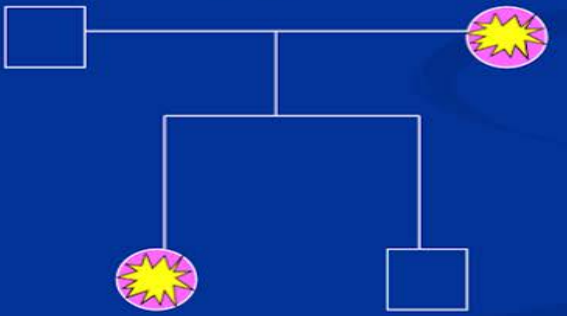
Applications of Genetics in Breast Health & Oncology

Kristy Cline Hose, APN-BC, AGN-BC, MSN

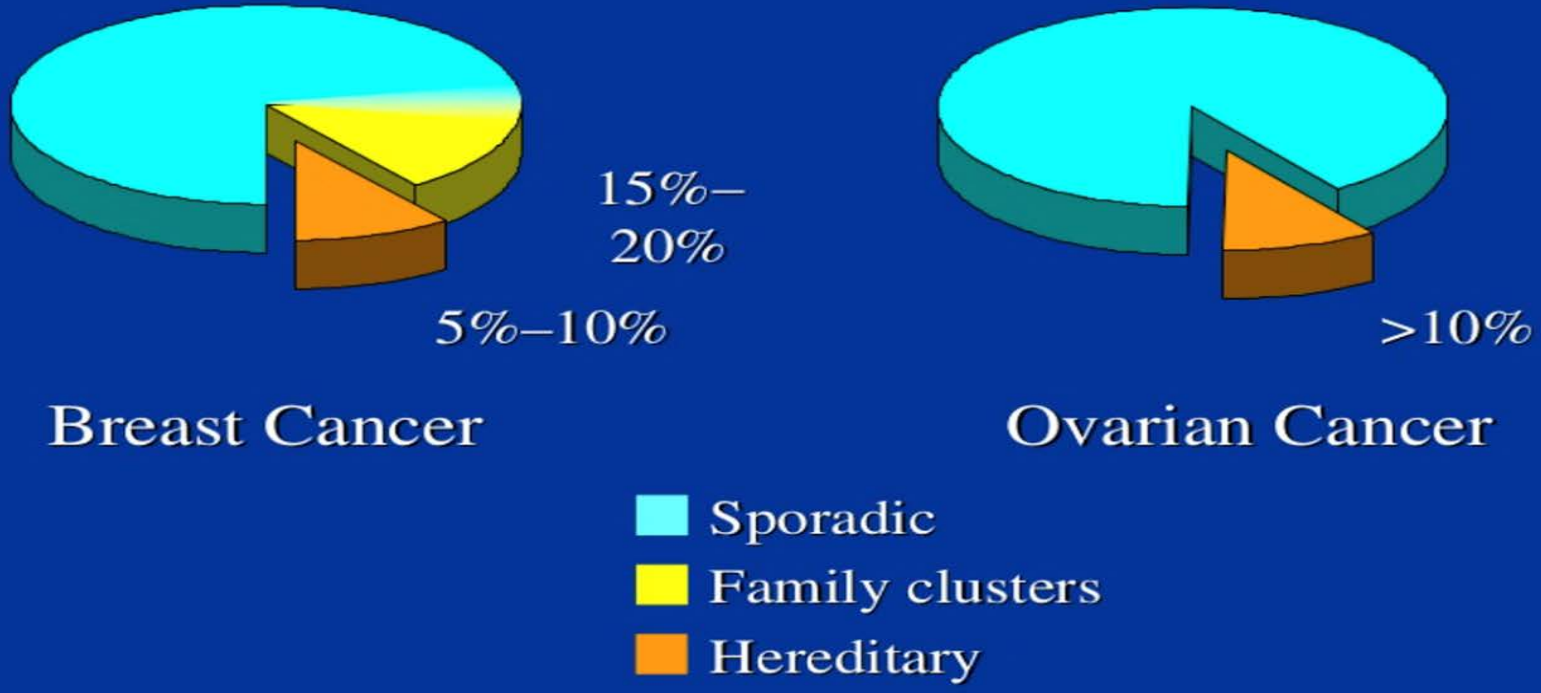
All cancers are genetic

BUT



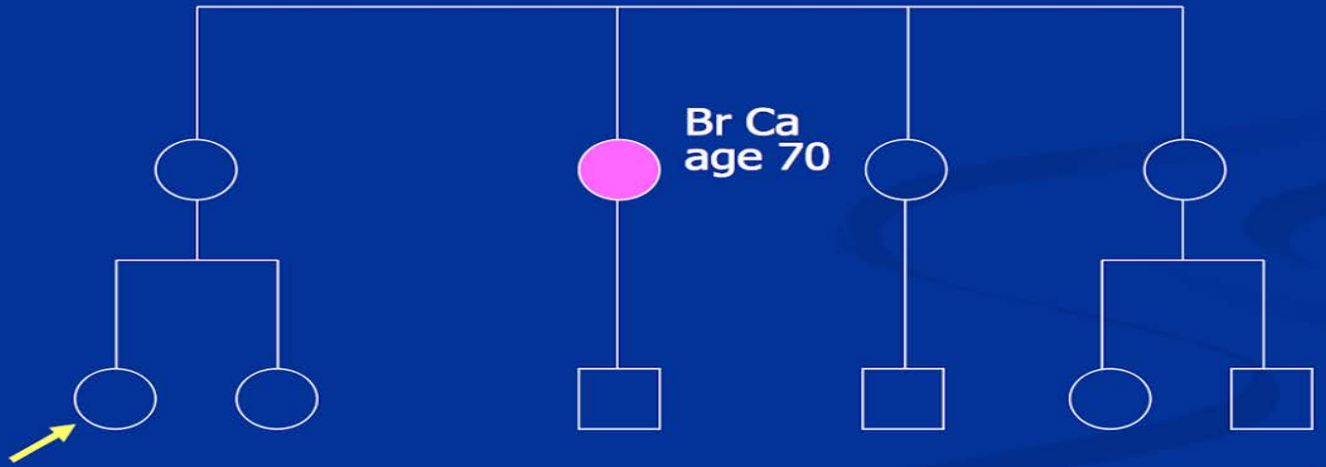
Not all cancers are *hereditary*

How Much Breast and Ovarian Cancer Is Hereditary?



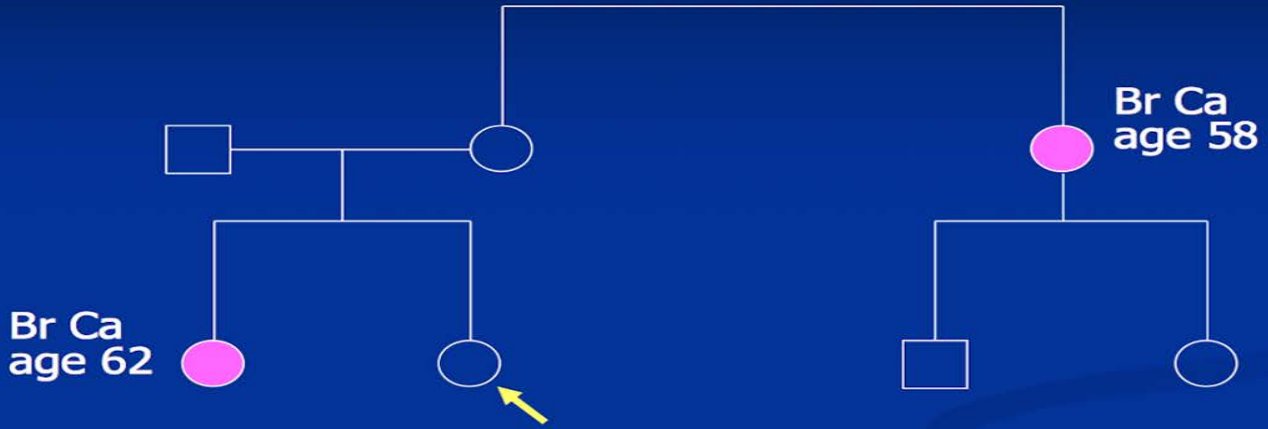
Sporadic Cancer = Single occurrence of cancer in family

- Majority of cases
- Not usually inherited
- Onset later in life



Low or no increased risk to family members beyond general population risk

Familial Cancer = Cluster of Cancer within Families

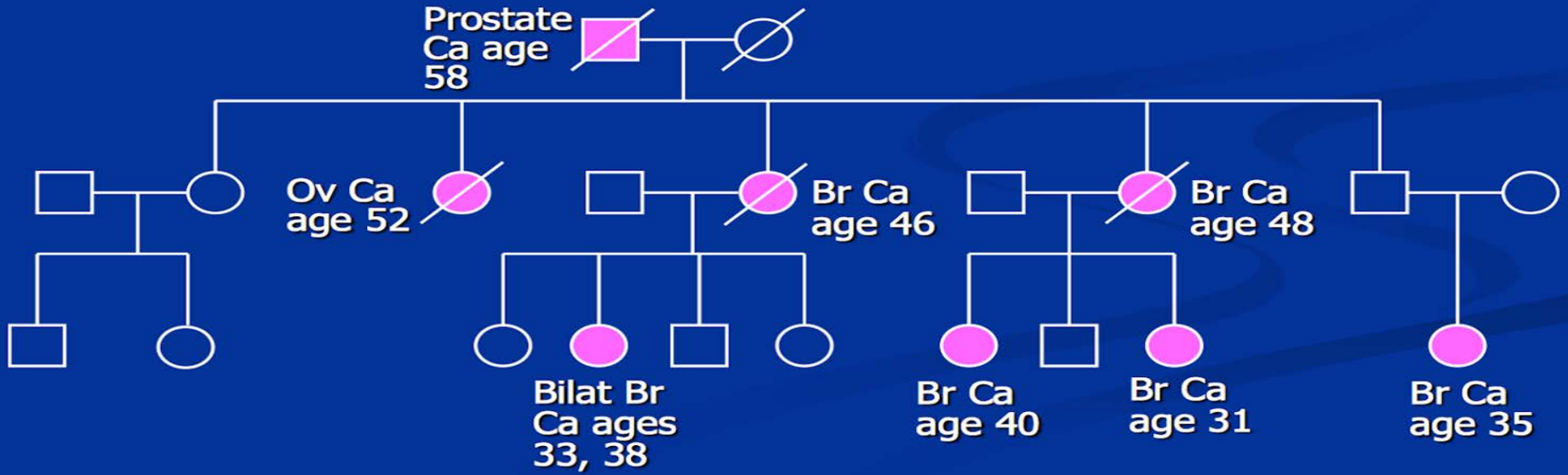


- 2 or more affected 1st or 2nd degree relatives
- Later onset
- Unilateral (one breast)
- Unclear inheritance pattern:
  - Chance alone
  - Common environment
  - Genetic factors (minor)

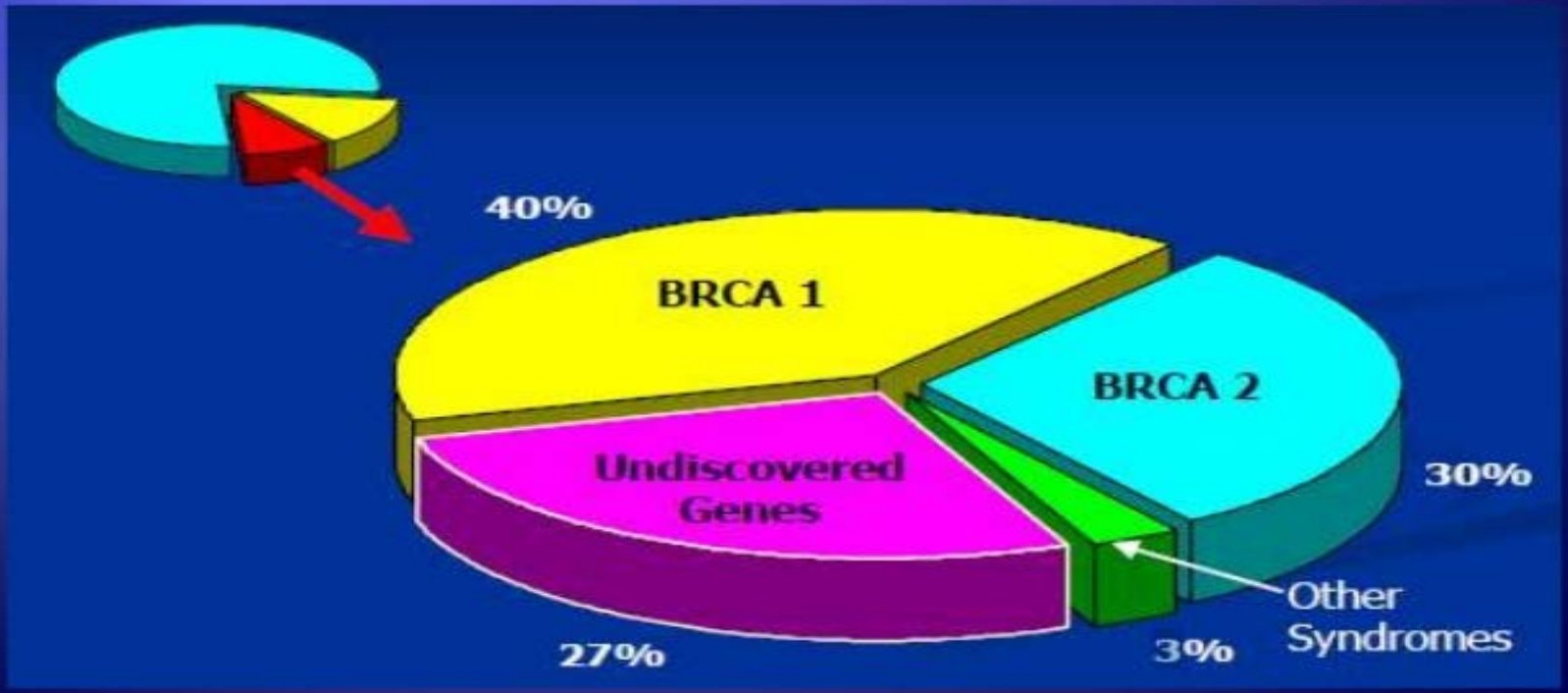
"Modest" increase in risk to family members ~ 2 fold general population

Hereditary Cancer

- Multiple affected individuals in multiple generations
- Early age of onset
- Multiple primary tumors
- Dominant inheritance
- Specific cancer clusters



Causes of Hereditary Susceptibility to Breast Cancer

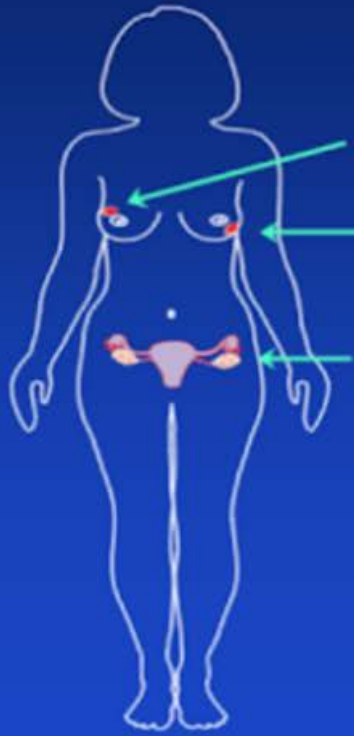


BRCA 1 and BRCA 2

- 1990 Mary-Claire King
- BRCA 1 - 1994 and BRCA 2 - 1995
- 1996 Myriad BRCAnalysis hits the Market
- Chromosome 17 and 13
- >2,000 Mutations
- Autosomal Dominant Inheritance
- Tumor Suppressor Gene
- Carrier Frequency 1 in 500-800
- 1 in 40-50 Ashkenazi Jewish Heritage

(**BRCA1** 185delAG, **BRCA1** 5382insC, **BRCA2** 6174delT)

BRCA1-Associated Cancers: Lifetime Risk



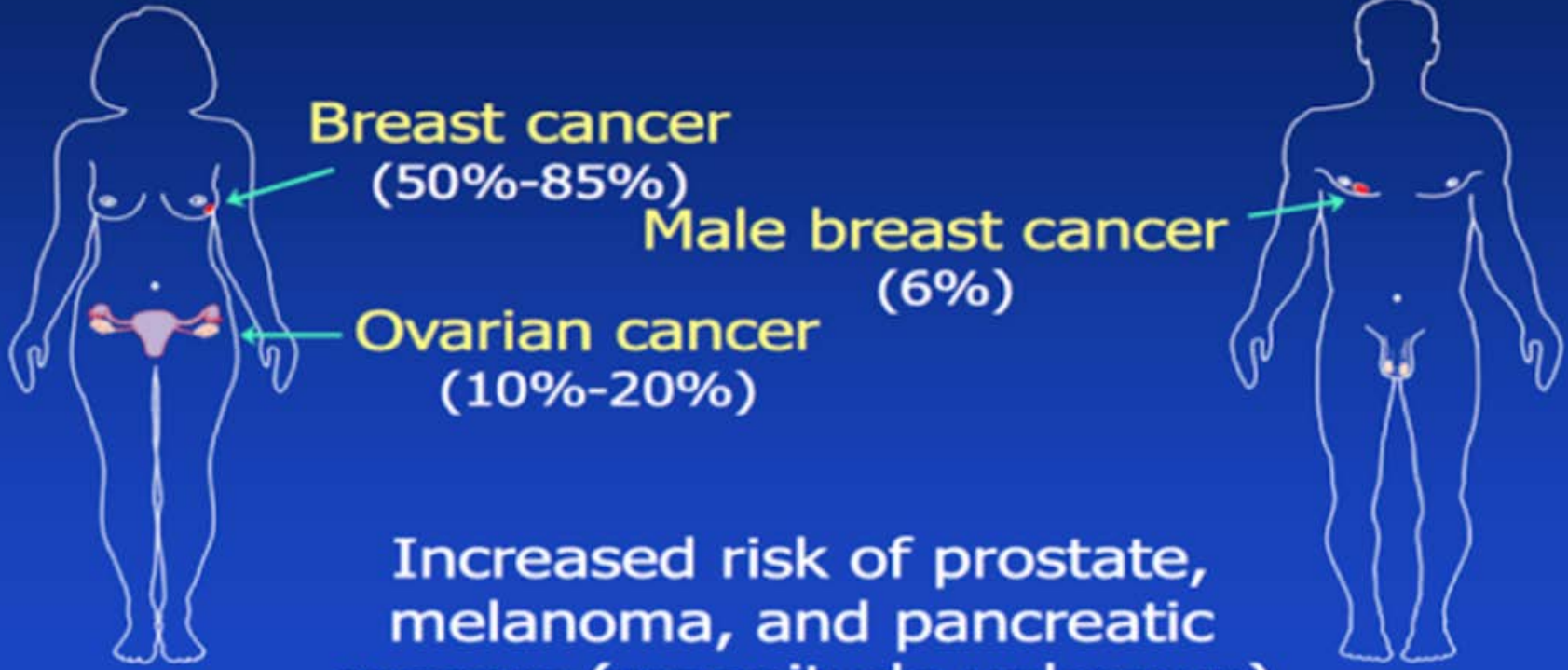
Breast cancer 50%-85%
(often early age at onset)

Second primary breast cancer 40%-60%

Ovarian cancer 15%-45%

Possible increased risk of other cancers (eg, prostate)

BRCA2-Associated Cancers: Lifetime Risk



Increased risk of prostate, melanoma, and pancreatic cancers (magnitude unknown)

