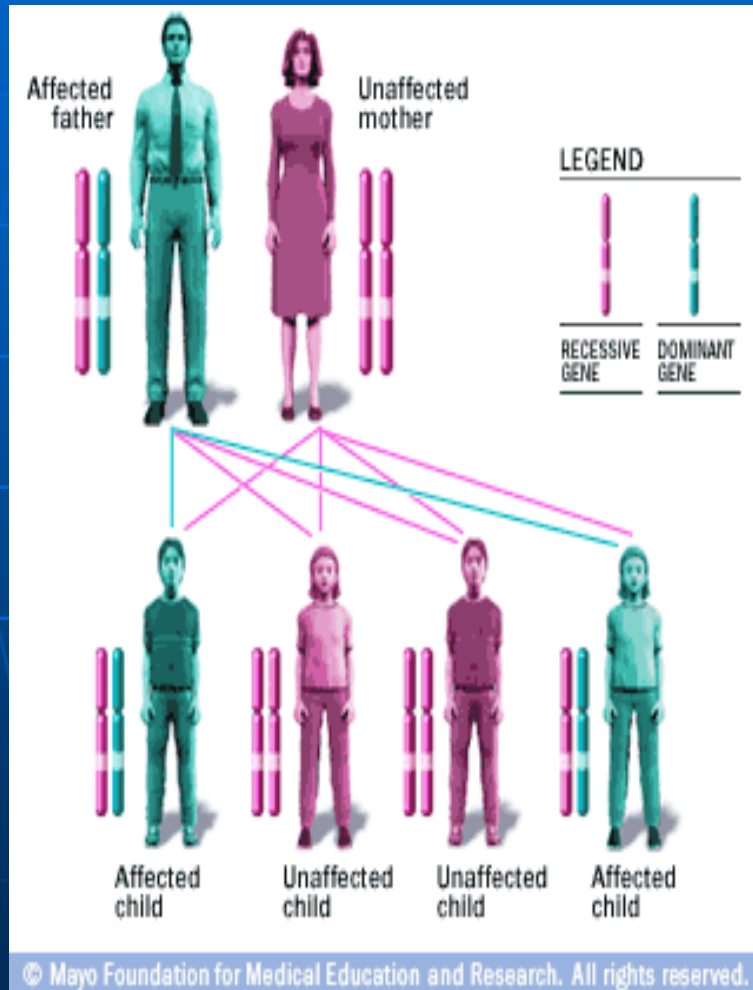
# Testing Strategy

- 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

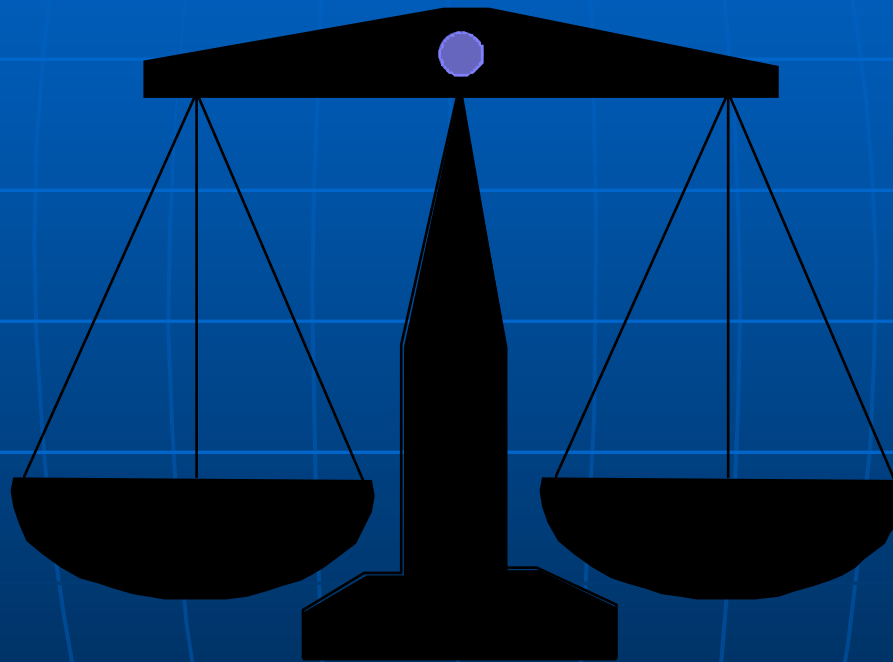
# Pros & Cons of Genetic Testing

## 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**