

# Gynecological Genetics

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# Objectives

- Understand the difference between sporadic, familial and hereditary causes of cancer and why it is important.
- Overview of hereditary breast cancer syndromes
- Causes of other gynecological cancers
- Advances in genetics of oncology and genetic testing.



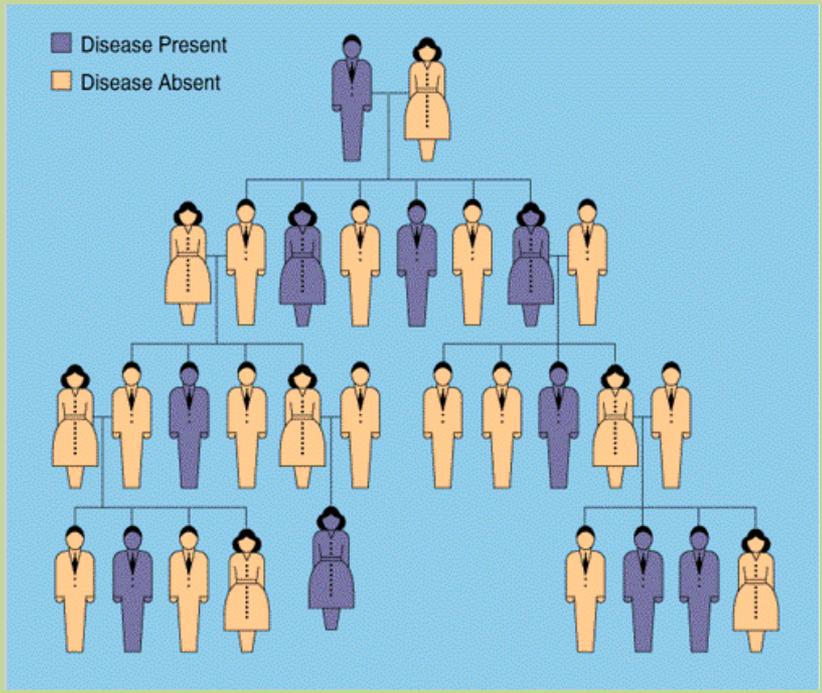
# Understanding genetics of cancer







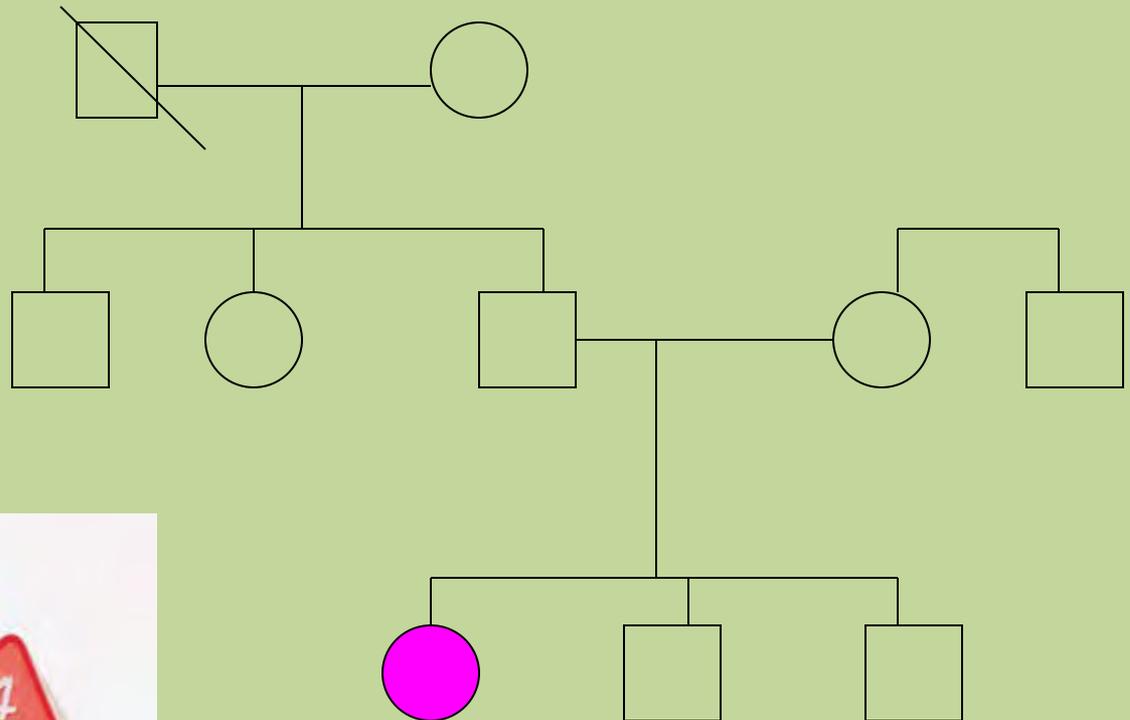