Age	BRCA1+	BRCA2+
30	0 %	0 %
40	3 %	2 %
50	21 %	2 %
60	40 %	6 %
70	46 %	12 %
80	54 %	23 %

Ovarian CA Risk
For Mutation Carrier

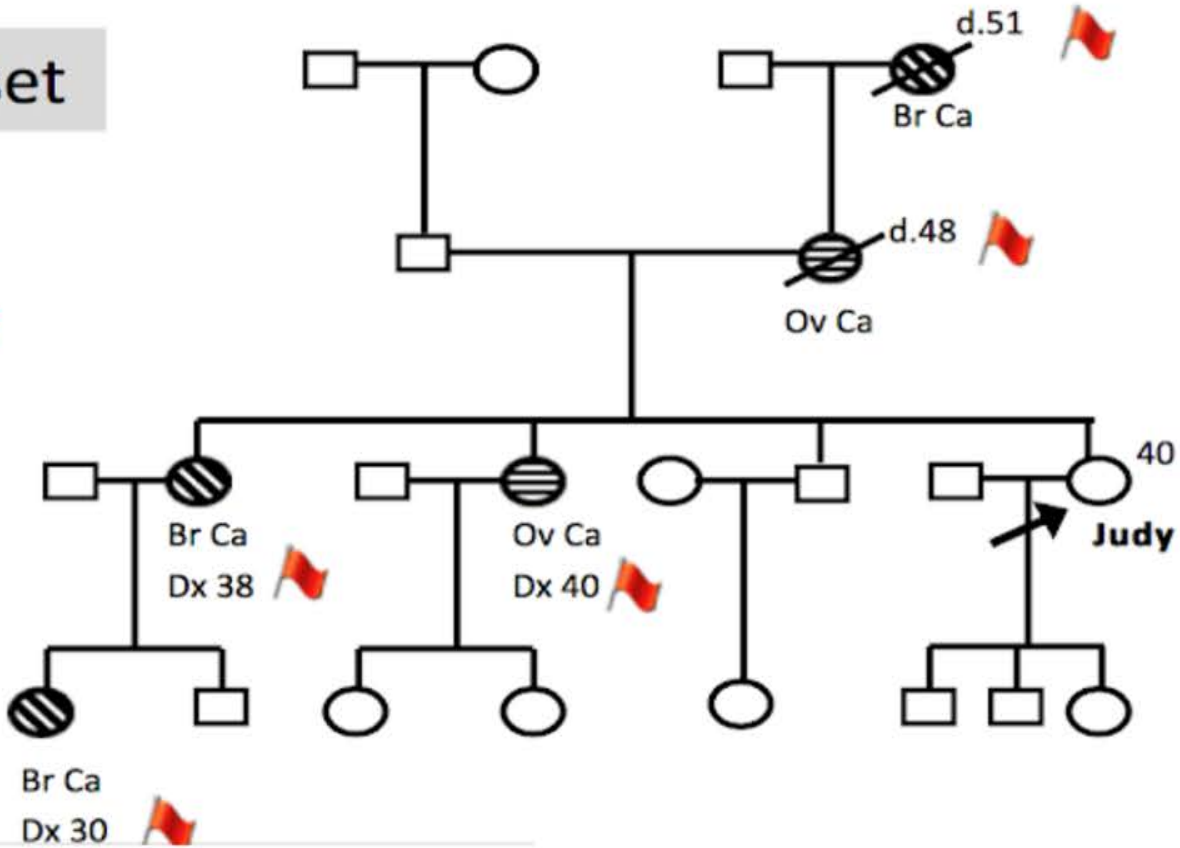
Breast CA Risk
For Mutation Carrier

Age	BRCA1+	BRCA2+
30	3.2 %	4.6 %
40	19.1 %	12 %
50	50.8 %	46 %
60	54.2 %	61 %
70	85 %	86 %

Early age of onset

NCCN - BRCA1/2 Testing Criteria

- Breast Cancer ≤ 45
- Breast Cancer ≤ 50 with ≥ Close Relative w/ BRCA Associated CA at any Age

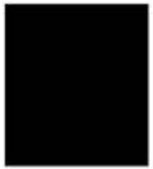


Ovarian Cancer or Male Breast Cancer

NCCN - BRCA1/2 Testing Criteria

- Ovarian Cancer
- Male Breast Cancer

Ov Ca dx age 45



Male Br Ca dx age 65

Multiple primary cancers in an individual

NCCN - BRCA1/2 Testing Criteria

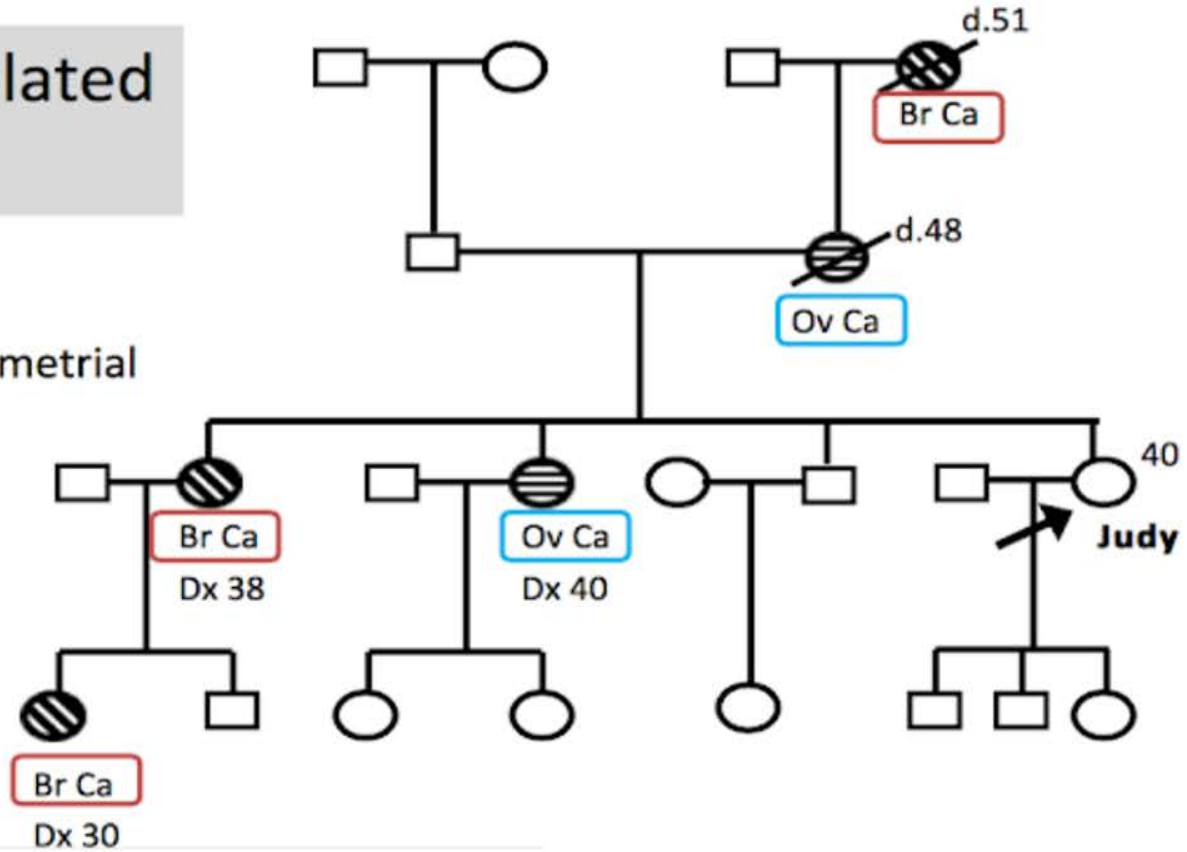
- Bilateral Breast Ca w/ 1st Ca dx ≤50
- Breast & Ov Ca in the same individual
- Breast CA ≤50 any additional Cancer primary

Br Ca dx age 33
Ov Ca dx age 45

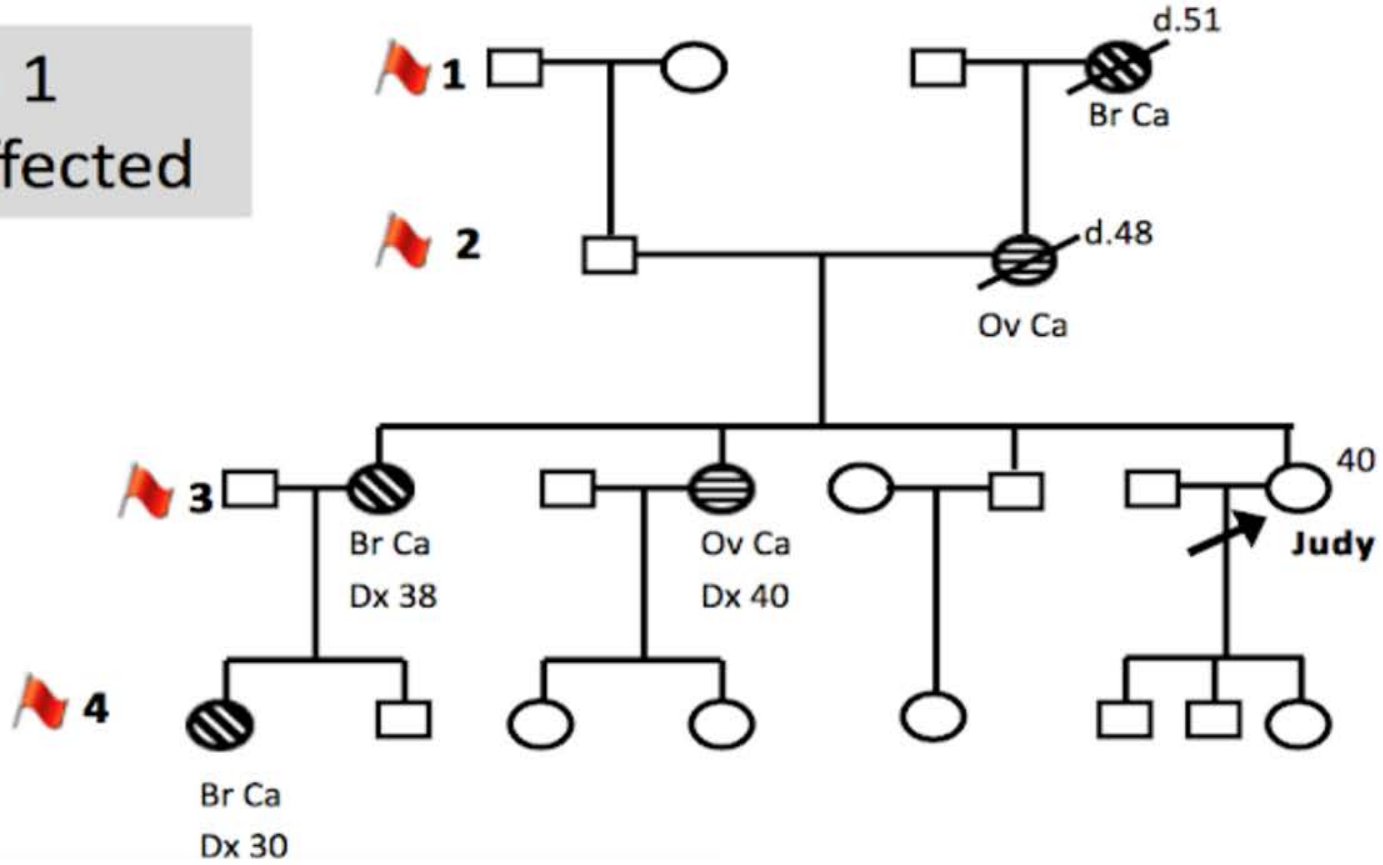
Br Ca (left) dx age 33
Br Ca (right) dx age 45

Clustering of related diseases

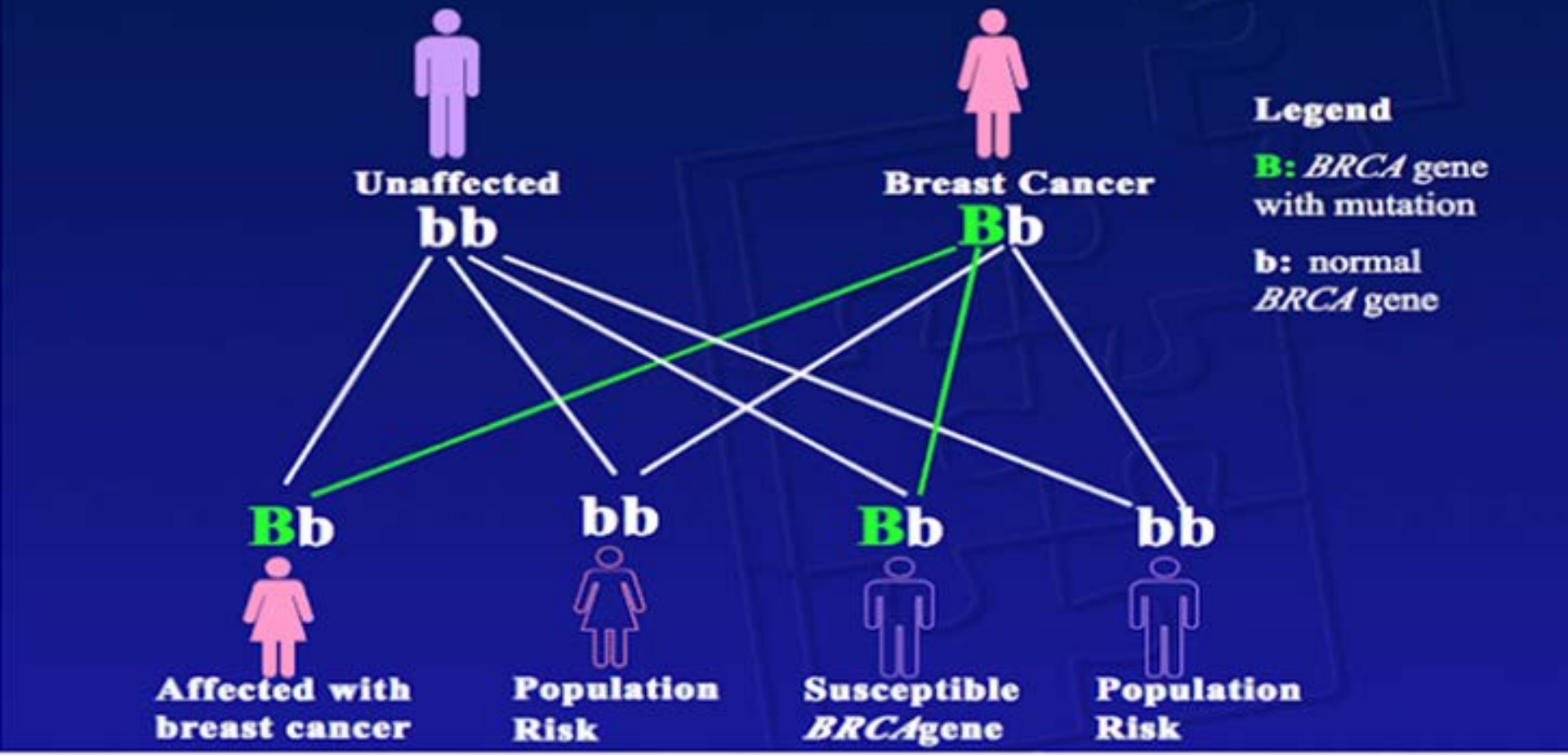
- Breast and ovarian
- Colorectal and endometrial



More than 1 generation affected



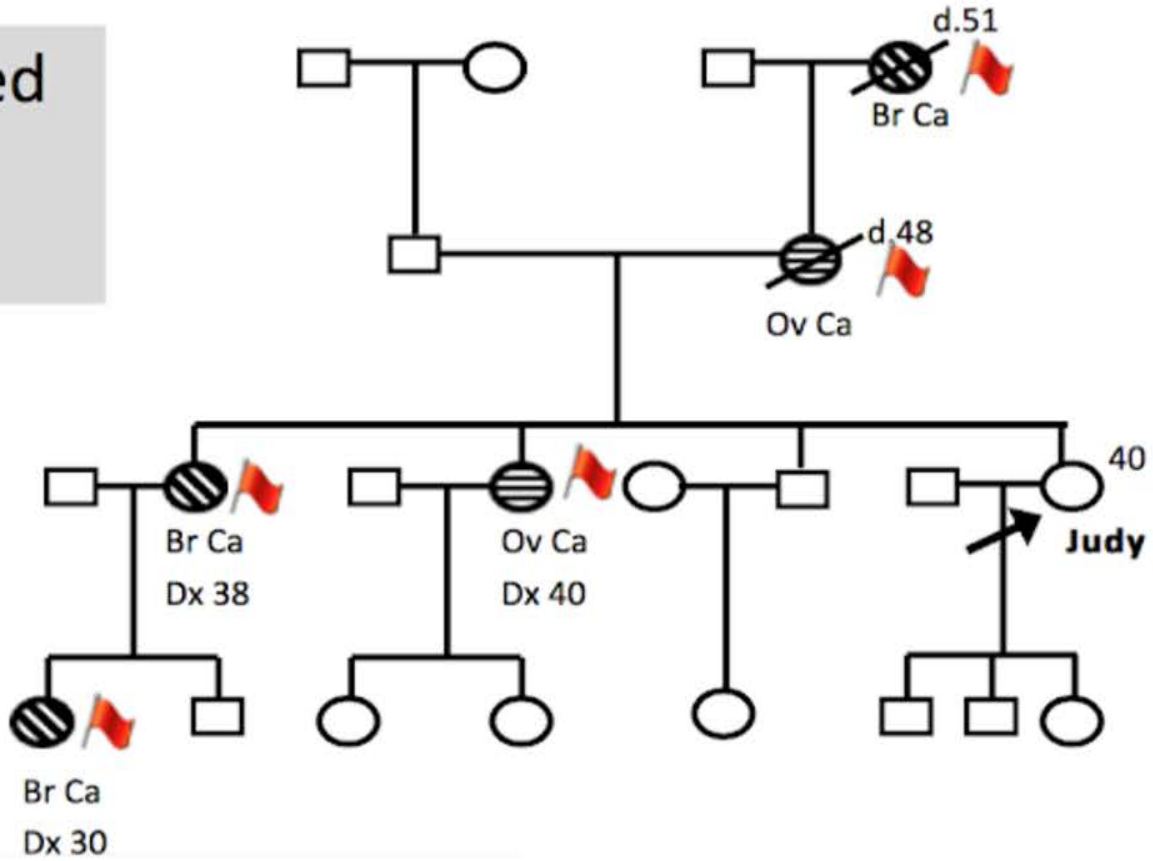
Autosomal Dominant Inheritance



Multiple affected relatives on same side of family

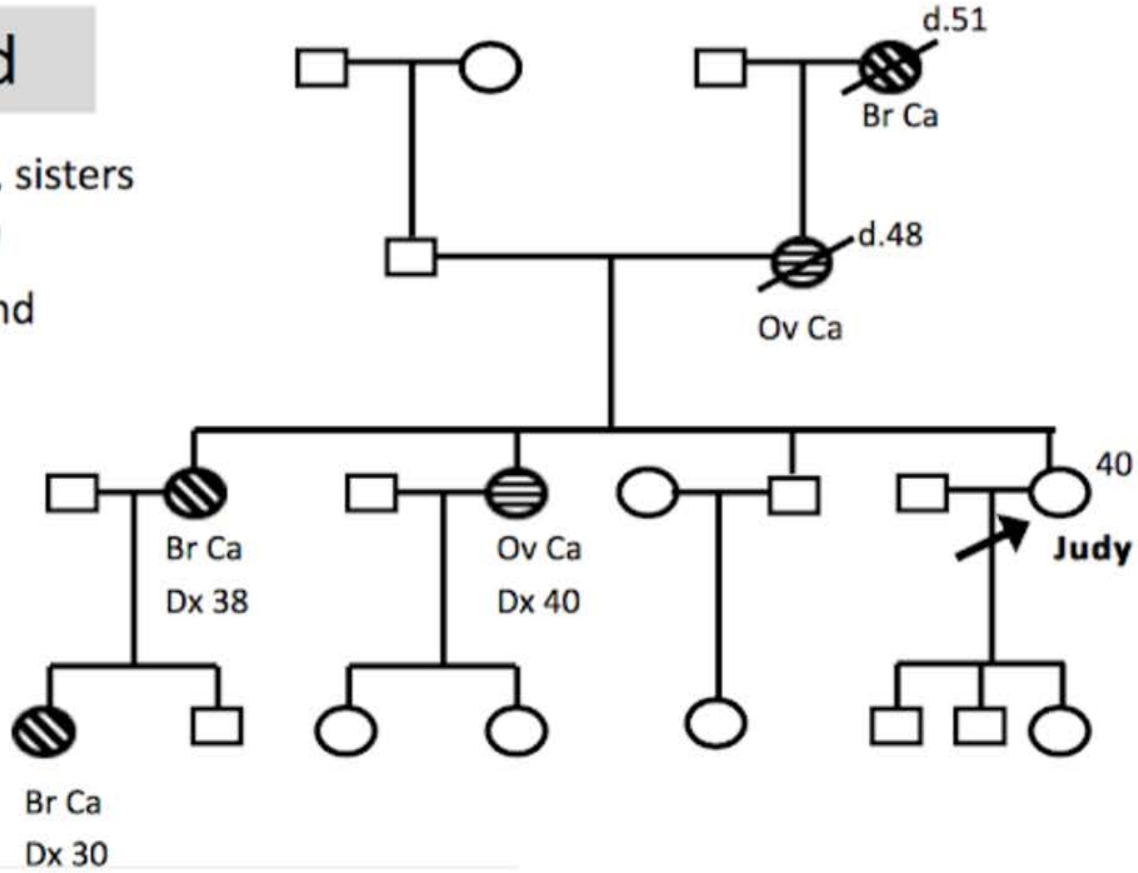
NCCN - BRCA1/2 Testing Criteria

- Breast Ca at any age w/ ≥2 relatives w/ prostate, pancreatic or Br Ca *(Interchangeable)



Closely related

- Mother and daughter, sisters (first degree relatives)
- Aunt and niece (second degree relatives)



NCCN - BRCA1/2 Testing Criteria

- Breast Ca at any age w/ ≥1 relatives w/ Ov Ca or Male Br Ca
- Br Ca at any age and of Ashkenazi Jewish Heritage

Additional NCCN BRCA 1/2 Testing Criteria

- Triple Negative Breast Ca diagnosed ≤ 60
- Metastatic Prostate Cancer
- Metastatic HER- Breast Cancer
- Individual with known BRCA mutation in family
- Breast Cancer ≤ 50 w/ an unknown or limited family history

If you think you can't keep up with all this...

Don't worry!

No one else can either!

BRCA Testing Criteria

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
BRCA-Related Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
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 or metastatic)
    - An unknown or limited family history[a]
  - Diagnosed ≤60 y with:
    - Triple negative breast cancer
  - Diagnosed at any age with:
    - ≥2 close blood relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score ≥7 or metastatic) at any age
    - ≥1 close blood relative[d] with breast cancer diagnosed ≤50 y
    - ≥1 close blood relative[d] with ovarian[e] carcinoma
    - 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 high-grade 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 or metastatic) at any age
- Personal history of metastatic prostate cancer (radiographic evidence of or biopsy-proven disease)
- 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 or metastatic) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- *BRCA1/2* pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis
- 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

BRCA testing criteria met → See Follow-up (BRCA-2)

If BRCA 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]For further details regarding the nuances of genetic counseling and testing.

[e]Includes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated

MOST Insurance Companies
Follow NCCN Criteria with some Exceptions!


CAUTION!

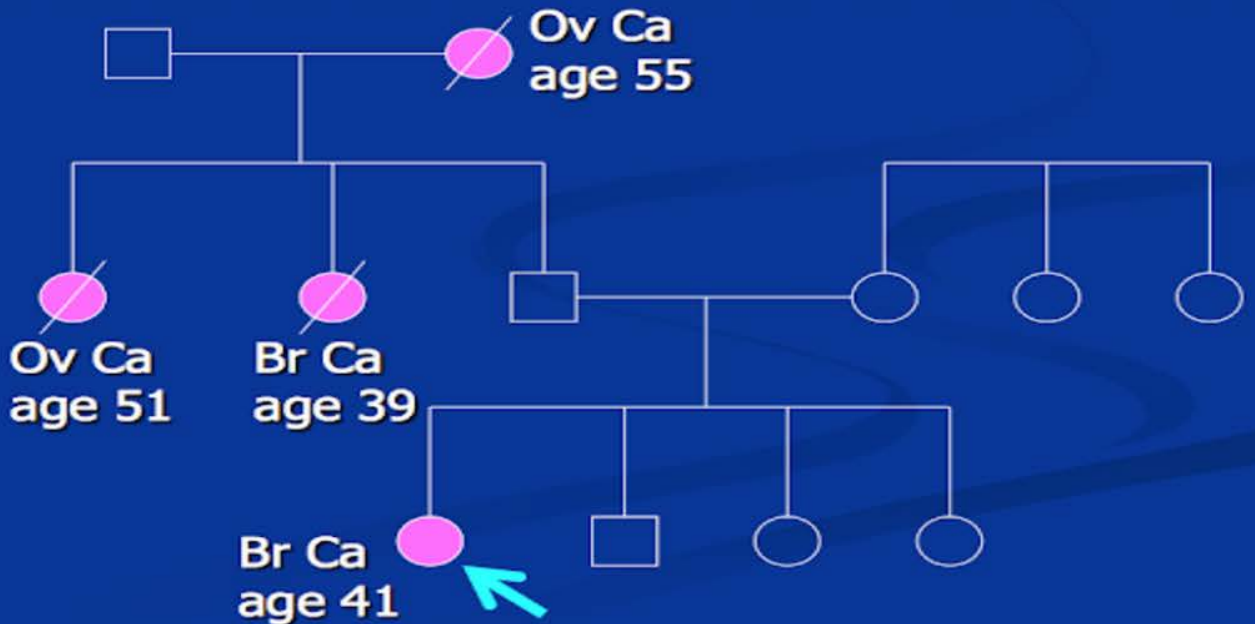
Importance of Paternal Family History

Probability of a BRCA1/2 mutation

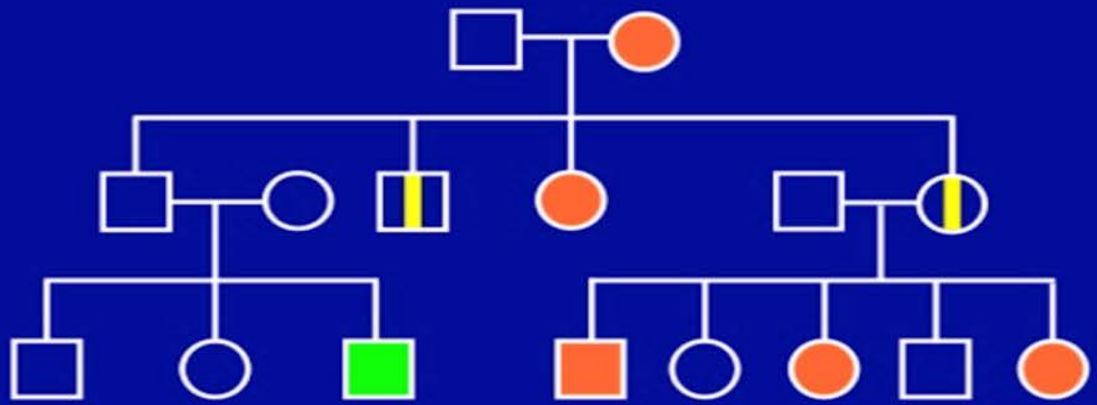
<3%

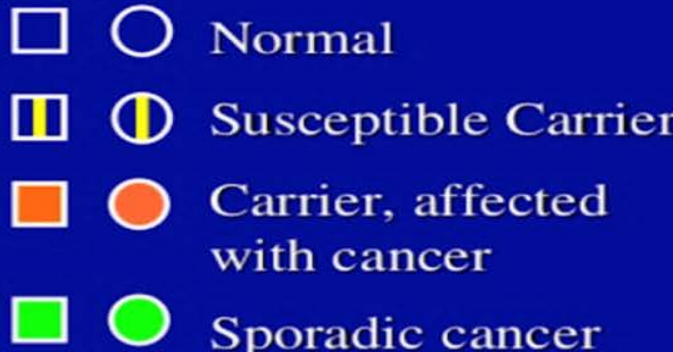
Probability of mutation with paternal history

35-70%



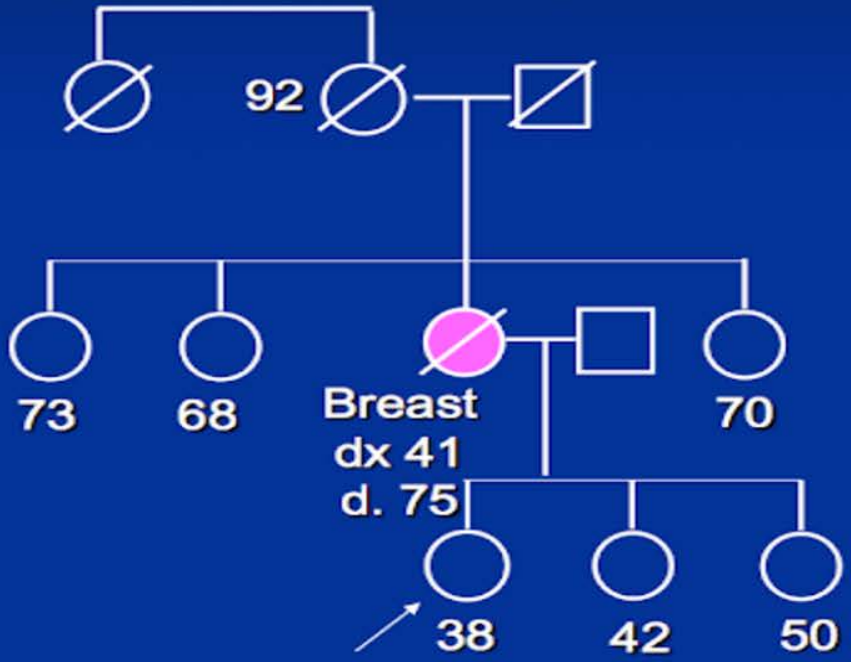
Inheritance Pattern: Autosomal Dominant with Incomplete Penetrance



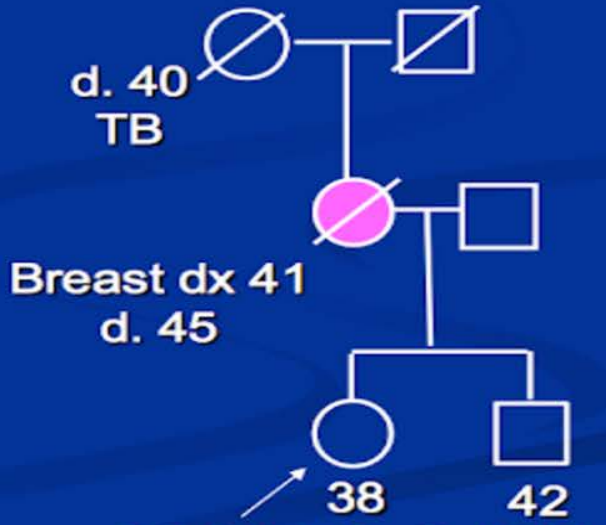


- Penetrance is often incomplete
- May appear to "skip" generations
- Individuals inherit altered cancer susceptibility gene, not cancer

The Problem of Limited Family Structure



BRCA1/2: < 2%



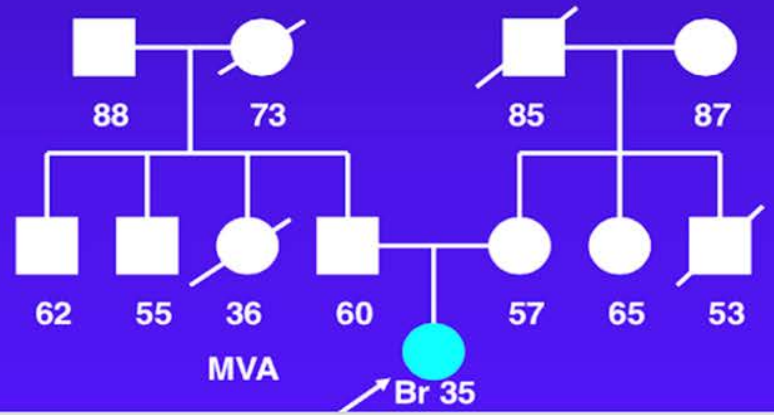
BRCA1/2: 5-10%

Family Structure Definitions

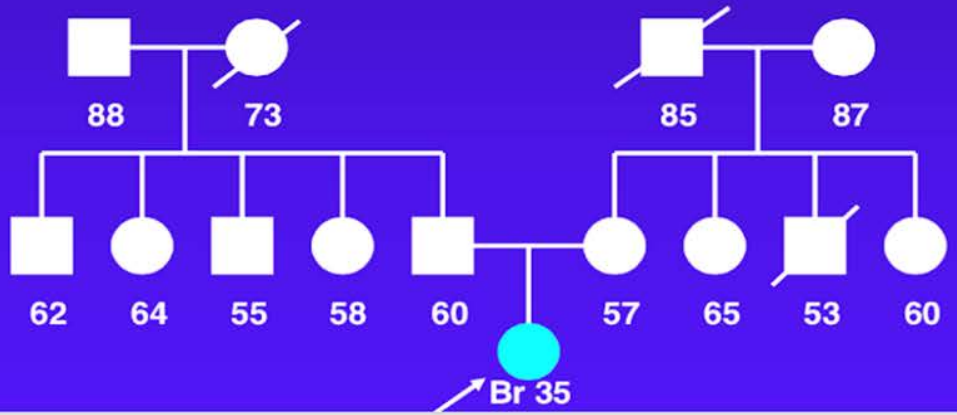
Limited Family Structure

less than 2 first or second-degree female relatives over the age of 45 in one lineage

Limited (truncated) Paternal Family Structure

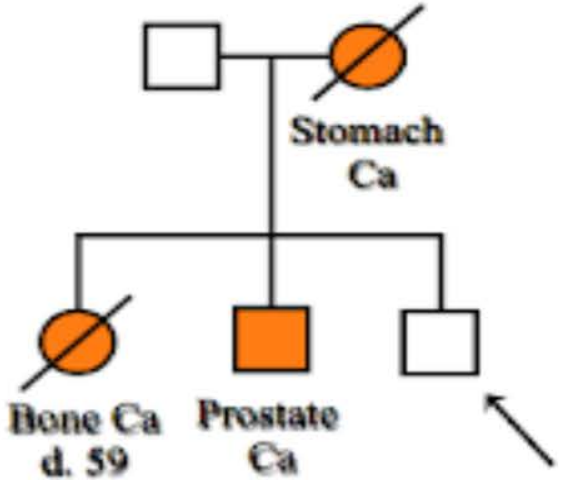


Adequate Family Structure for both sides

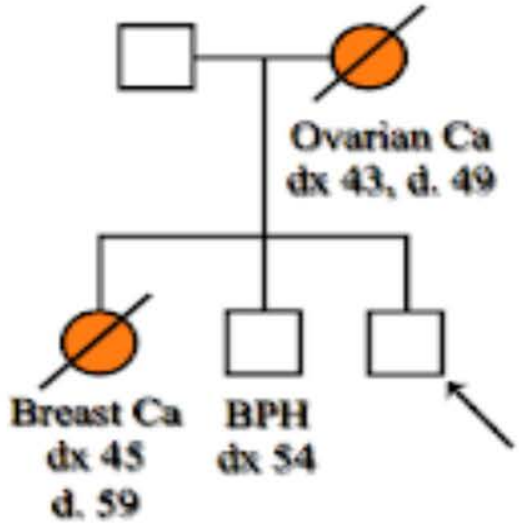


Verify Family History

Verbally reported pedigree



Revised pedigree based on pathology reports



BPH = benign prostatic hyperplasia

BRCAartoons

It’s all the extra mammograms.

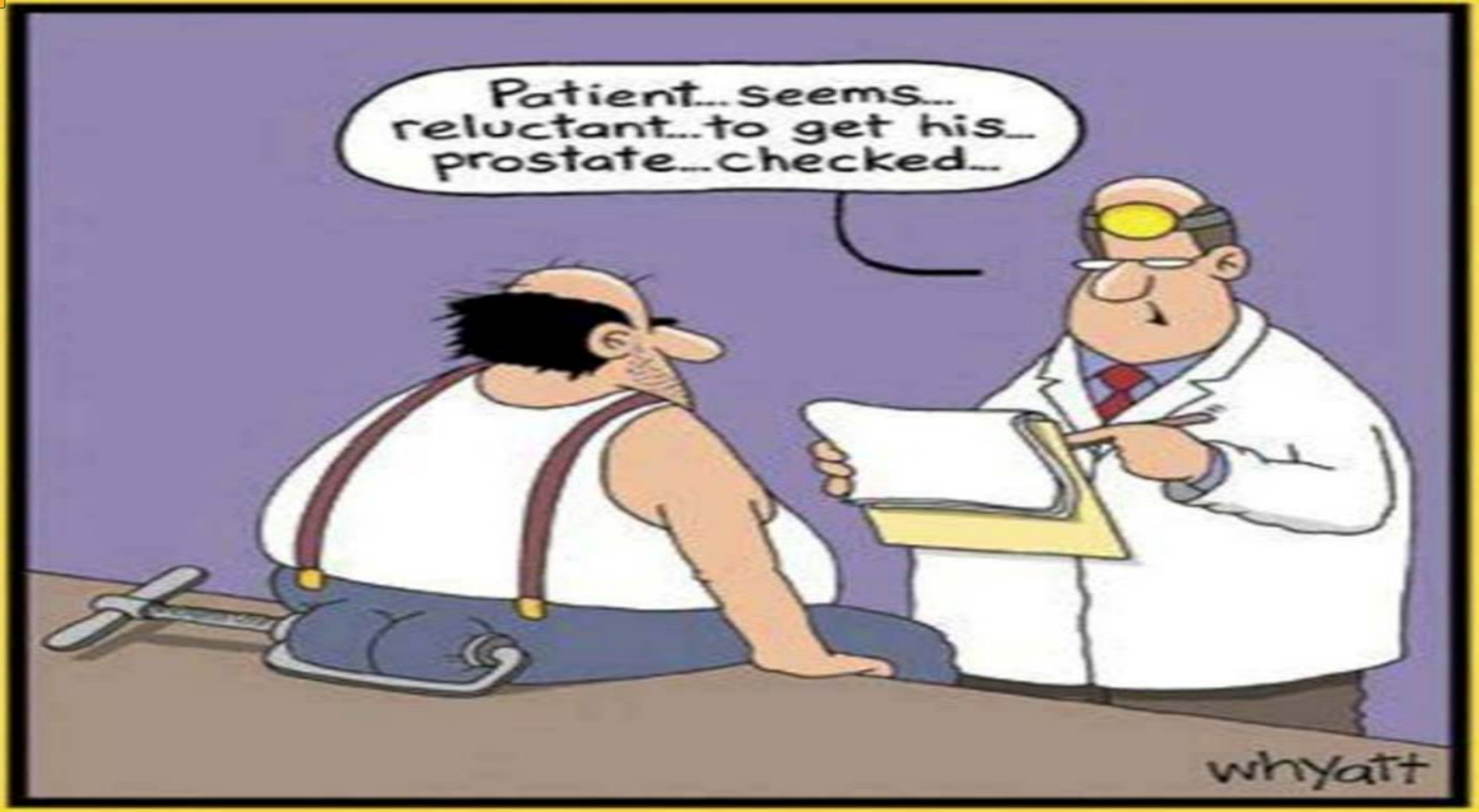
Prevention and Screening Options

Prophylactic Surgery:	Mastectomy Oophorectomy
Chemoprevention:	Tamoxifen Oral Contraceptives
Screening:	Mammograms MRI Ultrasound Clinical Breast Exams

Current Screening Recommendations for BRCA+ Women

- **Breast**
  - Monthly breast self-exams (begin by age 18)
  - Early clinical surveillance (begin by age 25)
    - Biannual clinical breast exams at a breast center
    - Annual mammography[1]
    - Sonography? MRI?
- **Ovarian: no good options**
  - Transvaginal ultrasound
  - CA-125 blood levels

[1]Burke et al. *JAMA* 277:997, 1997


Patient... seems... reluctant... to get his... prostate... checked...
whyatt

Obstacles to Imaging BRCA Carriers

- Carriers have denser breast tissue[1]
  - Younger
  - Some studies suggest that carriers have denser breast tissue than age-matched controls

- More false negatives in mammograms for BRCA1 carriers compared with controls[2]
  - True even when controlling for tumor size and breast density
  - Due to prominent "pushing margins"

→ For BRCA+ women, any mass at mammography should be regarded with suspicion

[1] Huo (2002) Radiology.