# Hereditary versus Sporadic





# Sporadic (environmental, by chance)

- No other family history
- Age of onset is typical



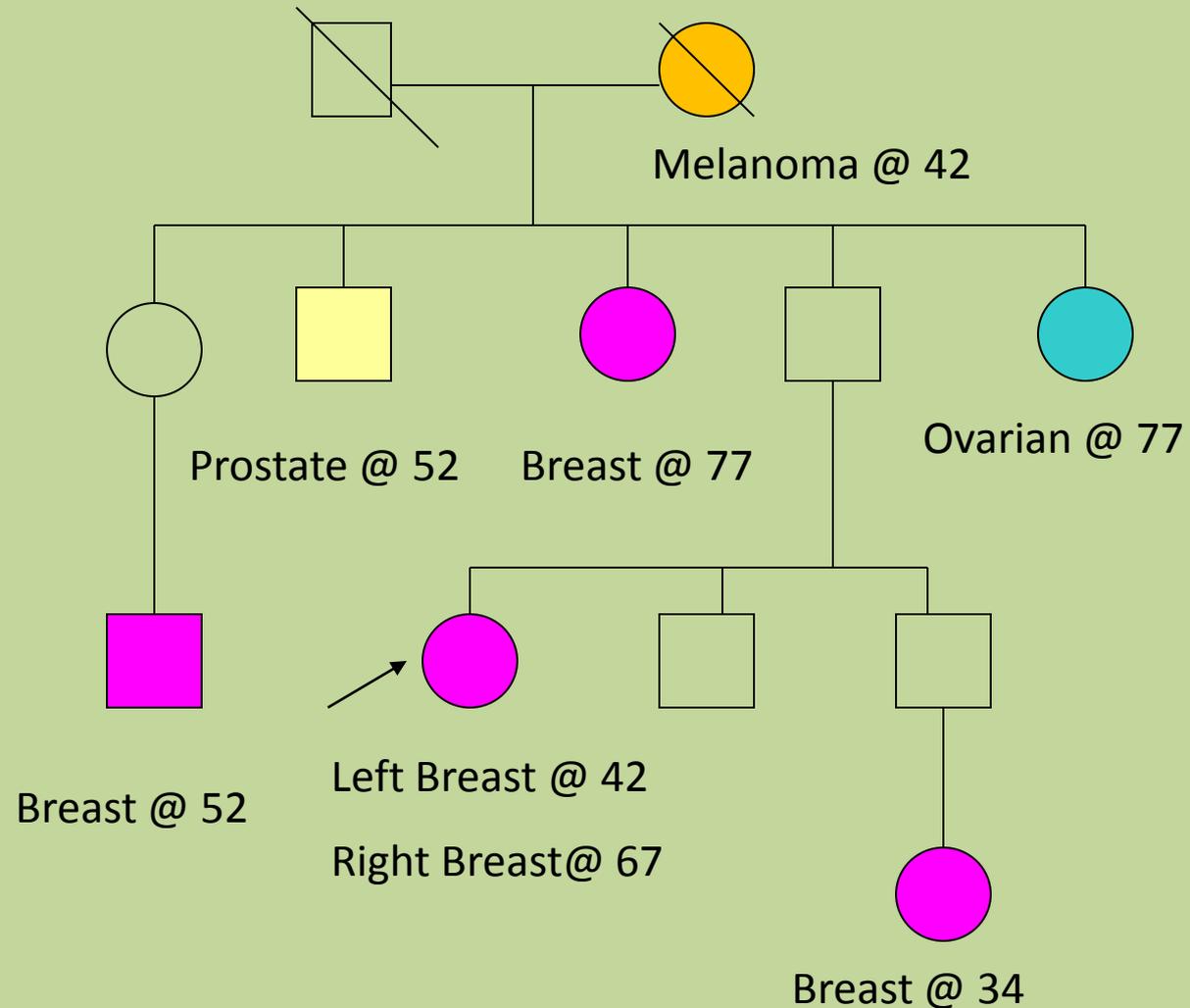
↖  
Breast @ 65





# Hereditary

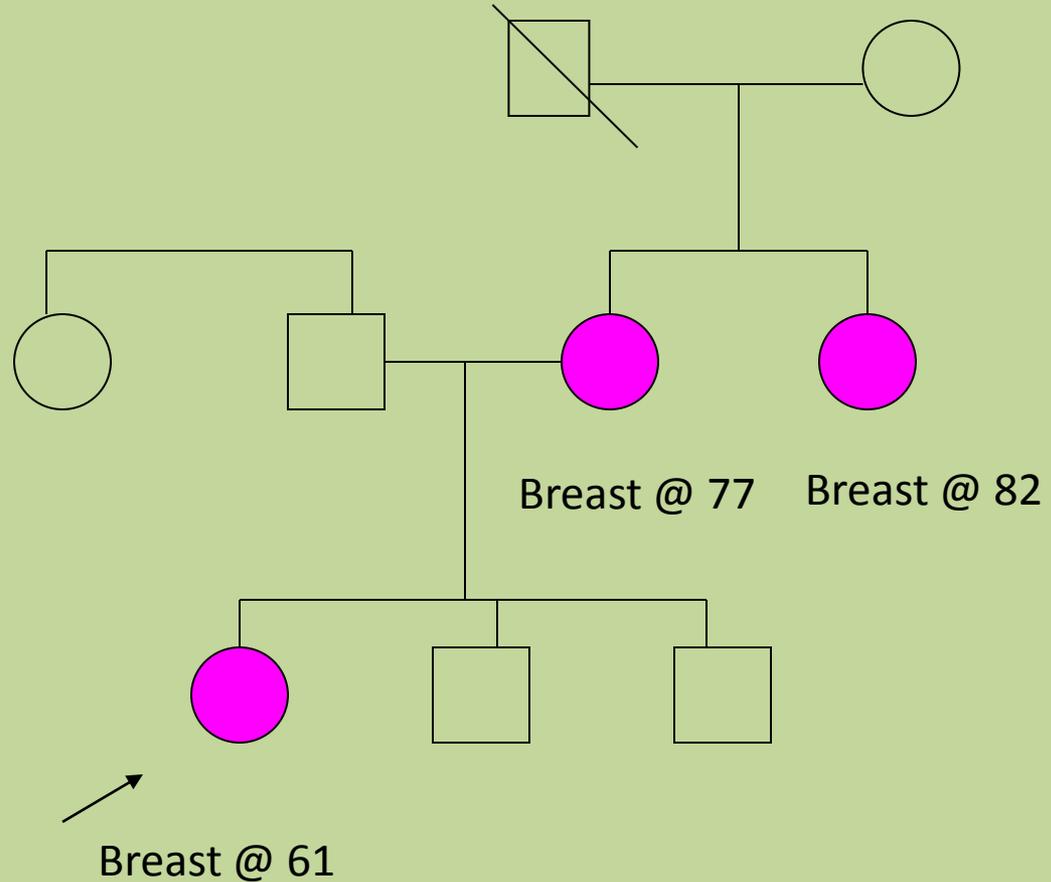
- Pattern of breast, ovary and other cancers
- Age of onset is early
- Multiple generation
- Multiple primary cancers





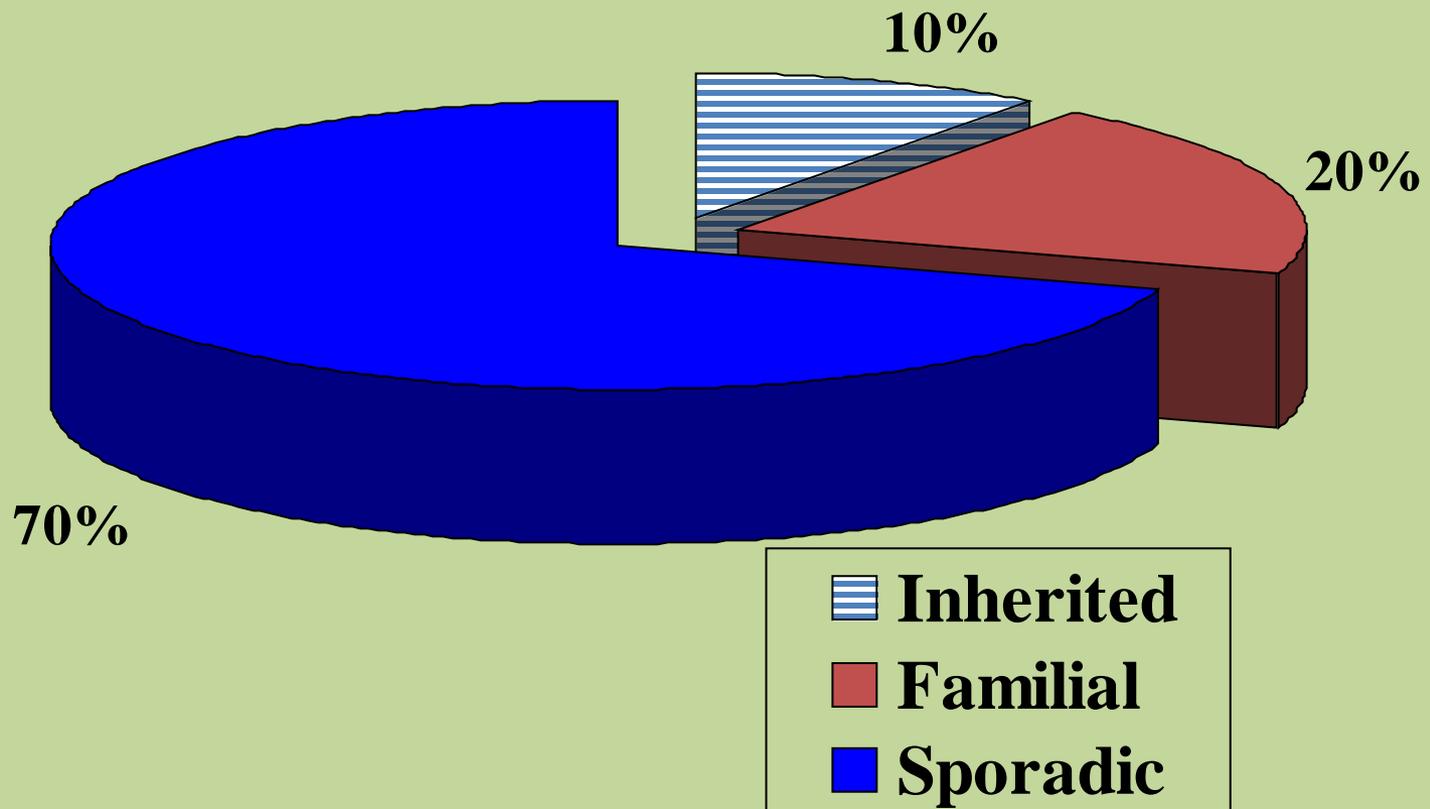
# Familial

- Clustering of breast cancer in same lineage
- Age of onset is typical
- Environment? Genetic? Both?