[2] Tilanus-Linthorst (2002) Int. J Cancer

Chemoprevention

The Jury is Still Out…

Tamoxifen

- 49% reduction of breast cancer incidence in high-risk women (mean follow-up of 5.75 years)[1]
- Data in BRCA1/2 carriers are limited[2,3,7]
  - Recent Study[7]-risk of CL Bst Ca reduced more than 50% in carriers (with ovaries) when TAM given as treatment for initial Bst Ca

Oral Contraceptives

- 40% reduction in risk of ovarian cancer[4]
- Some reduction of ovarian cancer risk in BRCA carriers[5]
- Possible increase in breast cancer risk in carriers[6]

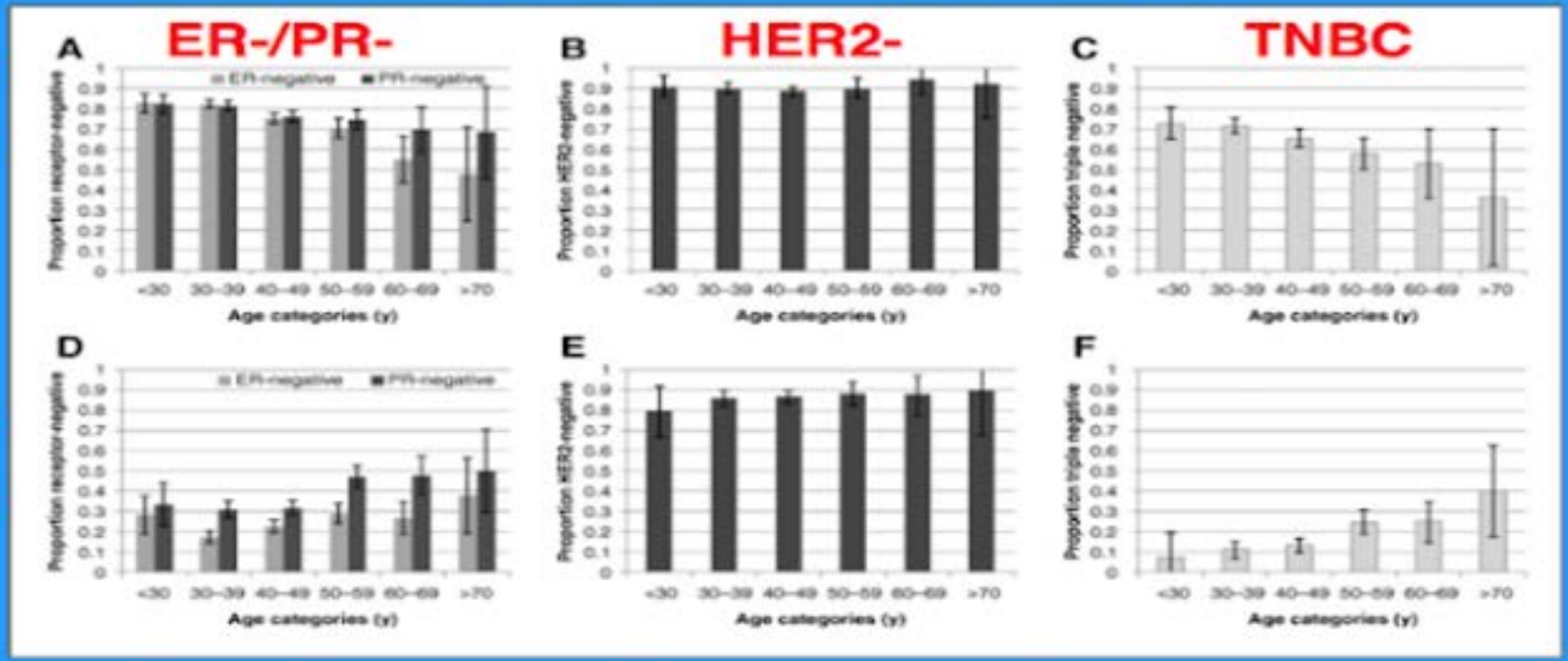
[1]Fisher B et al. *JNCI*. 90(18) 1998. NSAPB-P1
[2]King MC et al. *JAMA*. 286(18) 2001. NSABP-P1
[3]Narod S et al. *Lancet*. 356. 2000

[4]CASH Study. *N Engl J Med* 316(11). 1987
[5]Narod S et al. NEJM. 339(7) 1998.
[6]Narod S et al. JNCI 94(23) 2002.
[7] Gronwald J et al. Int. J. Cancer 118(9). 2006.

Age-specific proportions of pathologic subtypes of breast tumors arising in BRCA1 and BRCA2 mutation carriers

BRCA1

BRCA2



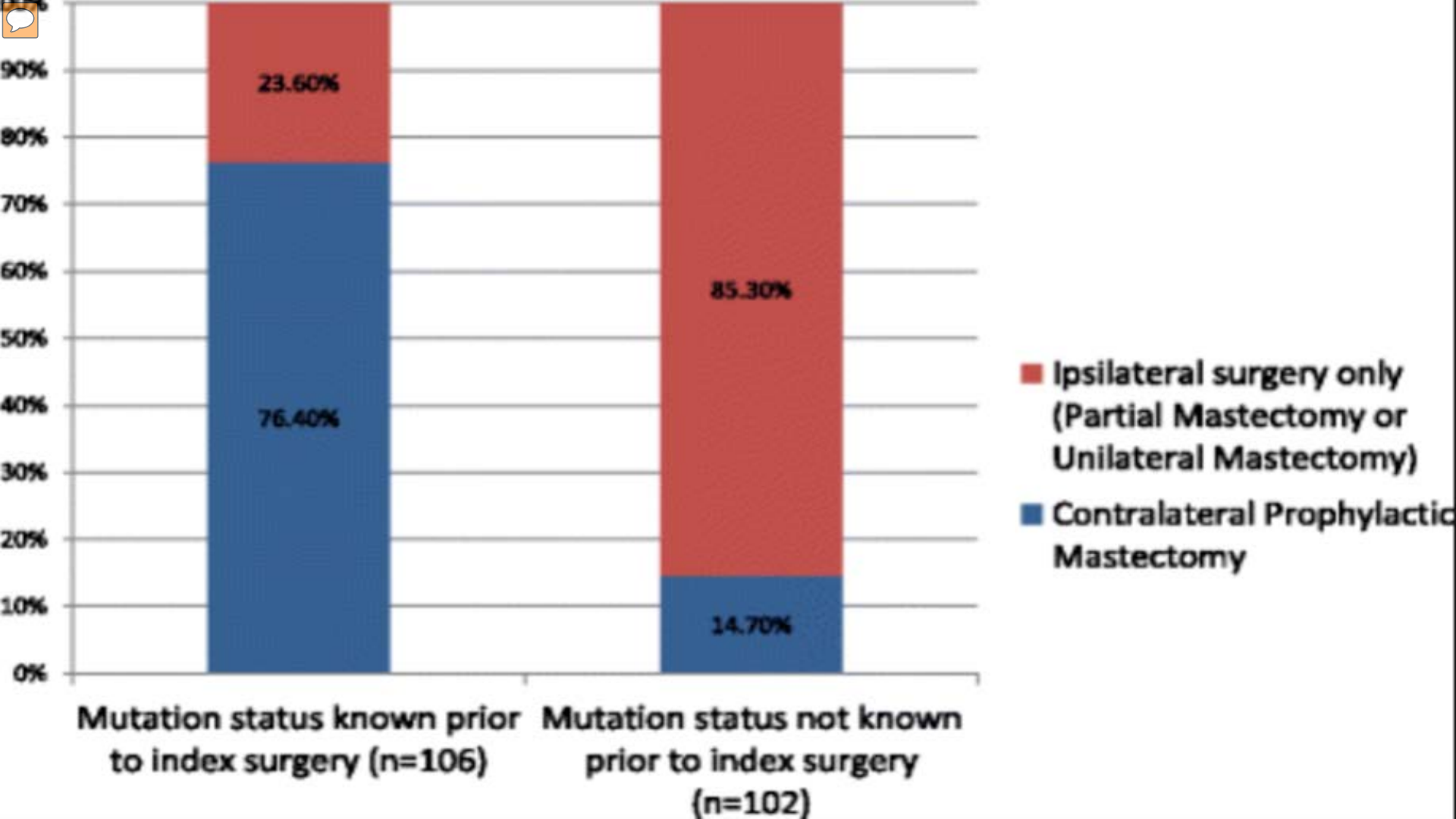
Mavaddat N et al. Cancer Epi Biomarkers Prev 2012;21:134-147

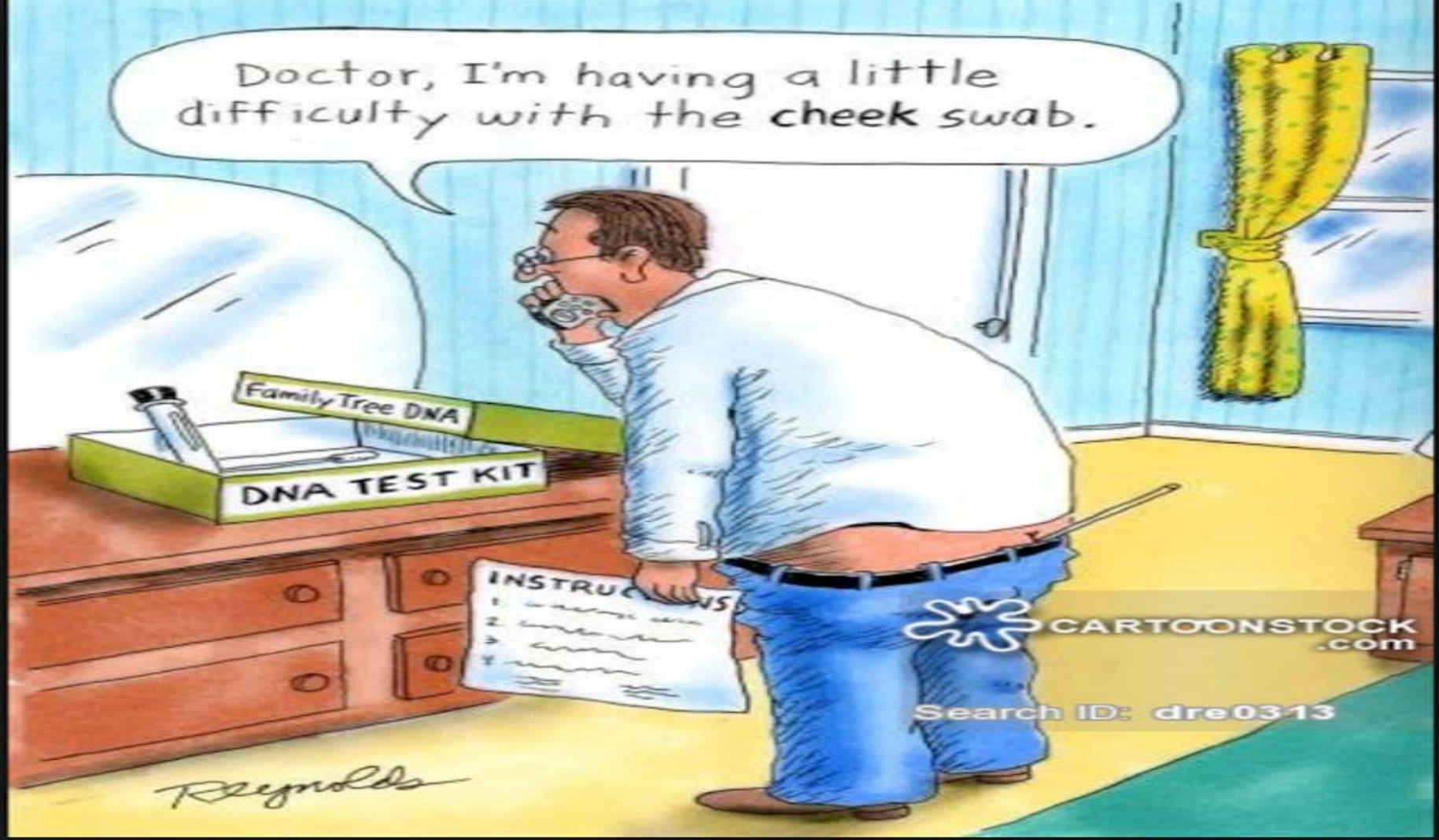
Prophylactic Surgery

Most effective method for reducing risk

- **Prophylactic Bilateral Mastectomy**
  - Reduces risk of breast cancer ≥90%[1,2]
- **Prophylactic Oophorectomy**
  - Reduces risk of ovarian cancer ~95%[3,4]
  - In premenopausal women, reduces breast cancer risk by 50%

[1]Meijers-Heijboer et al. *NEJM*. 345(3) 2001.
[2]Hartmann et al. *NEJM*. 340(2) 1999.
[3]Rebbeck et al. NEJM. 346(21). 2002
[4]Kauff et al. NEJM 346(21). 2002


90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
23.60%
76.40%
85.30%
14.70%
Mutation status known prior to index surgery (n=106)
Mutation status not known prior to index surgery (n=102)
Ipsilateral surgery only (Partial Mastectomy or Unilateral Mastectomy)
Contralateral Prophylactic Mastectomy


Doctor, I'm having a little difficulty with the cheek swab.
Family Tree DNA
DNA TEST KIT
INSTRU NS
CARTOONSTOCK .com
Search ID: dre0313
Reynolds

Pathogenic Variant Detected or Positive Result

- Increased Cancer Risks
- Apply Management Guidelines if available
- Test other family members if actionable

No Pathogenic Variant Detected or Negative Result

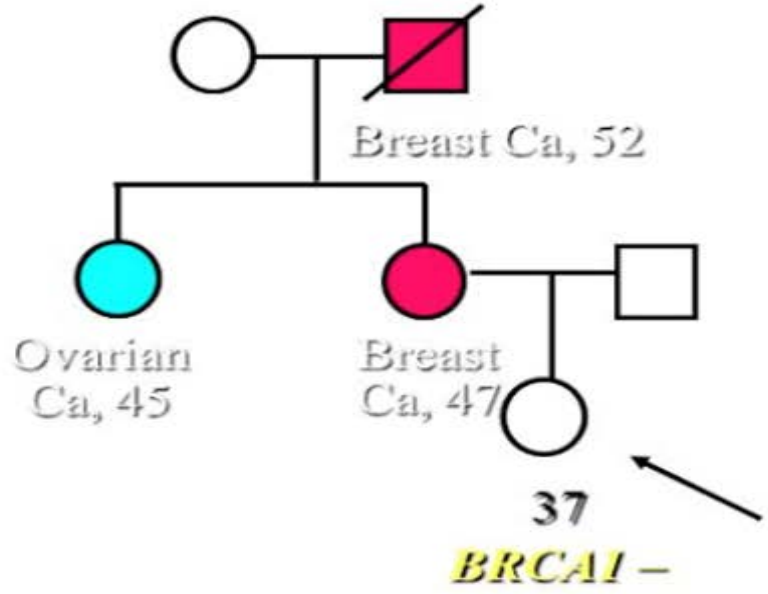
- Assess result based on family history
- Screen based on family history
  No genetic testing for unaffected family members

Variant of Uncertain Significance (VUS)

- Subtle DNA change
- Unknown if benign variant (normal) or disease causing
- Follow based on family history
- More info may become available

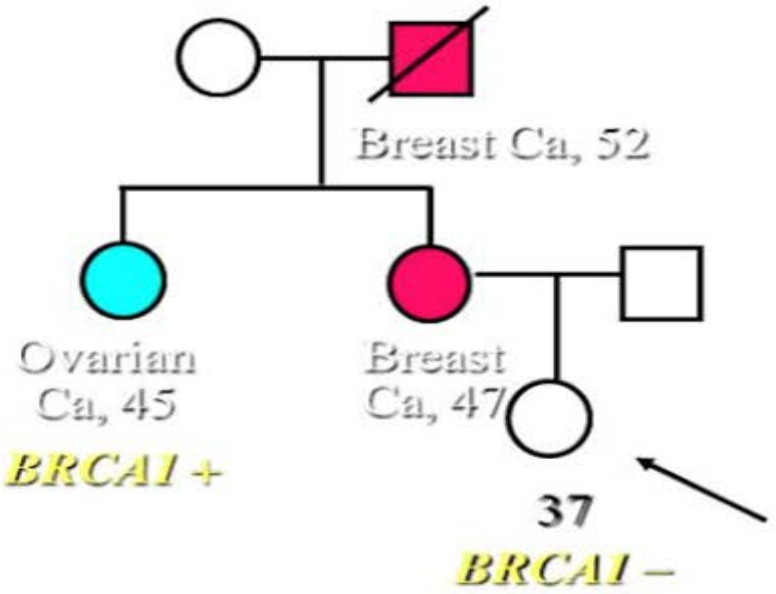
Interpreting a Negative Result

No identified mutation in family



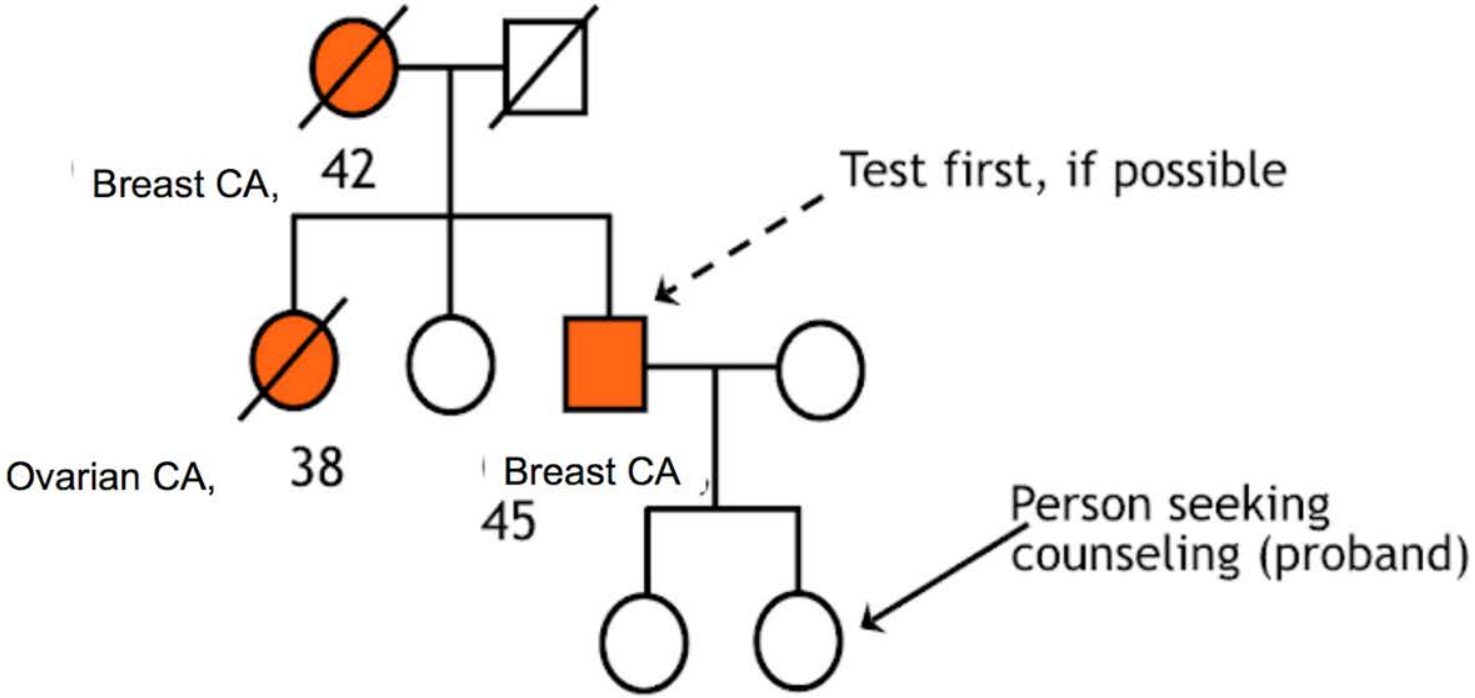
Inconclusive

Family with known mutation



True negative

Testing The More Appropriate Person in the Family



GINA—Genetic Information Nondiscrimination Act of 2008

Protections

- Health insurers/employers cannot request, require, or use genetic information to make decisions about:
  - Eligibility and premiums
  - hiring, promotion, or pay