# Most cancer is not due to hereditary causes





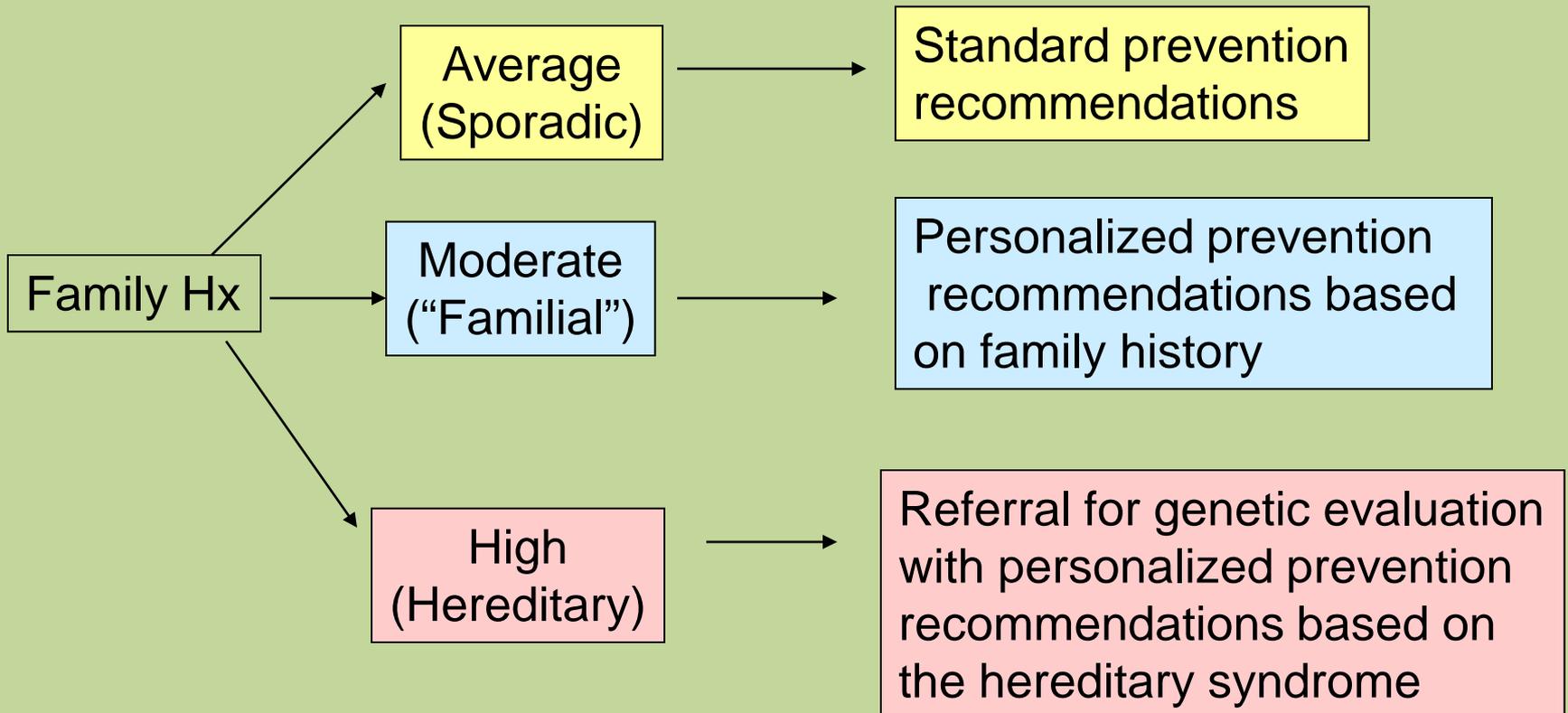
# Goal: Classification

## Who needs what?

Assessment

Risk Classification

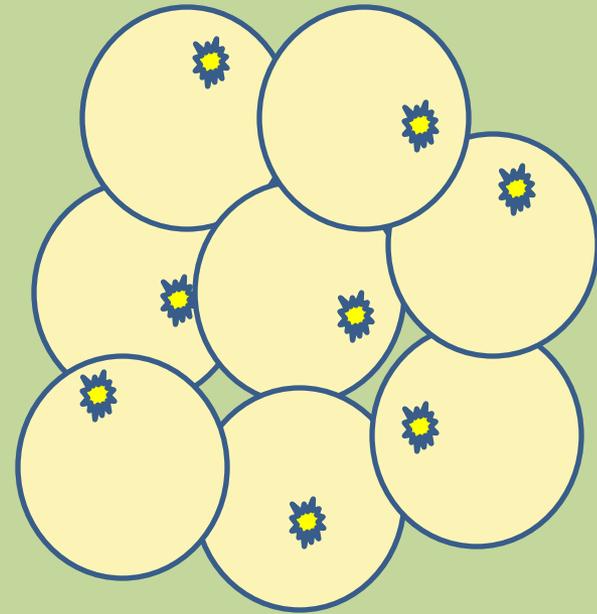
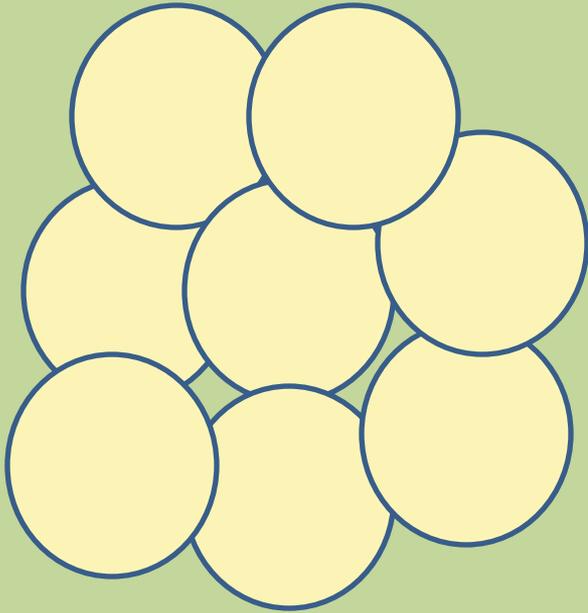
Intervention



Sporadic

Hereditary

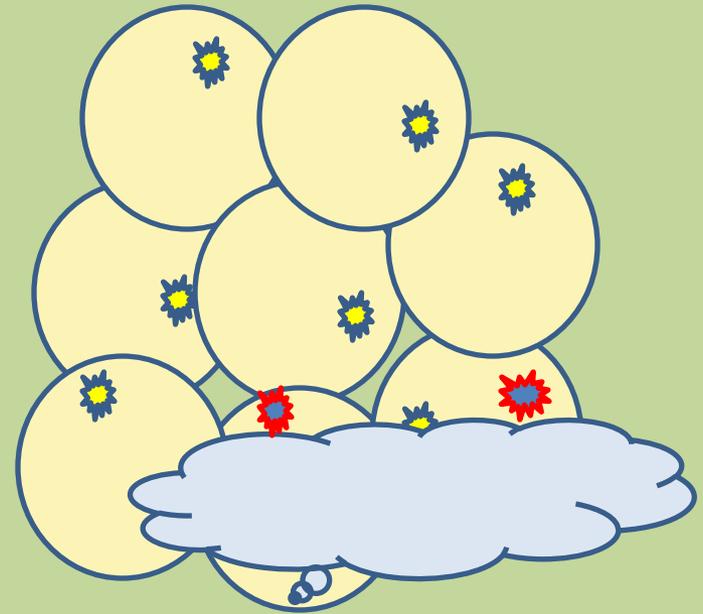
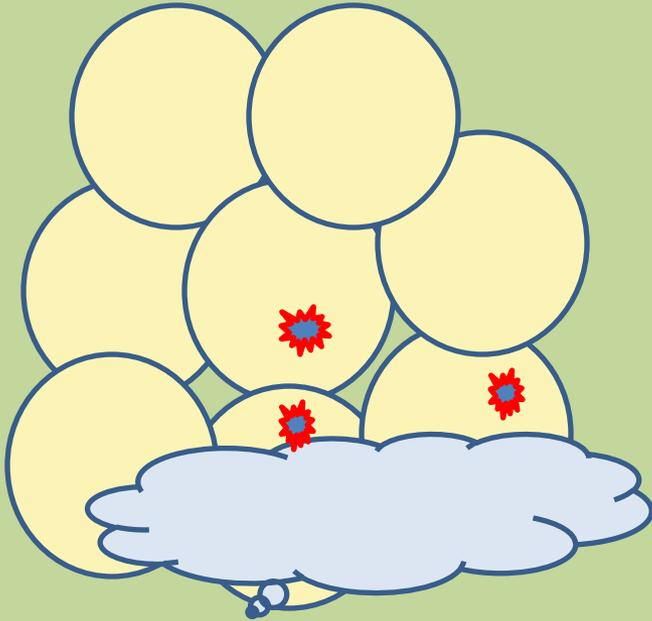
*At birth*



Sporadic

Hereditary

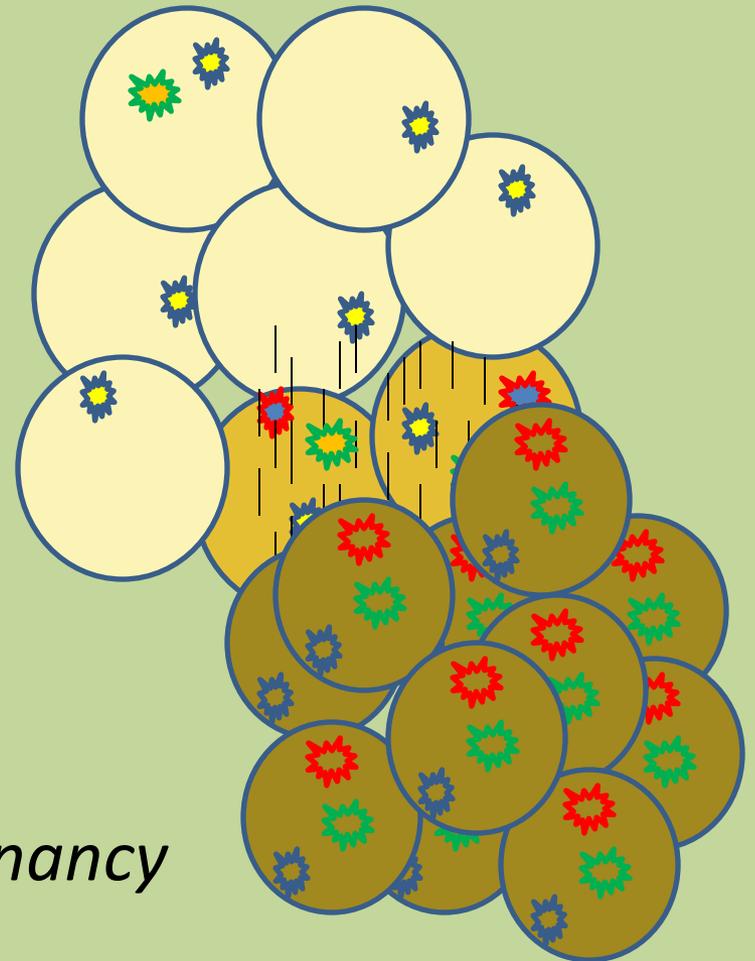
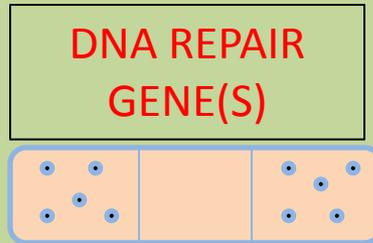
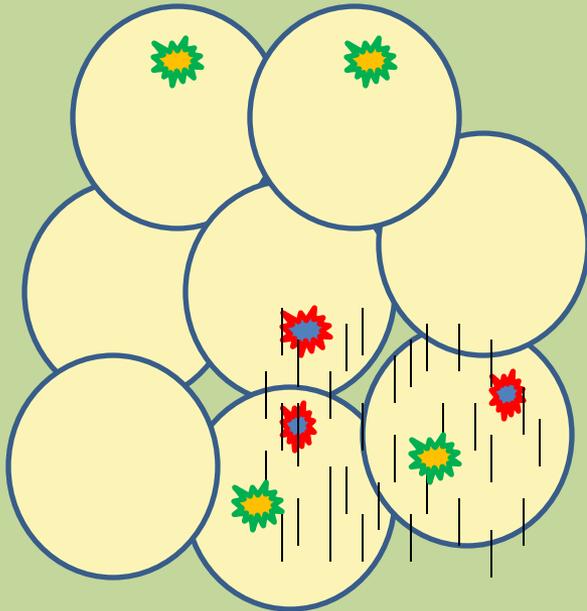
*~10-25 years*