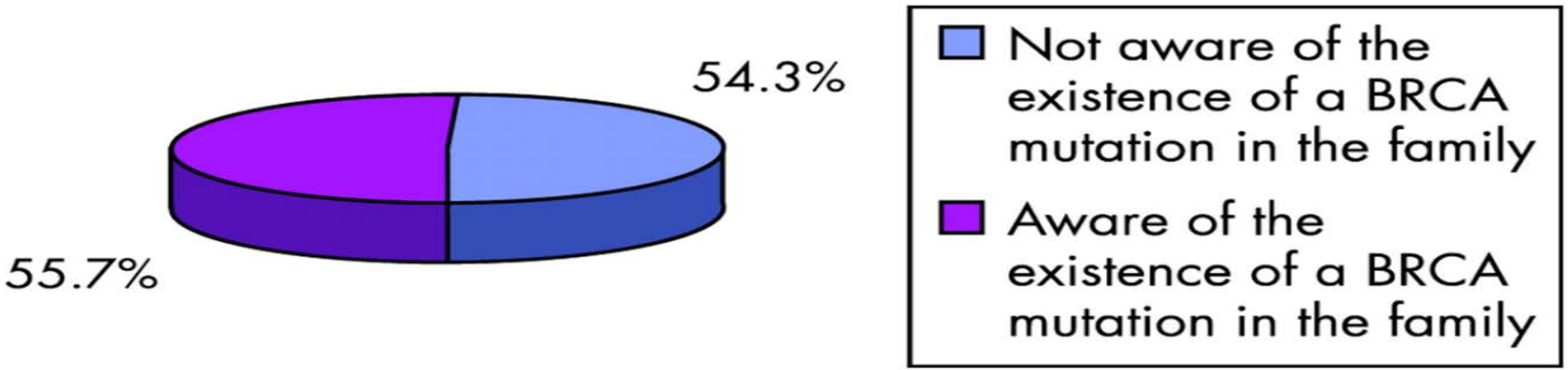
Limitations

- Does not protect those with life, disability, or long-term care insurance
- Only covers 15+ employees
- Does not cover an individual's manifested disease or current condition

Genetic Testing Has Implications for the Entire Family

- Consider the impact of testing on *all* family members
- Ultimately, testing is the *individual's* choice

Awareness of the existence of a BRCA mutation in the subject's own family.



E Sermijn et al. J Med Genet 2004;41:e23


Nice..
We have so many options!
- BRCA 1 & 2 - BCRAplus
- BRCAplus expanded - Myrisk
- BreastNext - GynPlus
How would you like to be sequenced?
Genomics Core Facility

- 1994-95 Identification of BRCA1/2 genes
  - Commercial sequencing at Myriad Genetics
  - Detects ~85%
- 2002 BRCA1
  - Increases det
- 2006 BRCA1/
  - Special cases
- 2012 (Octobe
  (BART) testing
- Myriad Gene

) started

rearrangement

les

6/2013

--History Matters--
Patients tested prior to October 12, 2012 may need additional BRCA1/2 testing to ensure a mutation is not present

CONFIDENTIAL

Comprehensive BRACAnalysis®
BRCA1 and *BRCA2* Analysis Result

PHYSICIAN	SPECIMEN	PATIENT
John Smith, MD Comprehensive Medical Center 1100 Grand Ave Away, GA 12345	Specimen: Blood Draw date: Aug 01, 2010 Accession date: Aug 02, 2010 Report Date: Jun 22, 2011	Name: Doe, Jane Date of Birth: April 1, 1492 Patient ID: 000000 Gender: Female Accession #: 00000000-BLD Requisition #: 000000

Test Results and Interpretation

NO MUTATION DETECTED

Test Performed:	Result:	Interpretation:
BRCA1 sequencing	No Mutation Detected	No Mutation Detected
5-site rearrangement panel	No Mutation Detected	No Mutation Detected
BRCA2 sequencing	No Mutation Detected	No Mutation Detected

It is our understanding that this patient was identified for testing due to a personal or family history suggestive of hereditary breast and ovarian cancer. Analysis consists of sequencing of all translated exons and immediately adjacent intronic regions of the BRCA1 and BRCA2 genes and a test for five specific BRCA1 rearrangements. There are additional large genomic rearrangements in BRCA1 and in BRCA2, which are not detected by this test, but can be identified with the BRACAnalysis Rearrangement Test (BART). The classification and interpretation of all variants identified in this assay reflects the current state of scientific understanding at the time this report was issued. In some instances, the classification and interpretation of such variants may change as new scientific information becomes available.

CONFIDENTIAL

Integrated BRACAnalysis®
BRCA1 and *BRCA2* Analysis Result

PHYSICIAN	SPECIMEN	PATIENT
John Smith, MD Comprehensive Medical Center 1100 Grand Ave Away, GA 12345	Specimen: Blood Draw date: Aug 01, 2010 Accession date: Aug 02, 2010 Report Date: Jun 22, 2011	Name: Doe, Jane Date of Birth: April 1, 1492 Patient ID: 000000 Gender: Female Accession #: 00000000-BLD Requisition #: 000000

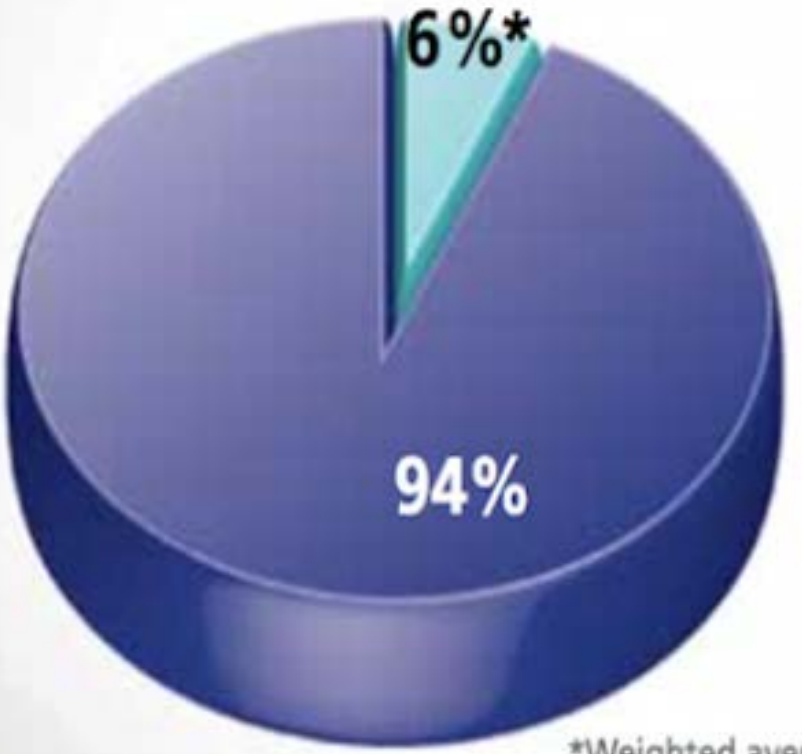
Test Results and Interpretation

NO MUTATION DETECTED

Test Performed:	Result:	Interpretation:
BRCA1 sequencing	No Mutation Detected	No Mutation Detected
comprehensive rearrangement	No Mutation Detected	No Mutation Detected
BRCA2 sequencing	No Mutation Detected	No Mutation Detected
comprehensive rearrangement	No Mutation Detected	No Mutation Detected

It is our understanding that this patient was identified for testing due to a personal or family history suggestive of hereditary breast and ovarian cancer. Analysis consists of sequencing of all translated exons and immediately adjacent intronic regions of the BRCA1 and BRCA2 genes and a comprehensive rearrangement test of both BRCA1 and BRCA2 by quantitative PCR analysis (BRACAnalysis Rearrangement Test; BART). The classification and interpretation of all variants identified in this assay reflects the current state of scientific understanding at the time this report was issued. In some instances, the classification and interpretation of such variants may change as new scientific information becomes available.

Mutation Distribution Between Sequencing and Large Rearrangements in Total Test Population



BART Mutations

Sequencing Mutations

*Weighted average of high risk BART and elective BART from 2007-2011

U.S. Supreme Court Strikes Down Human Gene Patents

13 June 2013

Ambry Genetics™

Cancer panels	Genes
BreastNext	17
OvaNext	24
ColoNext	17
PancNext	13
RenalNext	19
CancerNext	32, 49
$3700-$3900	$1500 OOP

INVITAE

Create your own panel:

Panel	Genes
Breast	17
Breast/ Ovarian	35
Colon	23
Pancreas	25
Cancer	34, 42
$1500	$475 OOP

MYRIAD®

MyRisk 25 cancer gene $4000

Gene Dx

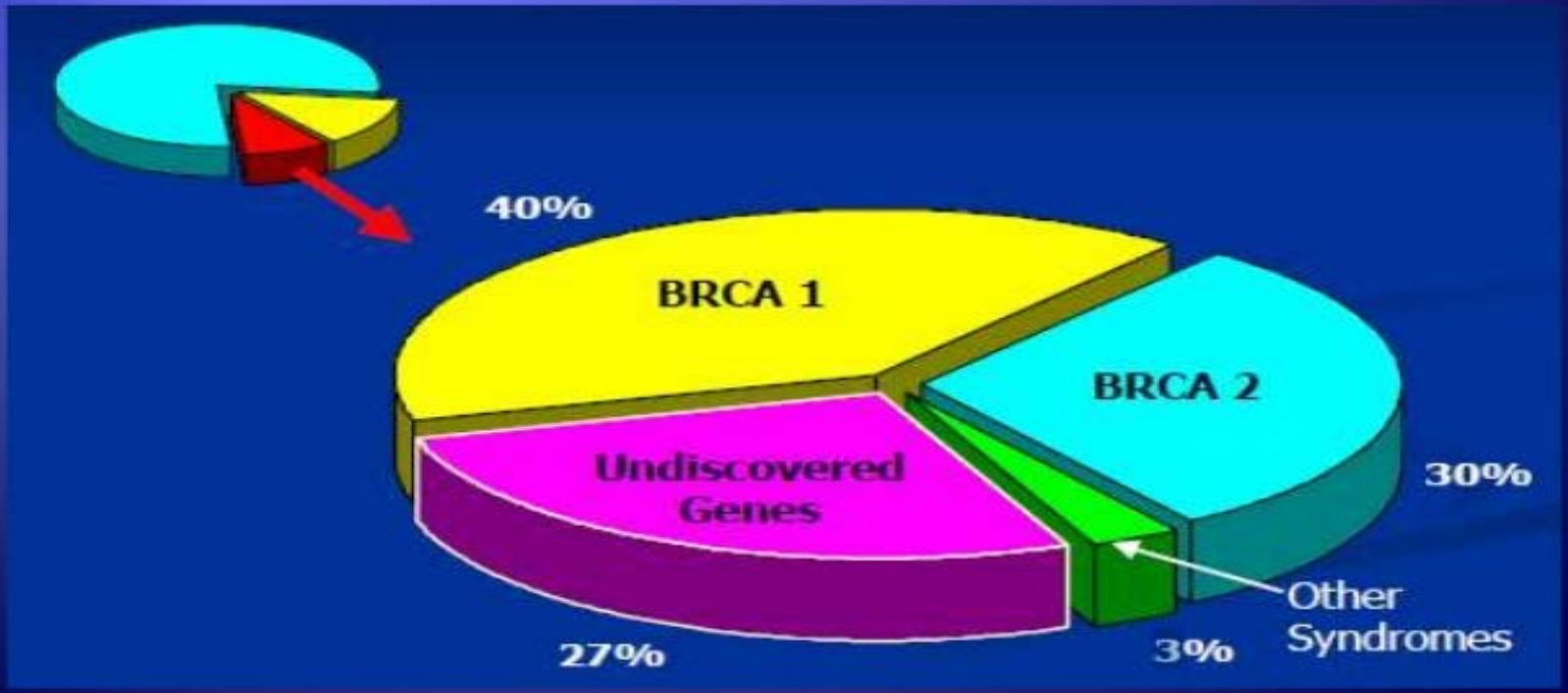
UW Medicine

UNIVERSITY OF WASHINGTON MEDICAL CENTER

BROCA Panel: 60 genes $3350
COLOSEQ: 22 genes $2300

Comprehensive Cancer Panel (32 Genes)
Breast/Ovarian Cancer Panel (21 Genes)
Colorectal Cancer Panel (19 Genes)
Pancreatic Cancer Panel (16 Genes)
$3500-$4000 $1500 OOP

Causes of Hereditary Susceptibility to Breast Cancer



High Cancer Risk Genes

- P53 (Li-Fraumeni Syndrome)
  - –Mutation prevalence 1/5,000-20,000; 7-20% de novo
  - –Sarcoma, brain, leukemia, colon, childhood cancers
  - –~30% breast cancer, age [31]: prevalence 7% in breast cancers <35
- PTEN (Cowden's Syndrome)
  - –Mutation prevalence 1/200,000; >75% de novo
  - –Uterine cancers, thyroid dysfunction, mucosal lesions, OFC>98%
  - –40-50% lifetime breast cancer risk; 10% thyroid, increased uterine & colon
- STK11 (Peutz Jeghers Syndrome)
  - –Mutation prevalence 1/60,000 - 300,000; 50% de novo
  - –High risk for breast (50%), colon (40%), ovarian (20%) and other cancers
  - –Lip freckles in childhood
- CDH1 (Hereditary Diffuse Gastric Cancer Syndrome)
  - –Mutation prevalence 1/100,000-300,000? De novo?
  - –60-80% develop gastric cancer
  - –30-40% lifetime risk of lobular breast cancer

Mascari ASCO 2005; Eng J Med Genet 2000; Pharoah Gastroenterology 2001; www.geneclinics.org

Li-Fraumeni Syndrome

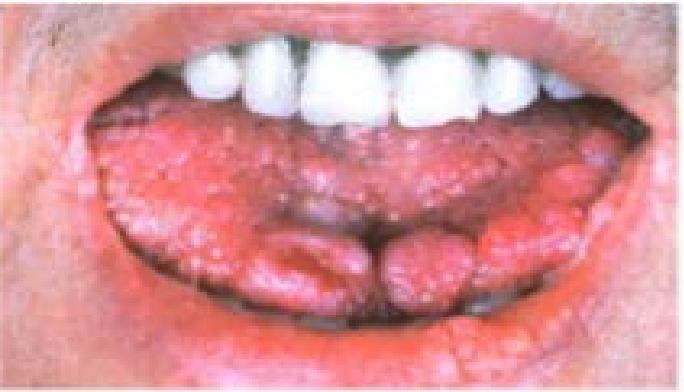
- Gene: TP53
- Inheritance: Autosomal Dominant
- Prevalence: 1 in 5,000-20,000
- De Novo 7-10%
- 25-85% Lifetime Risk of Breast Cancer
  - Screening Breast MRI start age 20
  - Consider RRM
- Average age of Diagnosis 38-46yo
- <1% overall of all breast cancer
- Risk of childhood cancers, Leukemia, Sarcoma, Colon & Brain CA

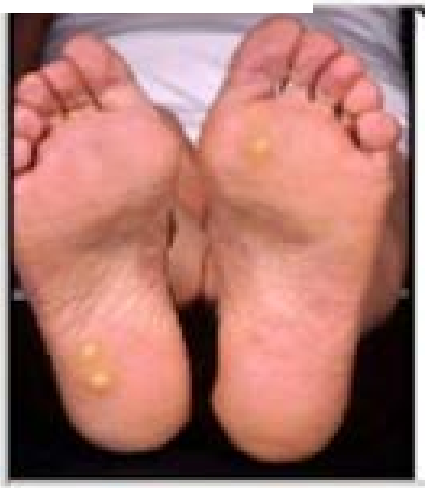
Cowden syndrome

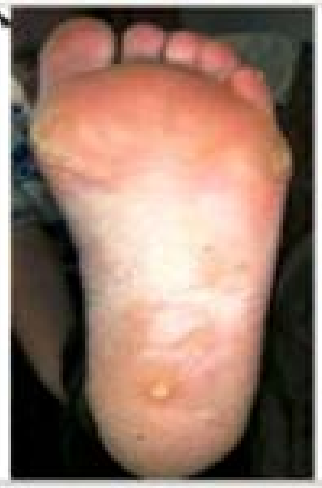
- Gene: PTEN
- Prevalence: 1 in 200,000
- De Novo Rate 10-47%
- 25-50% Lifetime Risk of Breast Cancer
  - Screening Breast MRI start age 30
  - Consider RRM
- Risk Thyroid, Uterine & Colon CA

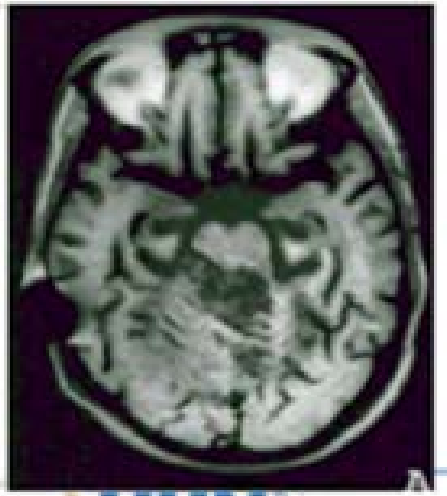
Physical Features

- Macrocephaly (Head Circumference >58-60)
- Papillomas on skin and mucosa
- Dysplastic gangliocytoma of cerebellum



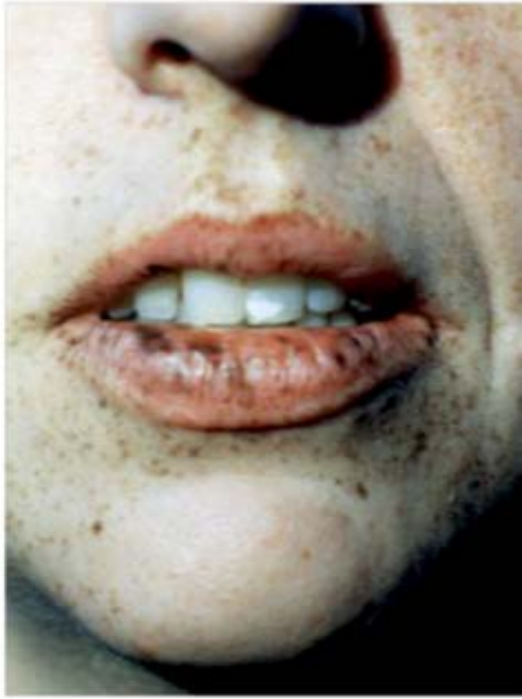






Peutz-Jeghers Syndrome

- Gene: STK11
- Inheritance: Autosomal Dominant
- Prevalence: 1 in 8,000-200,000
- Hamartomatous & Adenomatous Polyposis
  Especially of the Small Intestine
- 30-54% Lifetime Risk of Breast Cancer
  - Screening Breast MRI start age 25
  - RRM Evidence insufficient /?Family Hx
- Risk of Colon, Gastric, Pancreatic, Uterine, Ovarian, Sex Cord Tumor etc.