Sporadic

Hereditary

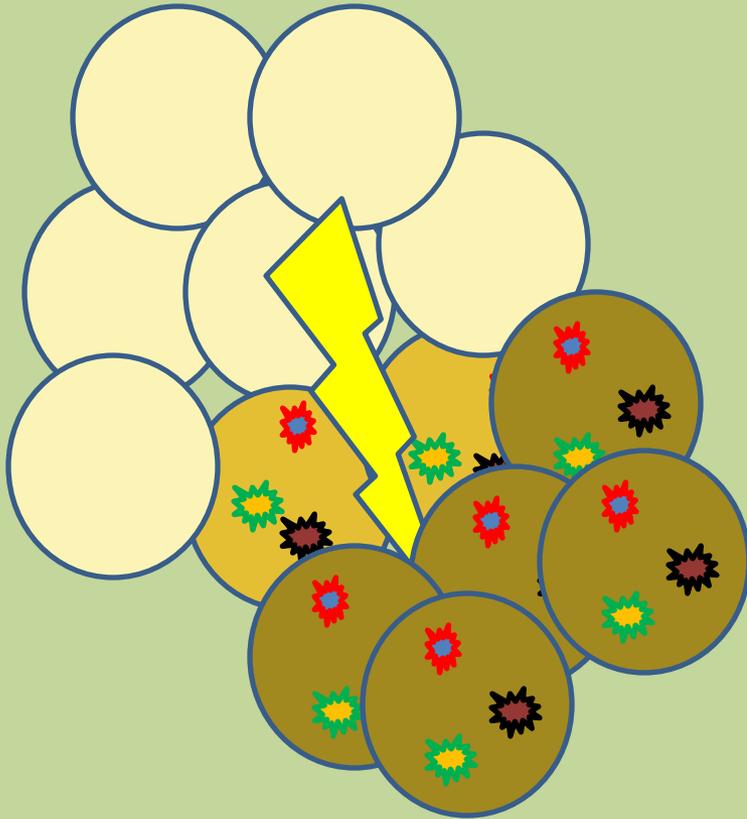
*~30-40 years*



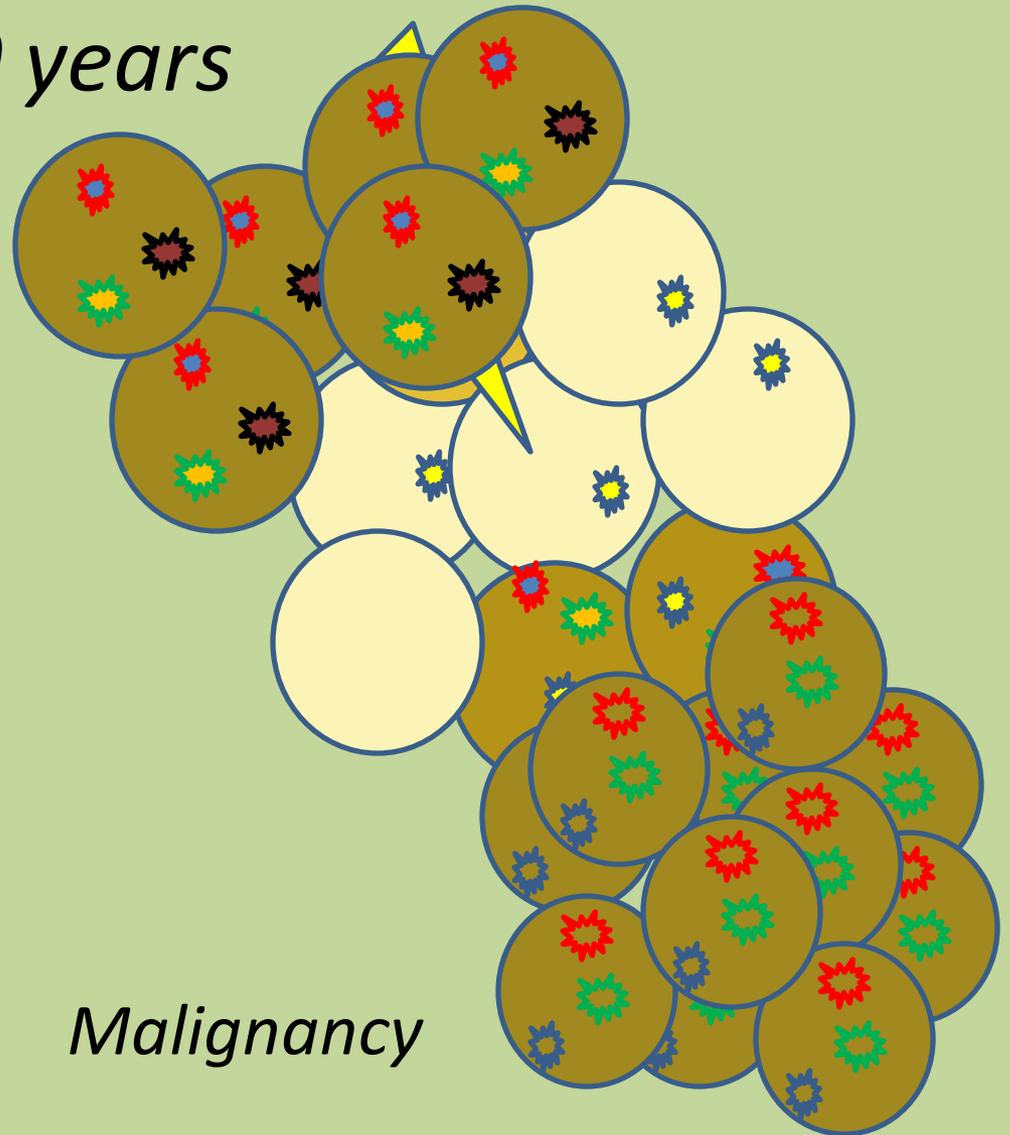
*Malignancy*

Sporadic

*~60-80 years*



Hereditary



*Malignancy*

# Summary

## Hereditary causes of cancer

- Earlier onset
- Higher risk
- At risk for more than one type of cancer



## Somatic vs. Inherited “germline” Genetic testing

- Hereditary “germline” genetic testing:
  - Ie. BRCA, TP53, PALB2
  - Test is done on blood
  - To determine if a person was born with a predisposition to cancer.
- Somatic genetic testing:
  - Ie. Her2neu, KRAS, BRAF, OncotypeDX
  - Test is done on the tumor cells.
  - To determine specific characteristics of the tumor for treatment decisions.

Hereditary cancer genes are good genes to have.





# BRCA1 and BRCA2 mutation carriers

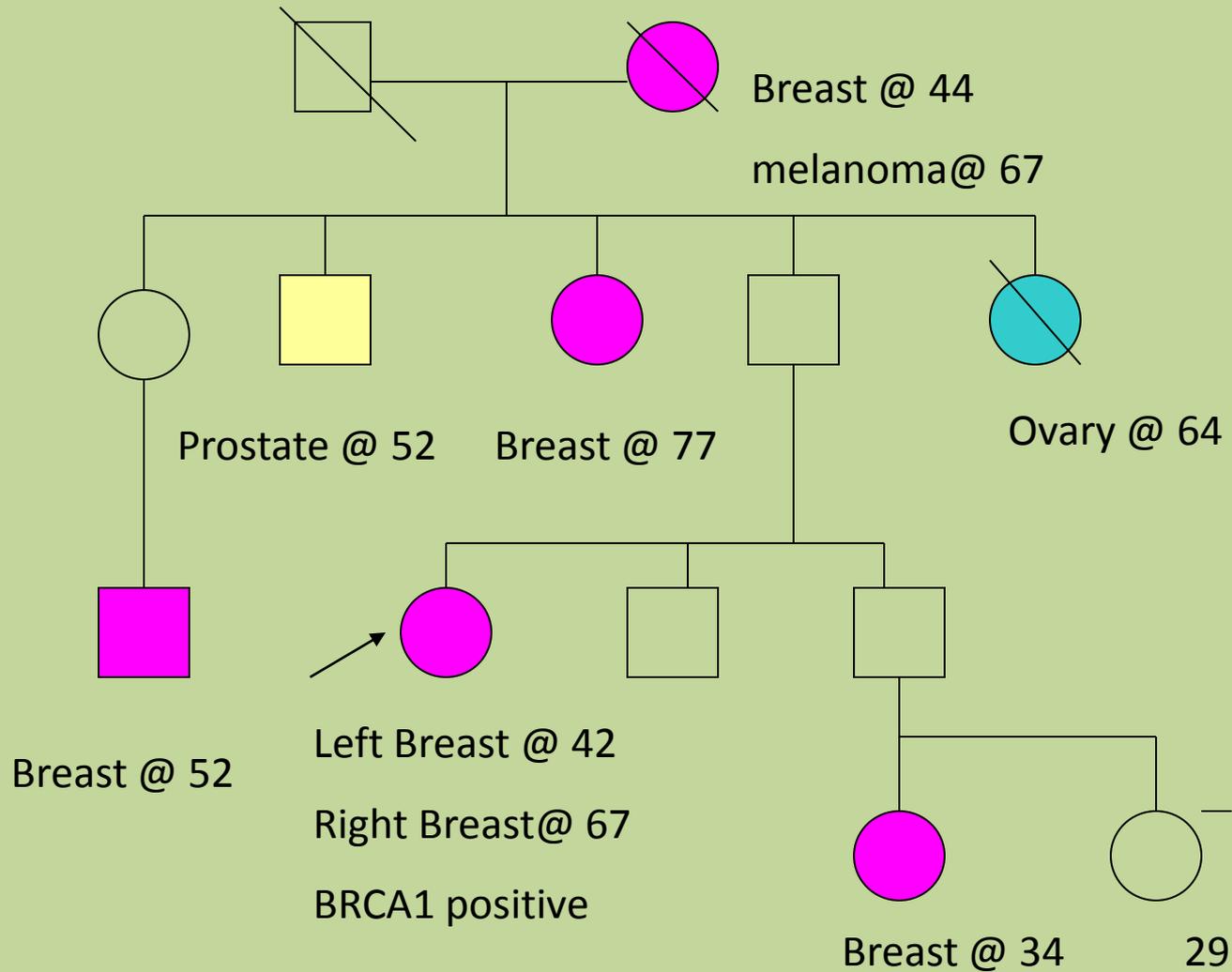


Hereditary Breast and  
Ovarian Cancer  
Syndrome (HBOC)





# Classic BRCA family





# Risks for cancer for BRCA1 and 2 carriers

Type of Cancer	General Population	BRCA1 mutation	BRCA2 mutation
Breast (women)	12%	50-80%	40-80%
Breast (men)	Less than 1%	1-2%	6%
Ovarian	1.4%	40-50%	10-30%
Fallopian tube, primary peritoneal	<1%	2-3%	2-3%
Colon	5%	Possibly increased for women	Unknown
Prostate	10%-15%	Increased	20%
Pancreas	1%	1.4%	3%-7%
Melanoma, stomach, buccal/phary nx	Various	-	1-2%
Gallbladder/bile ducts	-	-	1-2%

*Women with BRCA1 or BRCA2 mutation who have had breast cancer and did not have bilateral mastectomies have a 40—60% risk for a new breast cancer in the opposite breast.*



# Medical Management

## For Women:

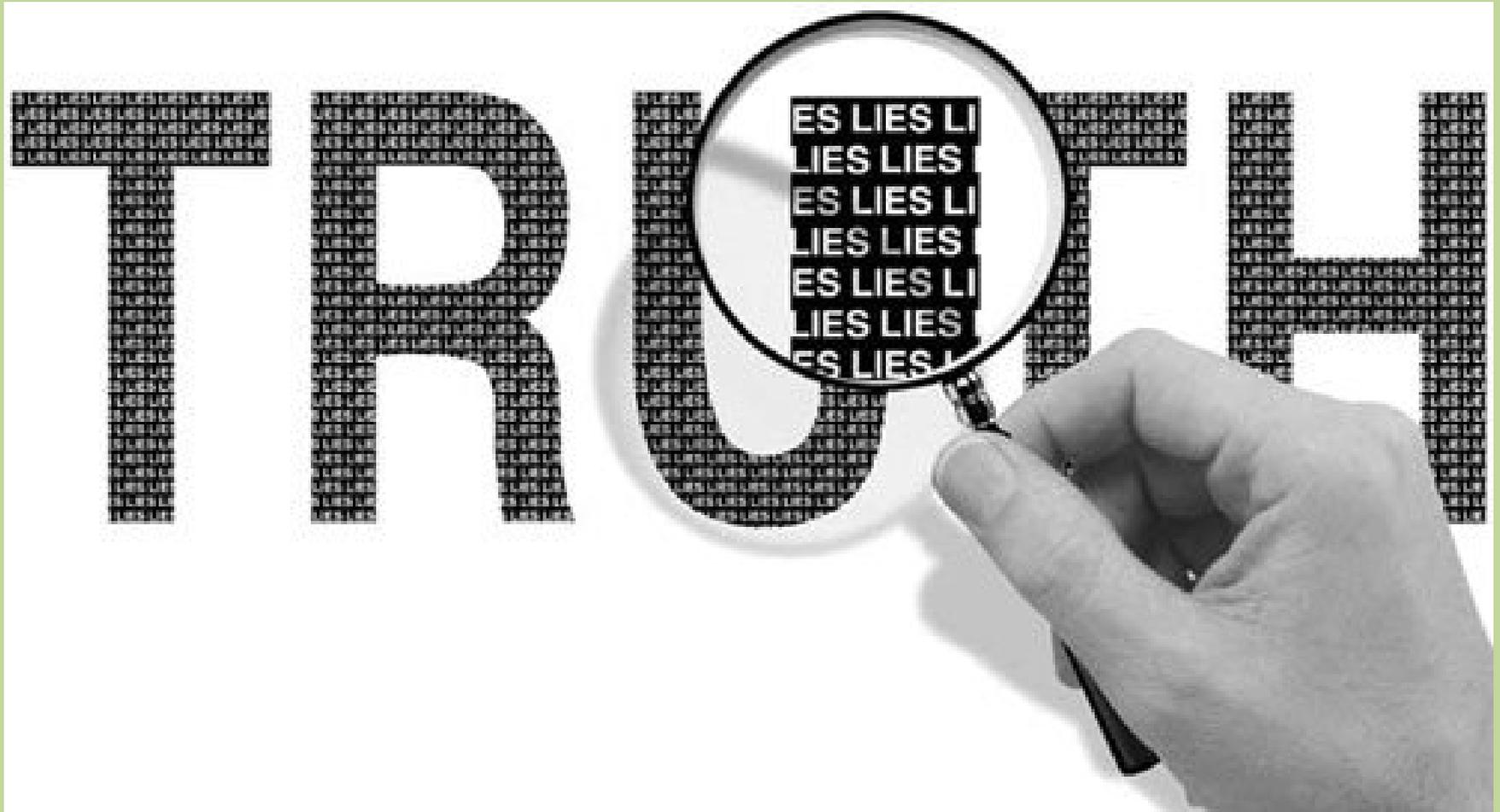
- **Breast:** Annual MRI @ 25. Annual mammogram @ 30
- **Ovarian:** Consider screening versus surgical risk reduction
- Risk reducing surgery:
  - Bilateral mastectomy
  - Salpingo-oophorectomy ideally between 35 and 40 and after childbearing or earlier depending on earliest ovarian cancer in family
- Risk reducing agents: (Chemoprevention): tamoxifen/raloxifene