Labial and oral mucosal hyperpigmentation- may fade with time

Hereditary Diffuse Gastric Cancer

- Gene: CD1

- Inheritance: Autosomal Dominant
- De Novo Variants have been reported

- 42% Lifetime Risk of LOBULAR Breast Cancer
  - Screening Breast MRI start age 30
  - Consider RRM

- 56-70% Lifetime Risk of Gastric Cancer
  - Average age of onset age 38
  - Gastrectomy recommended age 18-40yo

- Risk of Colon and Prostate Cancer

Moderate Cancer Risk Genes

- ATM
  - –Mutation prevalence 1/100
  - –OR =2-4 for breast cancer risk; OR =2 for colon cancer
  - –Possible pancreatic risk
- CHEK2
  - –Mutation prevalence up to 1/66 (Dutch); <1/100 others
  - –Breast (OR=2.6-4.8), colon (OR=2) cancer risks
  - –Possible prostate and thyroid cancer risk
- PALB2
  - –Mutation prevalence ~1/1000
  - –OR =3-5 for breast cancer risk
  - –Suggestion of increased ovarian and pancreatic cancer risks

Mascari ASCO 2005; Eng J Med Genet 2000; Pharoah Gastroenterology 2001; www.geneclinics.org

Lower Cancer Risk Genes

- BRIP1, BARD1, RAD51C, RAD51D
  - –Prevalence uncertain
  - –OR= 2-3 for breast cancer
  - –OR 3-6 for ovarian cancer with BRIP1, RAD51D
- RAD 50, MRE11A, NBN
  - –Prevalence uncertain
  - –1.5-2.5 OR breast cancer risk
  - –Possibly ovarian cancer risk
- NF1, Lynch, MUTYH
  - –Traditionally not breast cancer genes; other defining symptoms
  - –Prevalence much more common; 1/ 3000, 1/300, 1/50
  - –Breast cancer risk varies (OR= 2-5 fold)

Mascari ASCO 2005; Eng J Med Genet 2000; Pharoah Gastroenterology 2001; www.geneclinics.org

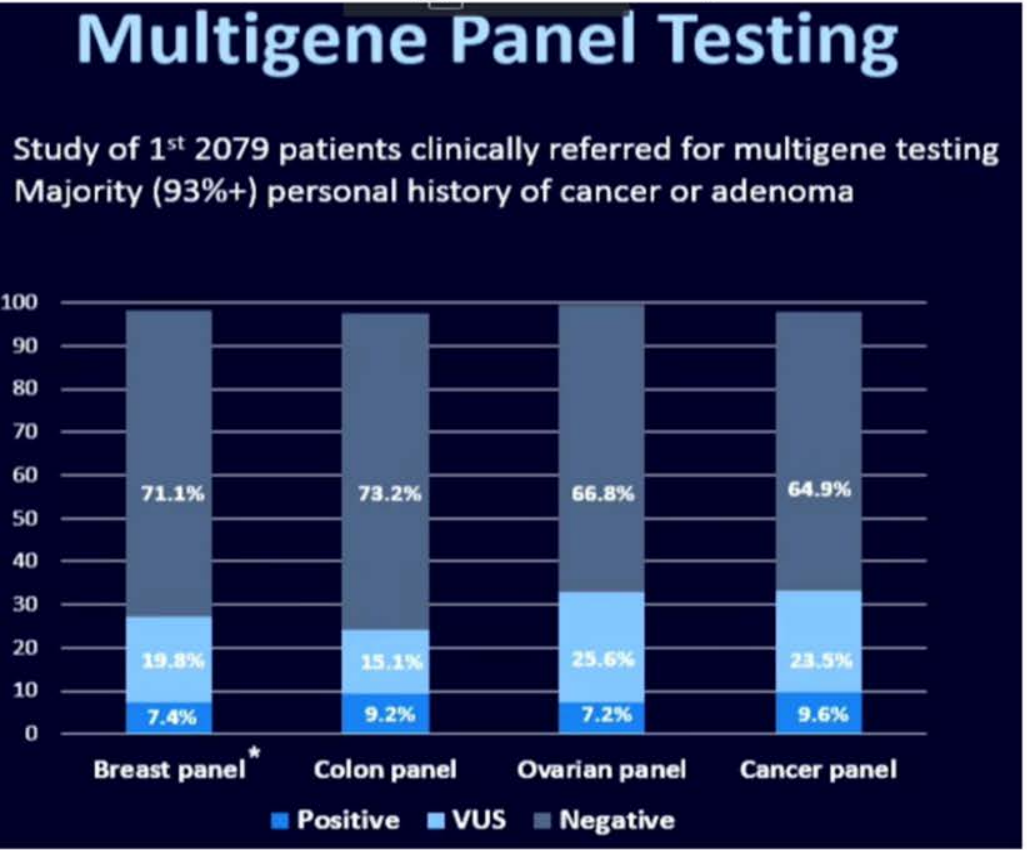
Multigene Panels - Advantages

- New cost effective genetic testing
- Broadest available gene panels
- Double the chance of identifying risk mutation
- ~3% have double mutations
- Mutation allows targeted screening and prevention
- Mutation allows relatives site specific testing

Multigene Panels - Disadvantages

- Variants of Uncertain Significance Common (25-50%)
- Genes with low risk may not have guidelines
- Low risk mutations may be a partial answer
- Full tumor risk and spectrum not well defined
- “Out of context” mutations; what are the risks?

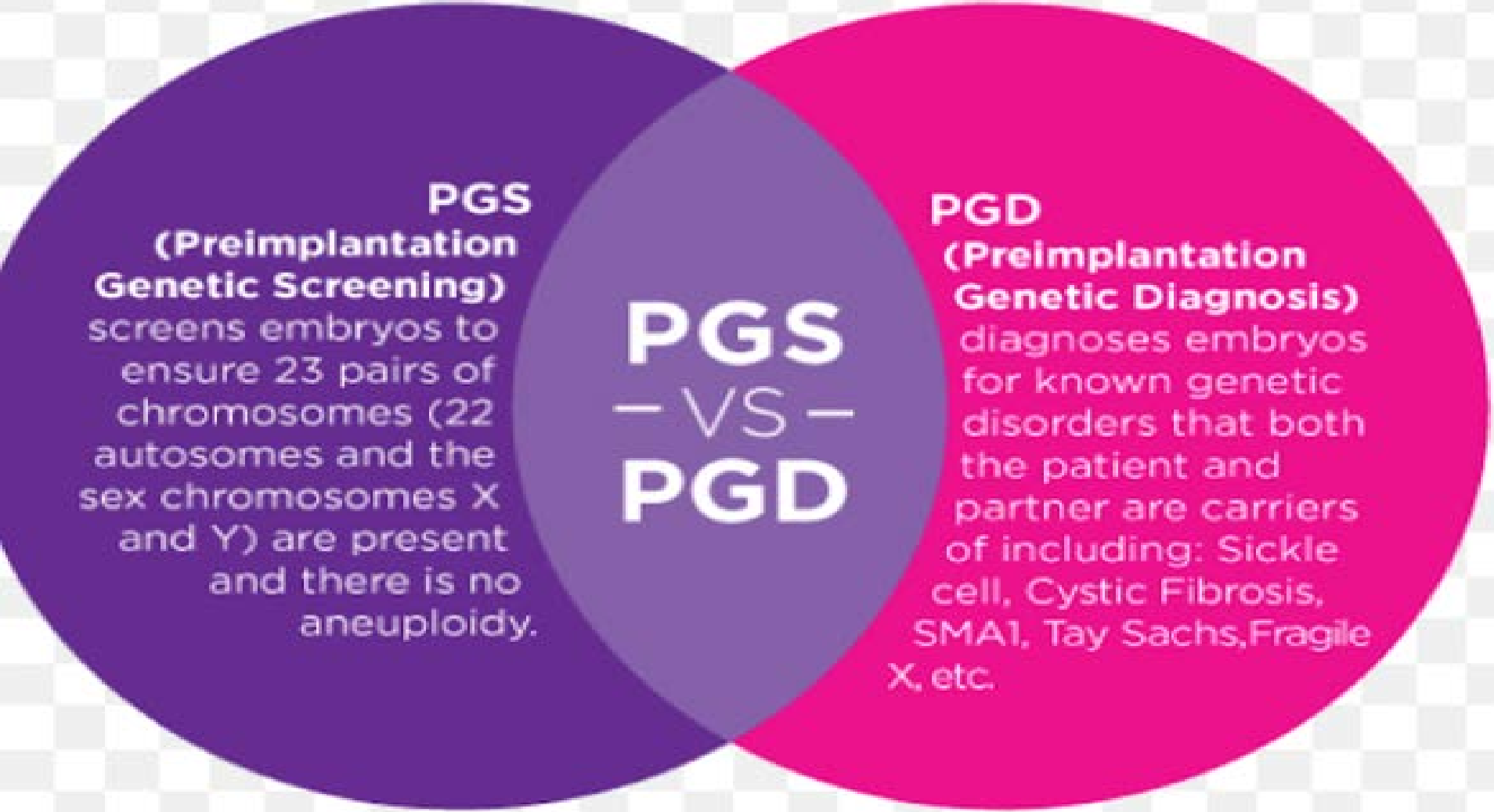
Multigene panels-beware of VUS (variants of uncertain significance)



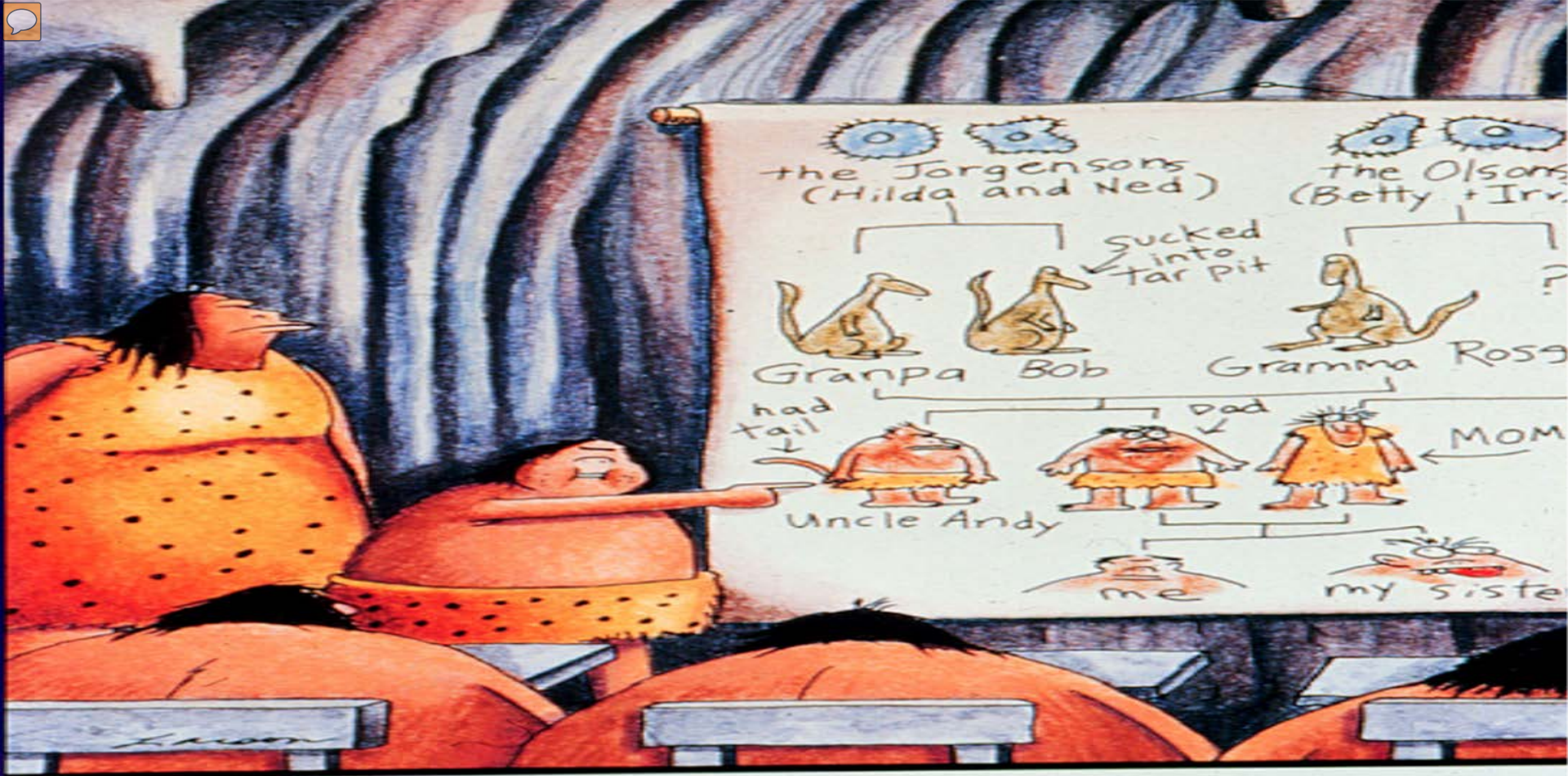
- Unclear if variant is undefined deleterious mutation, benign polymorphism, or variant with intermediate risk of cancer
- 2-3% VUS rate with BRCA 1/2
- 15-30% VUS rate with panels
- Many VUS will be reclassified as benign over time
  - Online registry-PROMPT
- VUS do NOT influence patient management or family member testing
  - Treat is as negative result

Multigene Panels Recessive Risks

- Multiple genes on these panels have recessive correlates with implications for reproduction:
  - **Fanconi Anemia**
  - **Ataxia Telangiectasia**
  - **MUTYH Polyposis**

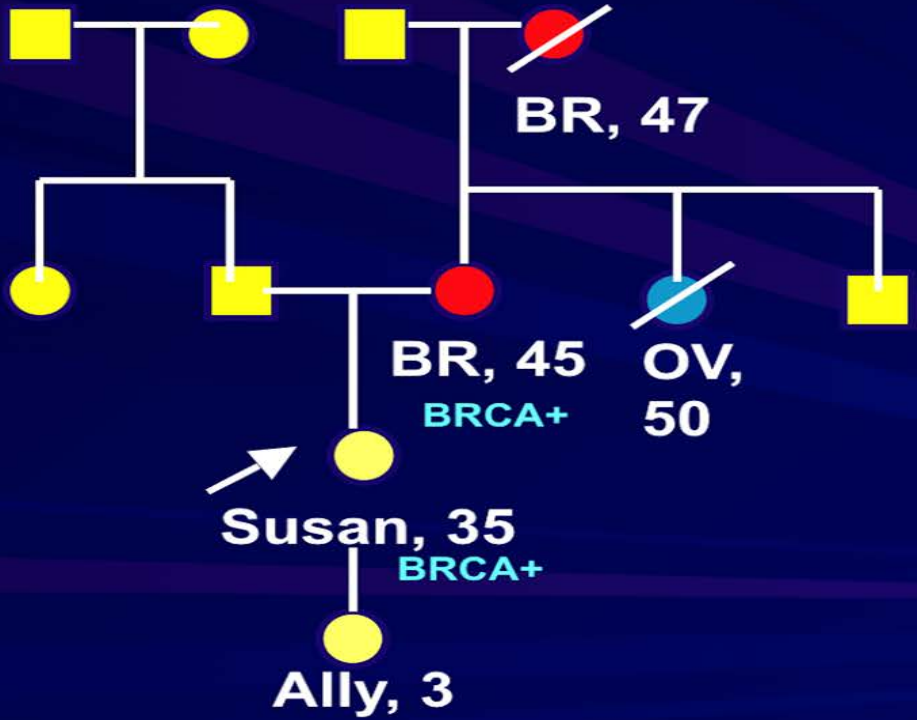

PGS
(Preimplantation Genetic Screening)
screens embryos to ensure 23 pairs of chromosomes (22 autosomes and the sex chromosomes X and Y) are present and there is no aneuploidy.
PGS
VS
PGD
PGD
(Preimplantation Genetic Diagnosis)
diagnoses embryos for known genetic disorders that both the patient and partner are carriers of including: Sickle cell, Cystic Fibrosis, SMA1, Tay Sachs,Fragile X, etc.

- Informed Consent
- Pre-test Counseling
- Post-test Counseling
- Risk reduction counseling

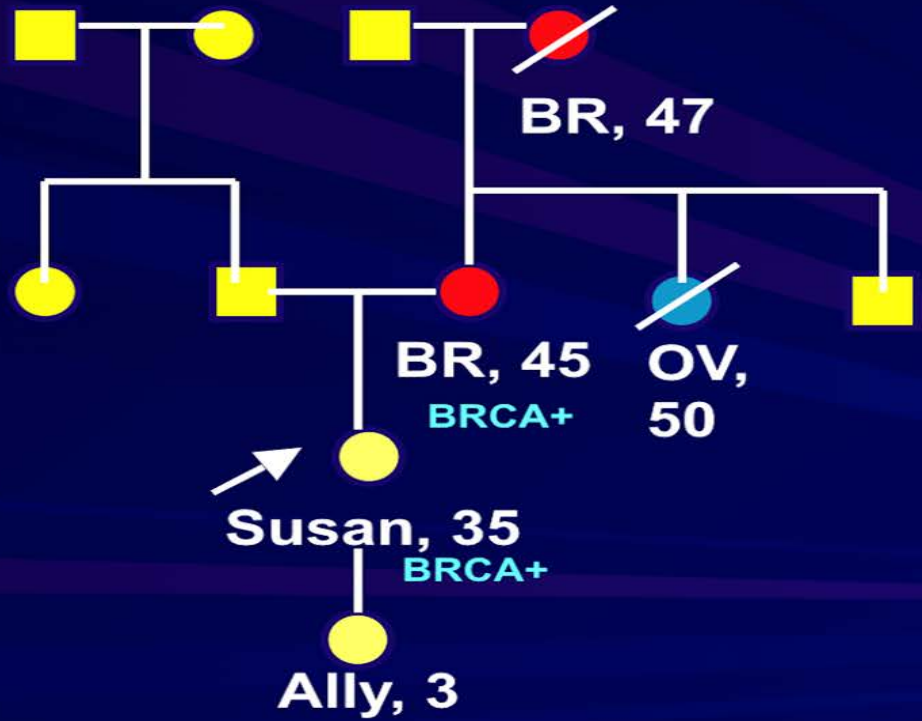


Dirk brings his family tree to class.

Do we test children?



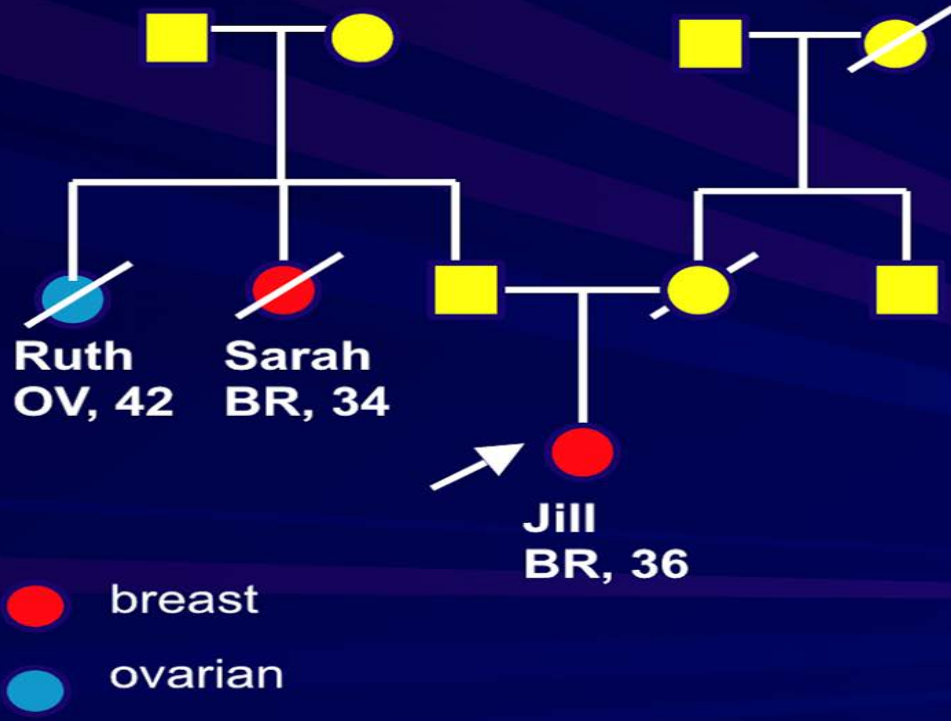
Do we test children?



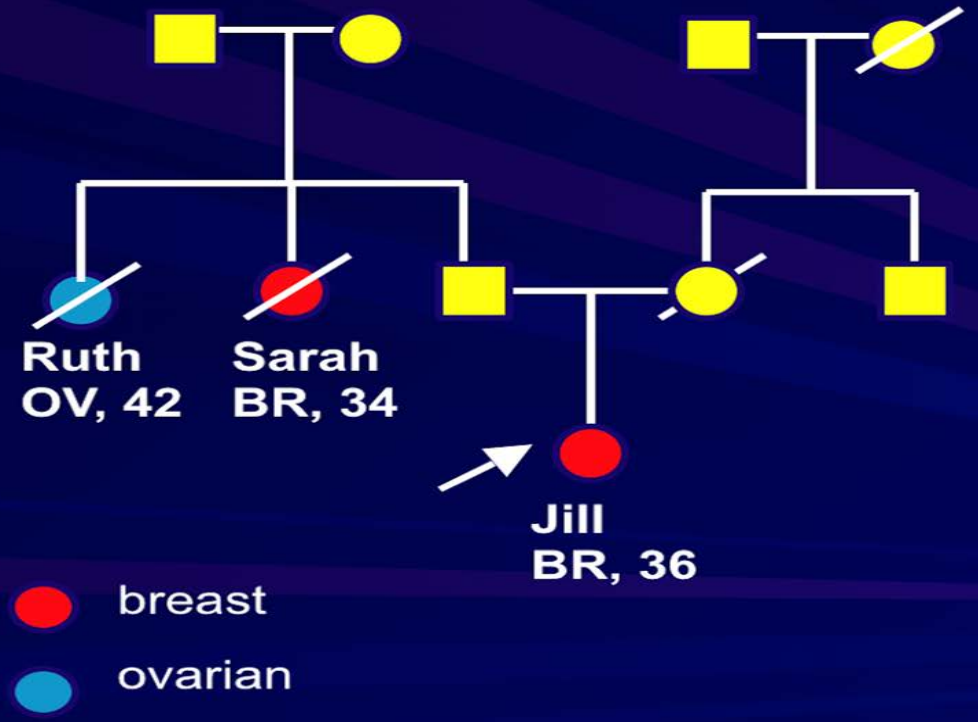
Not for BRCA mutations. Because risk of cancer is negligible in childhood and no preventive measures exist, there is not a medical necessity to test children. Doing so would violate their autonomy.

This is in contrast to other genetic diseases

Is testing appropriate for newly diagnosed women?

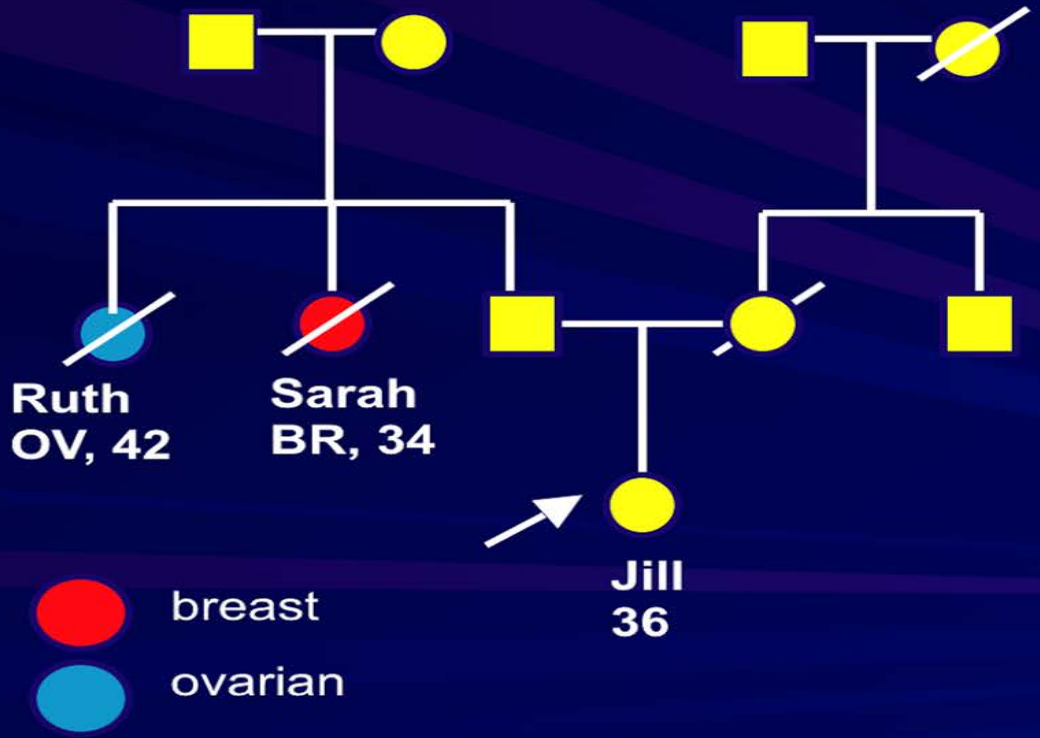


Is testing appropriate for newly diagnosed women?

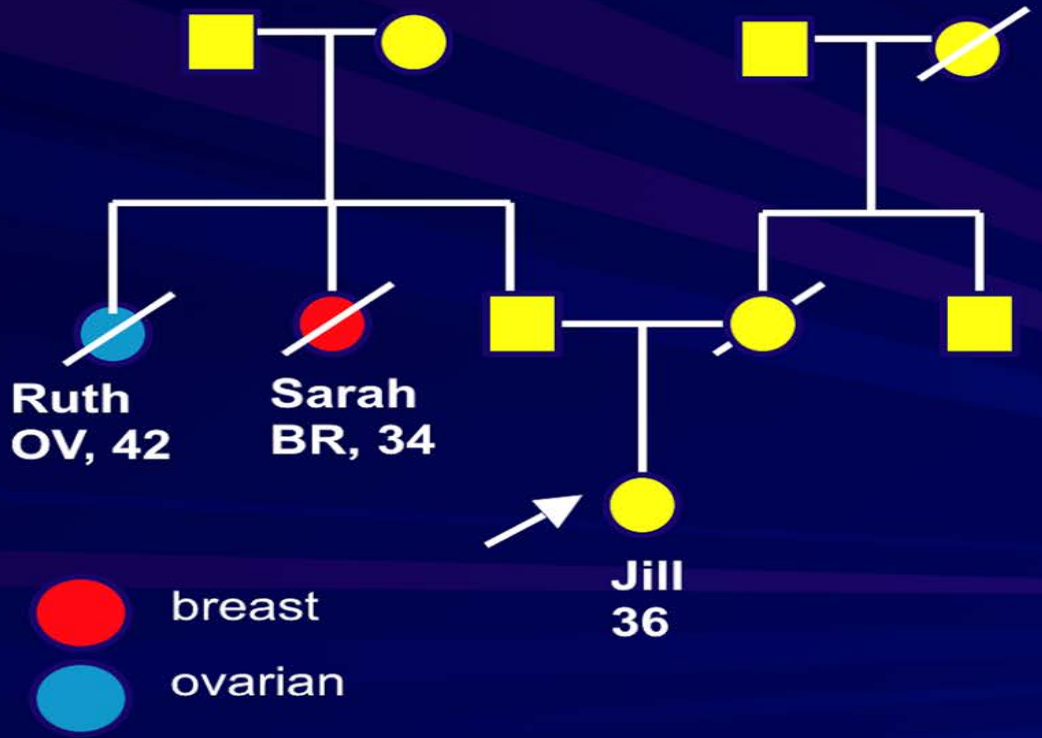


Yes. Obtaining genetic testing results before a woman's primary surgery can allow her to have prophylactic surgery at the same time as her primary surgical treatment.

Does paternal history matter?

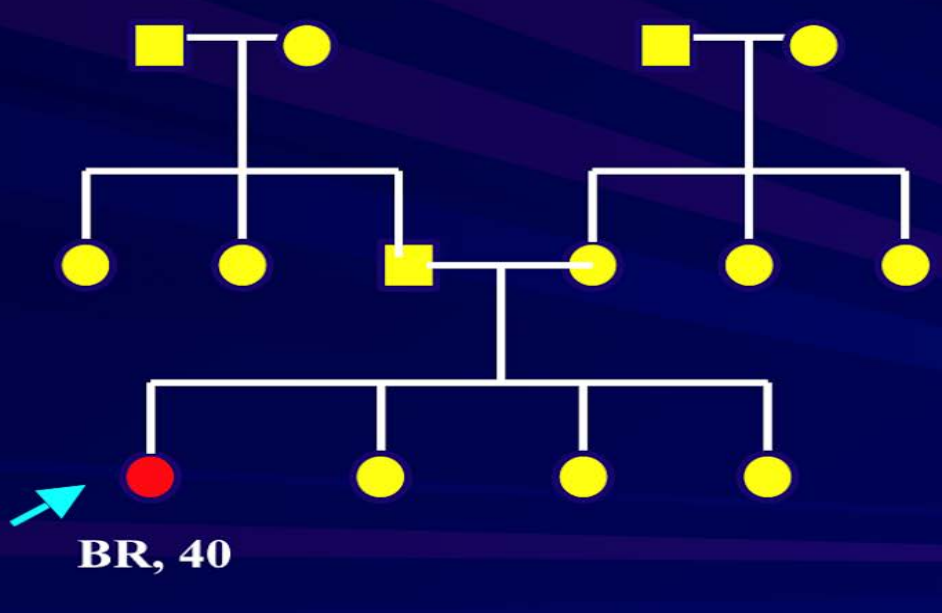


Does paternal history matter?



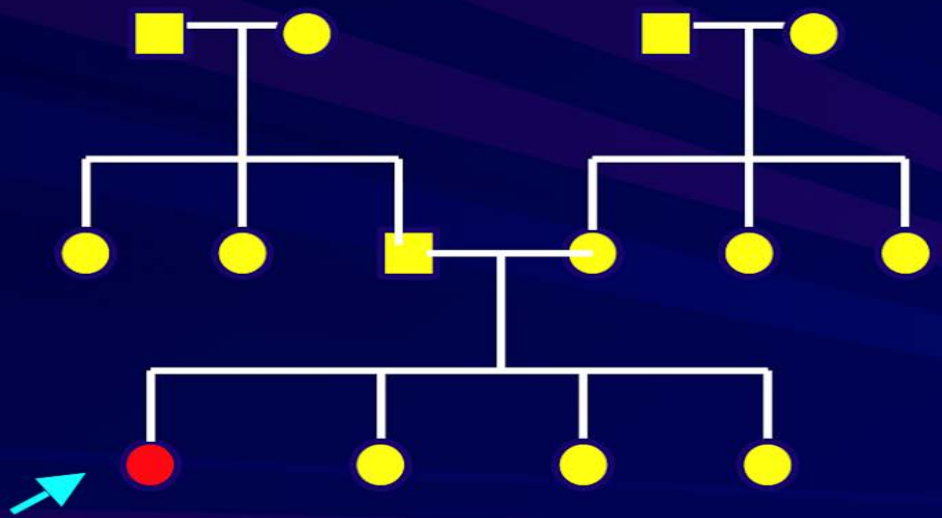
Yes. BRCA mutations can be passed on through mother or father. Paternal history is as relevant as maternal history.

Do we offer testing?



= breast cancer

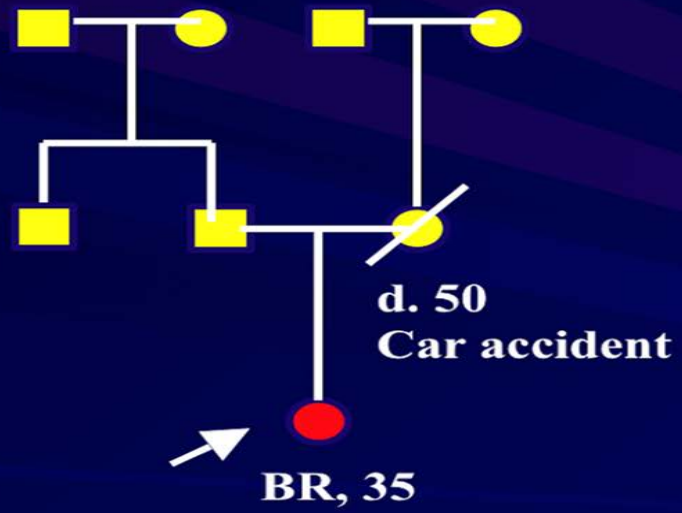
Do we offer testing?



Larger families are easier to assess. If there are many relatives who have lived to older ages without developing cancer, the chances of a BRCA mutation are lowered. However, we would offer given her age

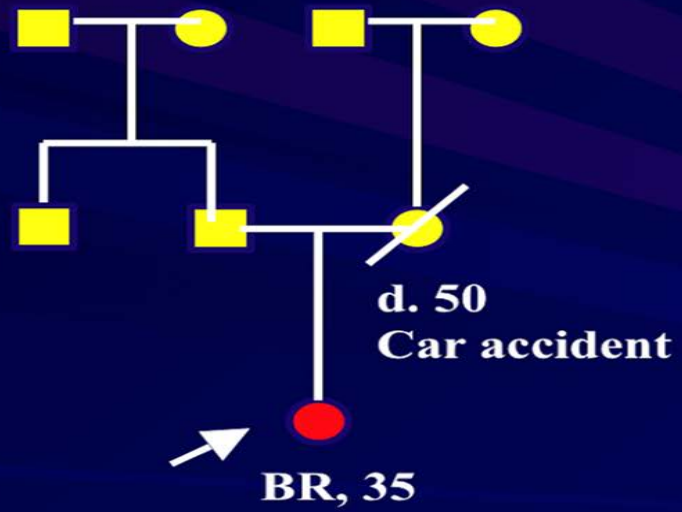
= breast cancer

Diagnosis at a young age
Do we offer testing?



= breast cancer

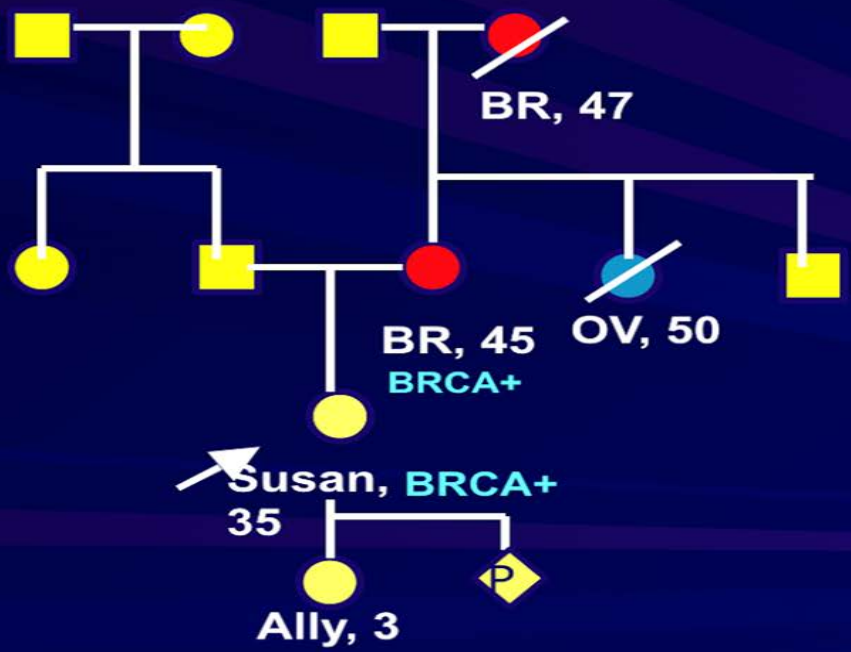
Diagnosis at a young age
Do we offer testing?



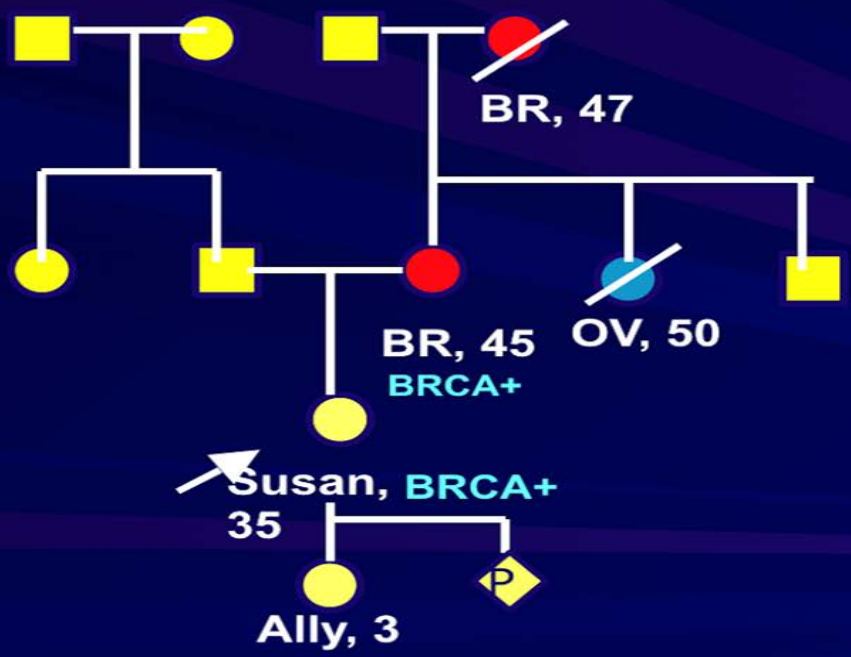
Yes, women diagnosed ≤35 have ~10% chance of harboring a BRCA mutation

= breast cancer

Do We Offer Prenatal Testing?