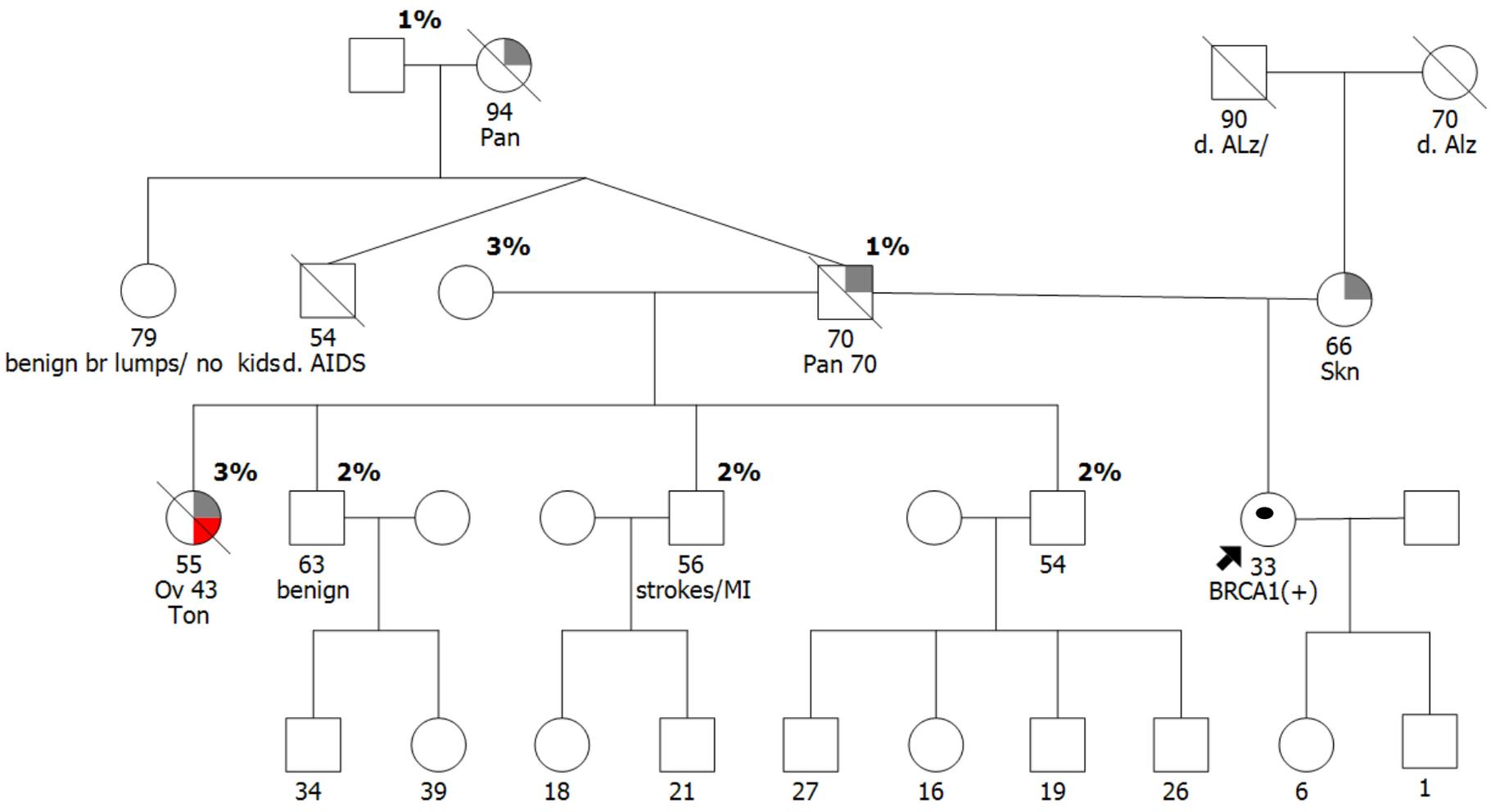
## For Men:

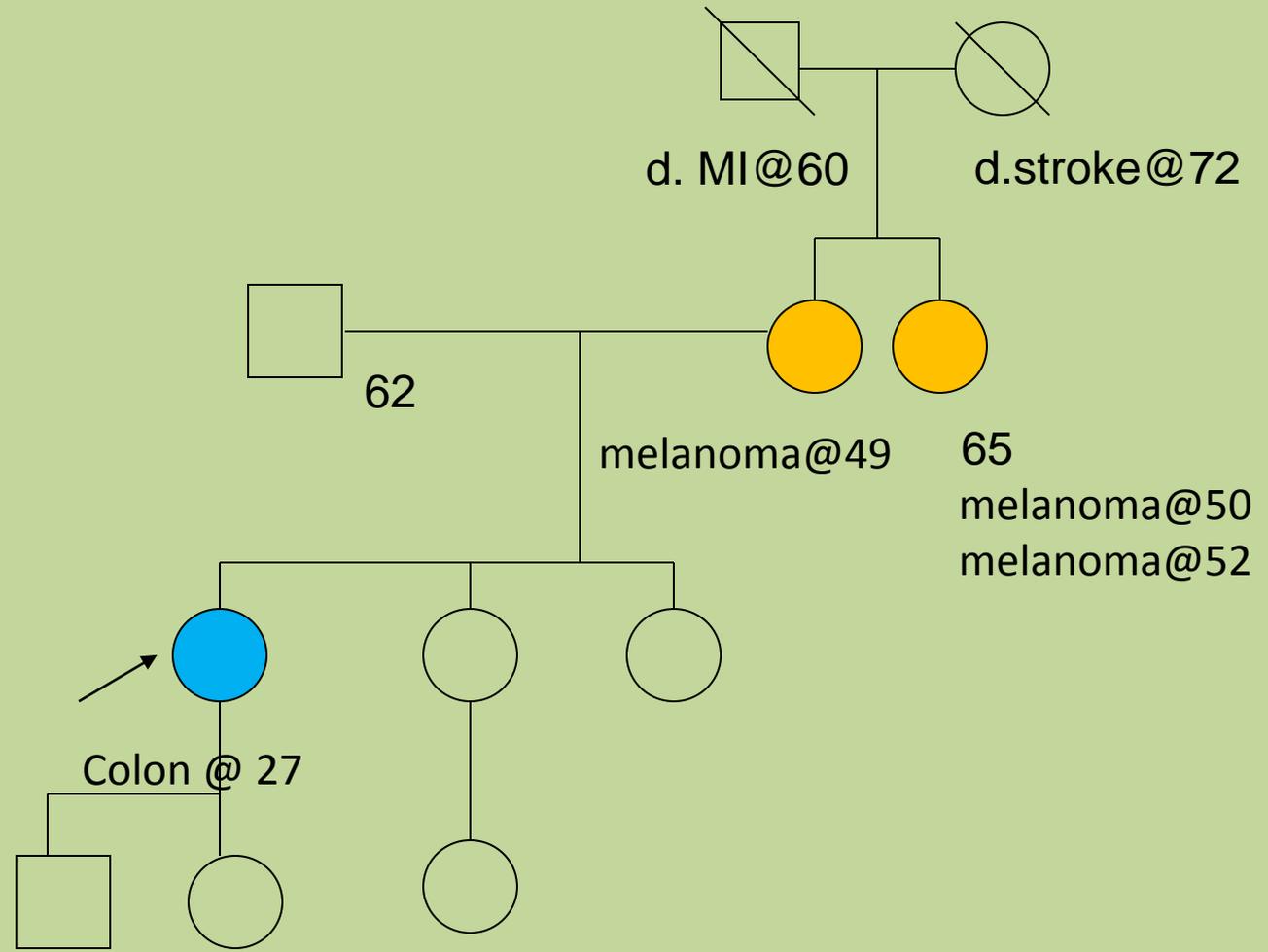
- Prostate cancer: Adhere to screening guidelines. Consider baseline digital rectal exam (DSE) and PSA level at age 40.
- Breast cancer: monthly self-breast examination and education starting at 35 and clinical breast exam twice a year starting at age 35. Consider baseline mammogram at age 40.