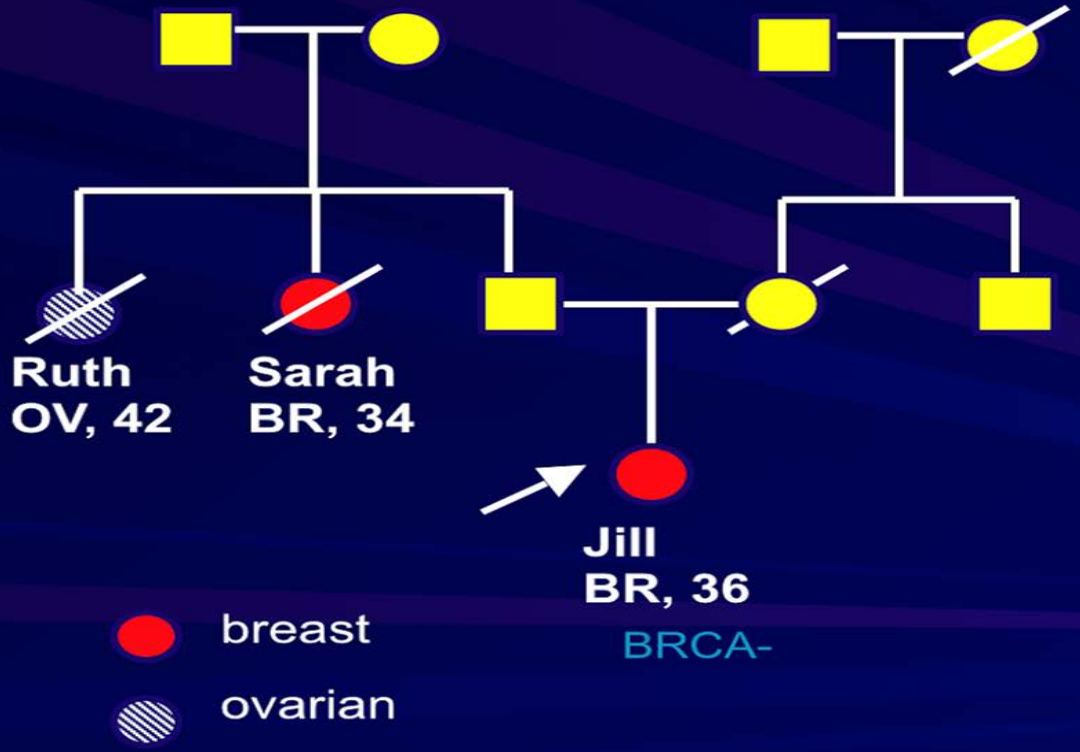


Do We Offer Prenatal Testing?

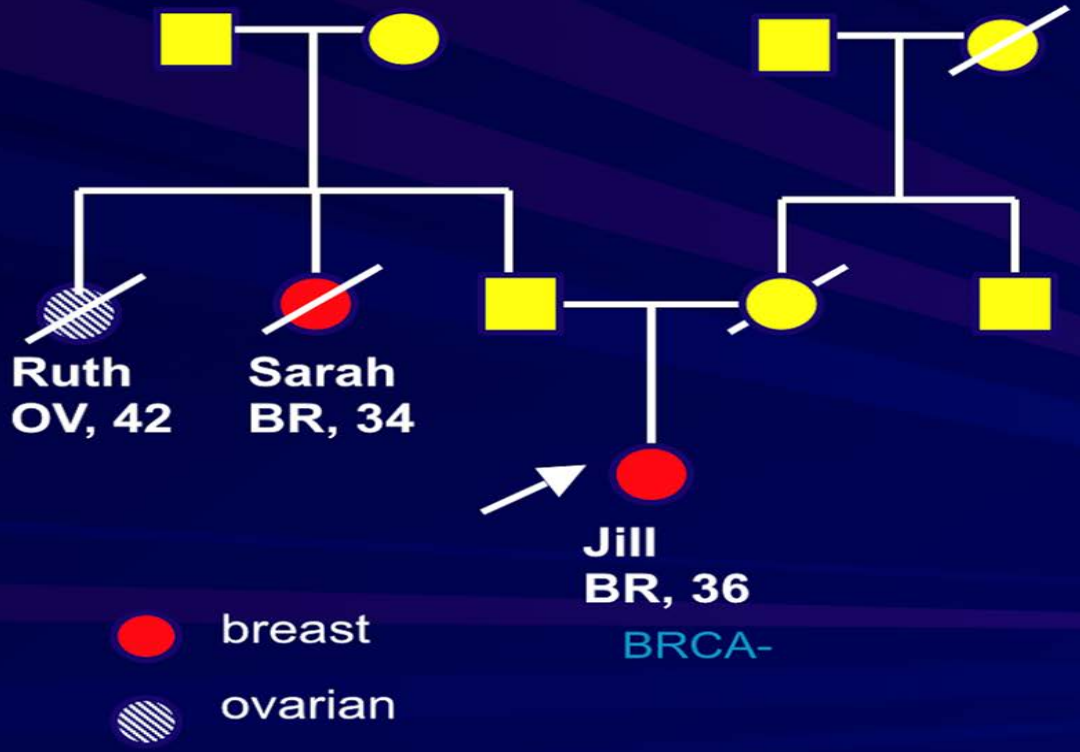


Yes. Preimplantation genetic screening and diagnosis. Consider testing partner for some mutations.

Do we believe this negative result?

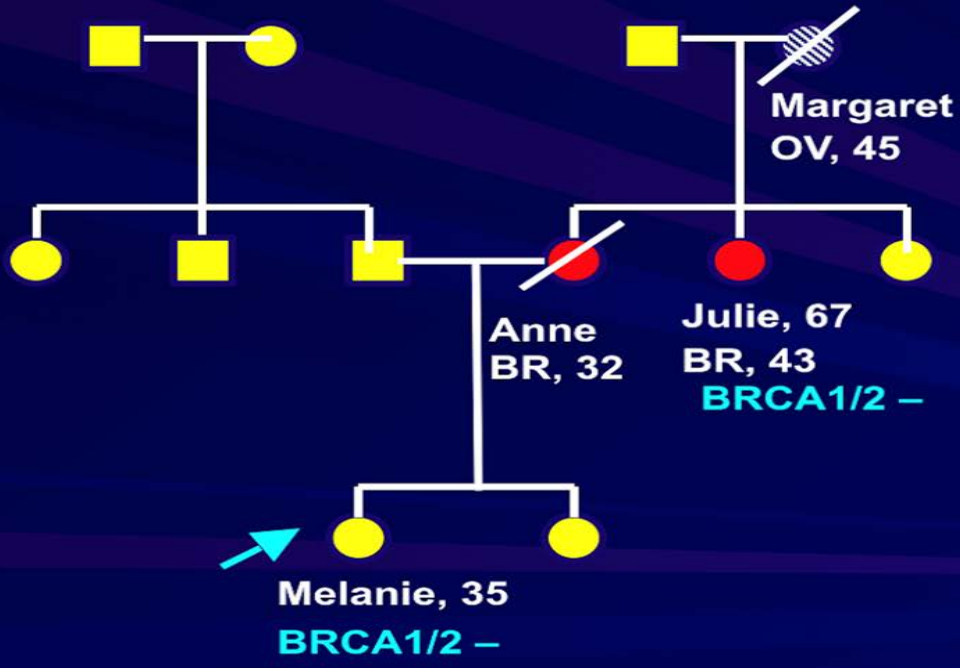


Do we believe this negative result?

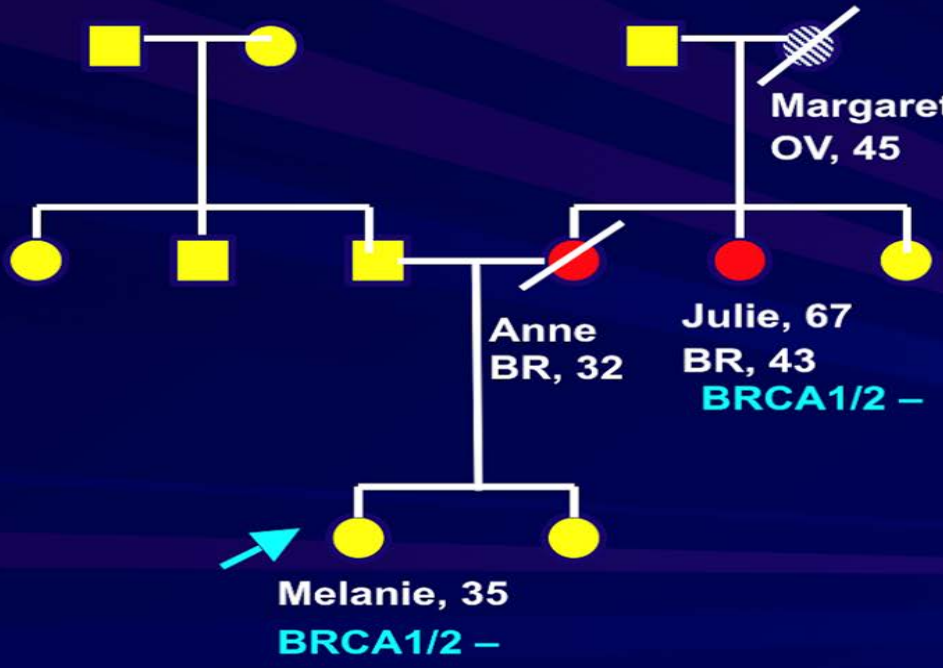


No, the mutation was most likely not detected by our current technology, thus residual risk remains

Do we believe this negative result?



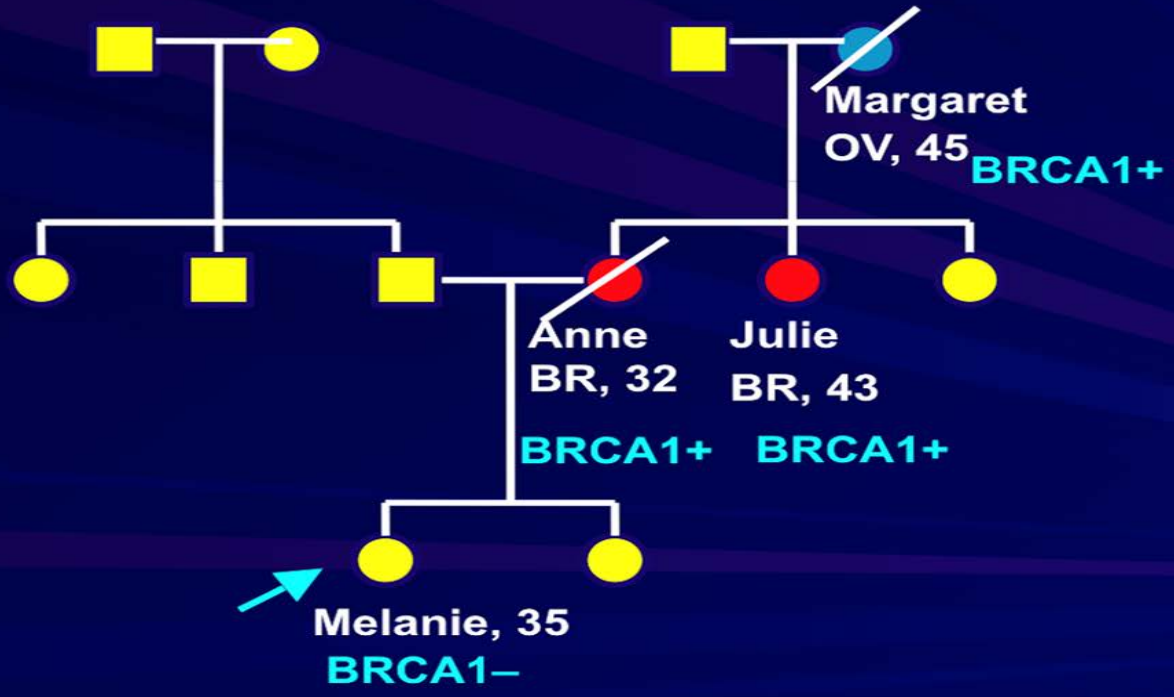
Do we believe this negative result?



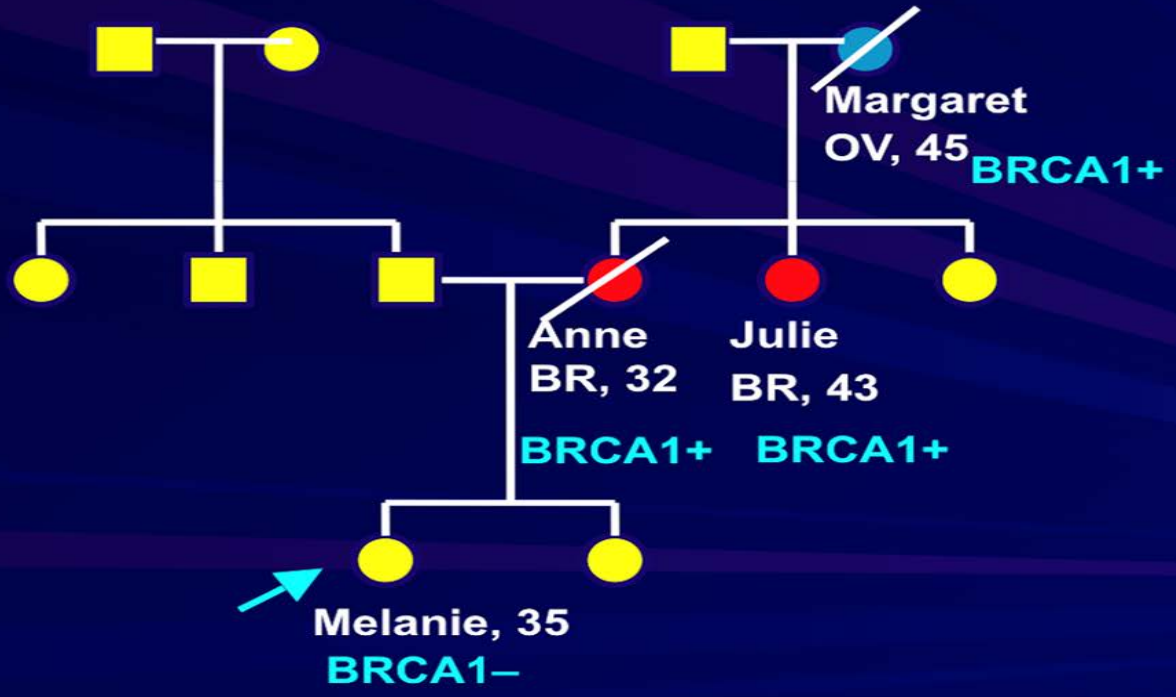
Uninformative Result-If we cannot identify a mutation in a family, it generally does not make sense to offer testing to unaffected family members.

If a priori risk of harboring a mutation is very high, we don't believe negative tests.

Do we believe this negative result?

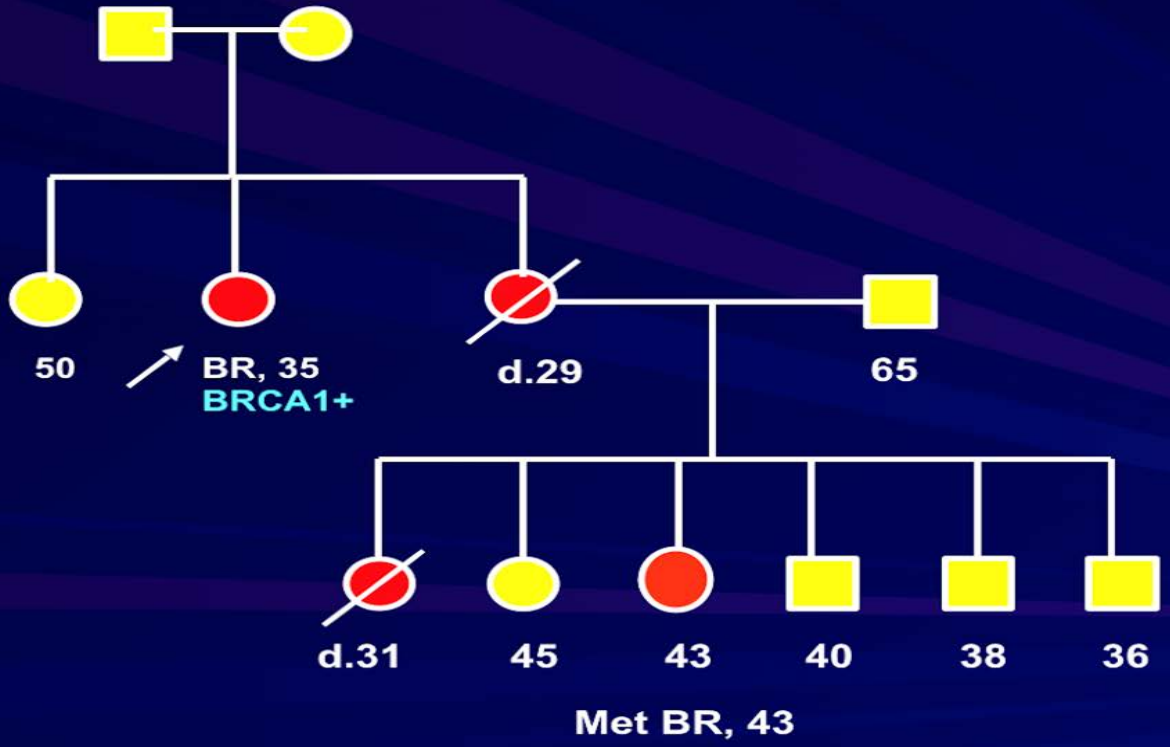


Do we believe this negative result?

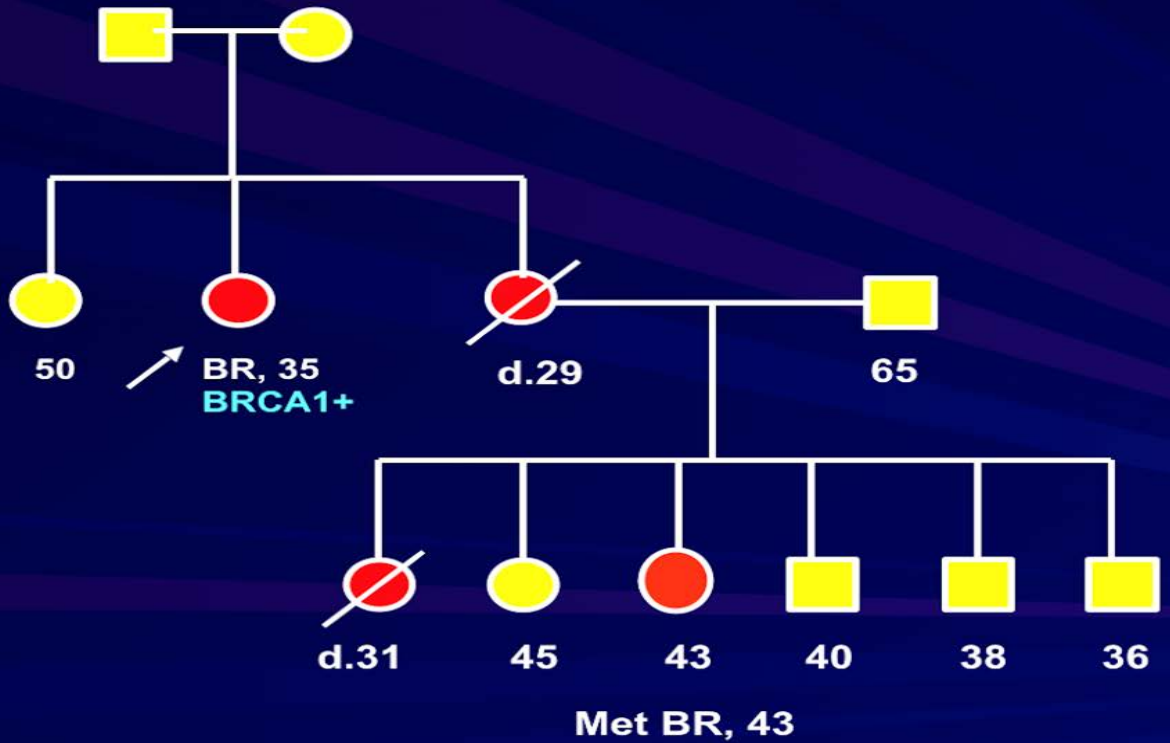


Yes, true negative-With 100% certainty, Melanie did not inherit the breast cancer risk in her family. She is therefore at general population risk.

Should we as clinicians inform at-risk family members?



Should we as clinicians inform at-risk family members?



Generally not. When a family member with a BRCA mutation does not inform family members, there is very little we can do.

Without such information, however, family members might not take preventive measures to reduce their risk.


HAMBURGER $2.35
CHEESEBURGER $2.95
TUNA SALAD $2.75
EGG SALAD $2.65
OMELETTE $3.10
BEEF STEW $3.45
FISH FILI $3.10
RISKS
BENEFITS