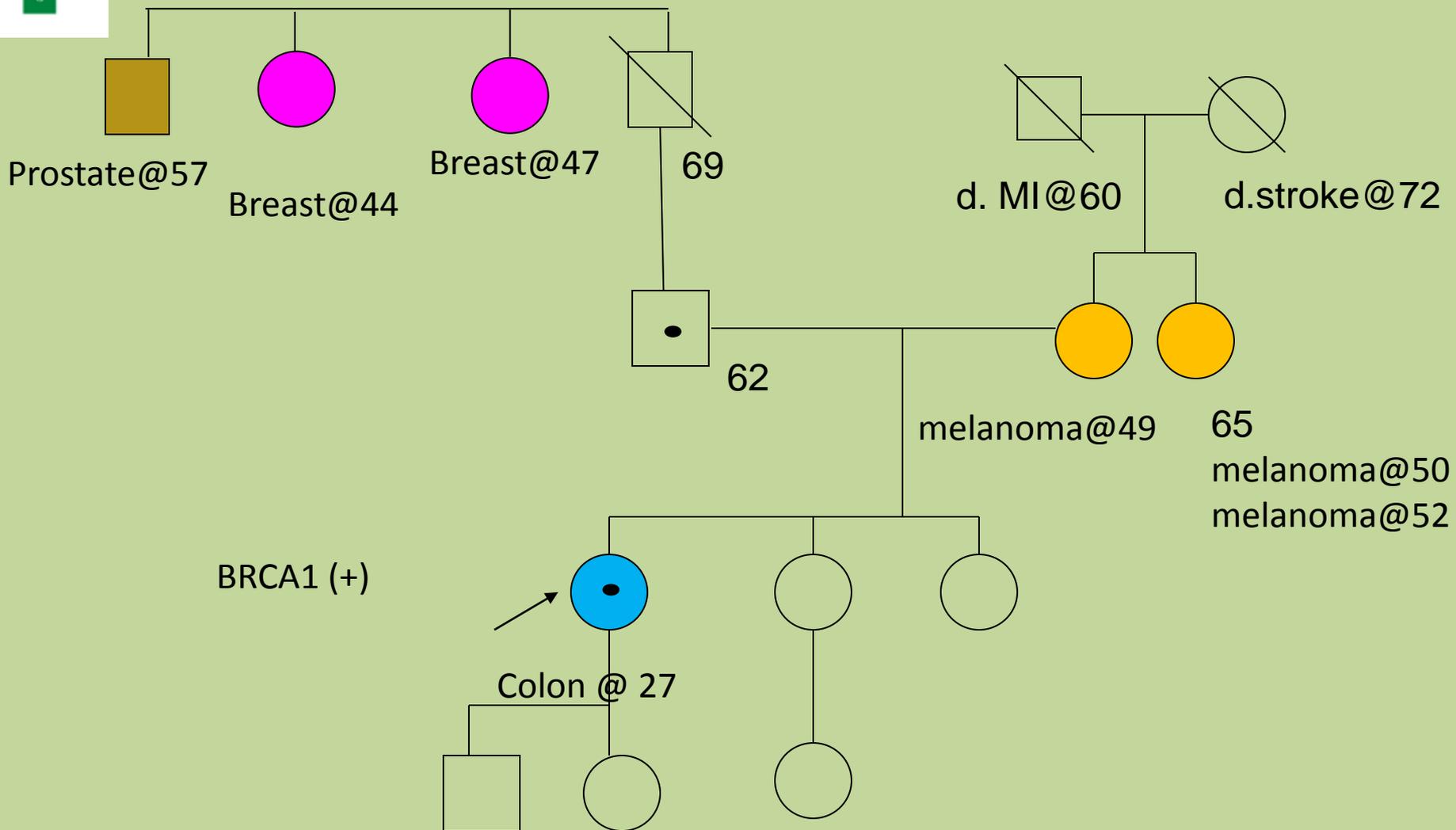


# Don't be fooled











## The New York Times

- Study Shows Third Gene as Indicator for Breast Cancer

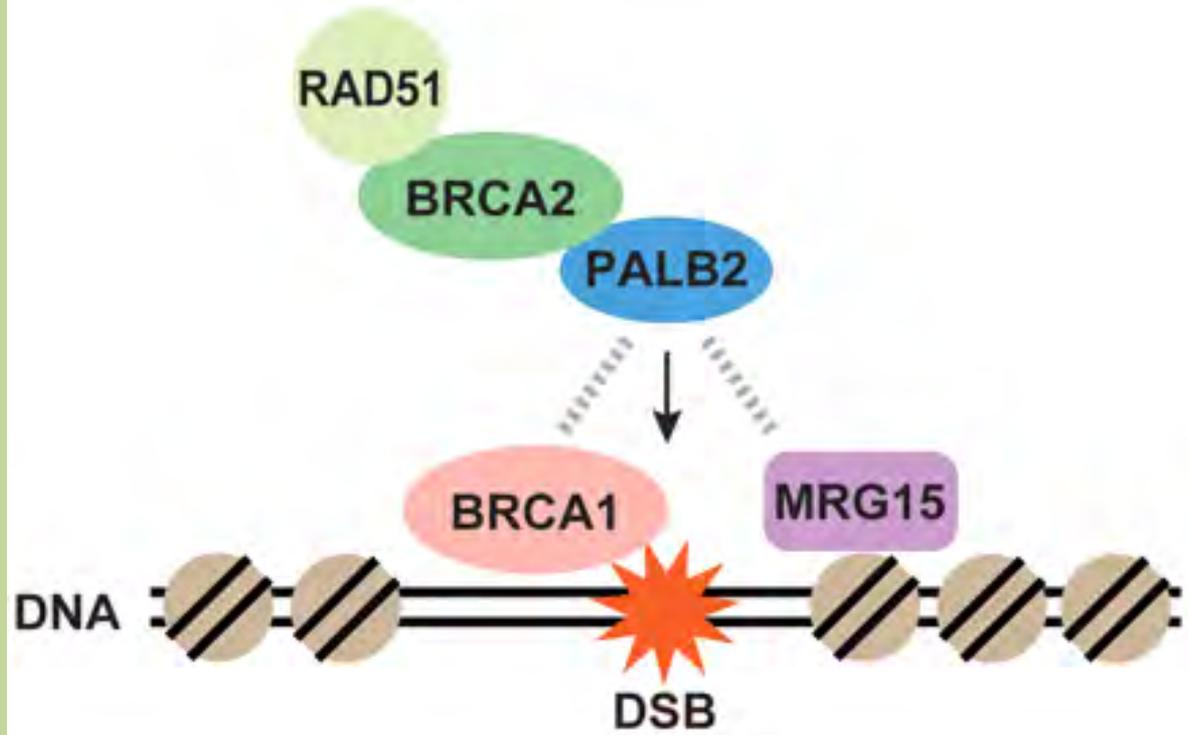
# PALB2

The next “BRCA3”  
gene???

Women'sHealth

The New Breast Cancer Gene  
You Need to Know About





**Fig. 6.**

**Proposed model for the role of PALB2 in linking MRG15 and the BRCA complex into a pathway of HR.** We propose that by directly binding PALB2, BRCA1 and MRG15 independently regulate site selection and chromatin accessibility, respectively, in PALB2 recruitment to sites of DNA damage. Once it is localized, PALB2 is proposed to be responsible for the recruitment of BRCA2 and RAD51.

# PALB2

- Breast cancer: 2-6 fold risk
- Pancreatic: “increased”
- Other: ???

# ATM

Autosomal Recessive:

Ataxia Telangiectasia (AT)



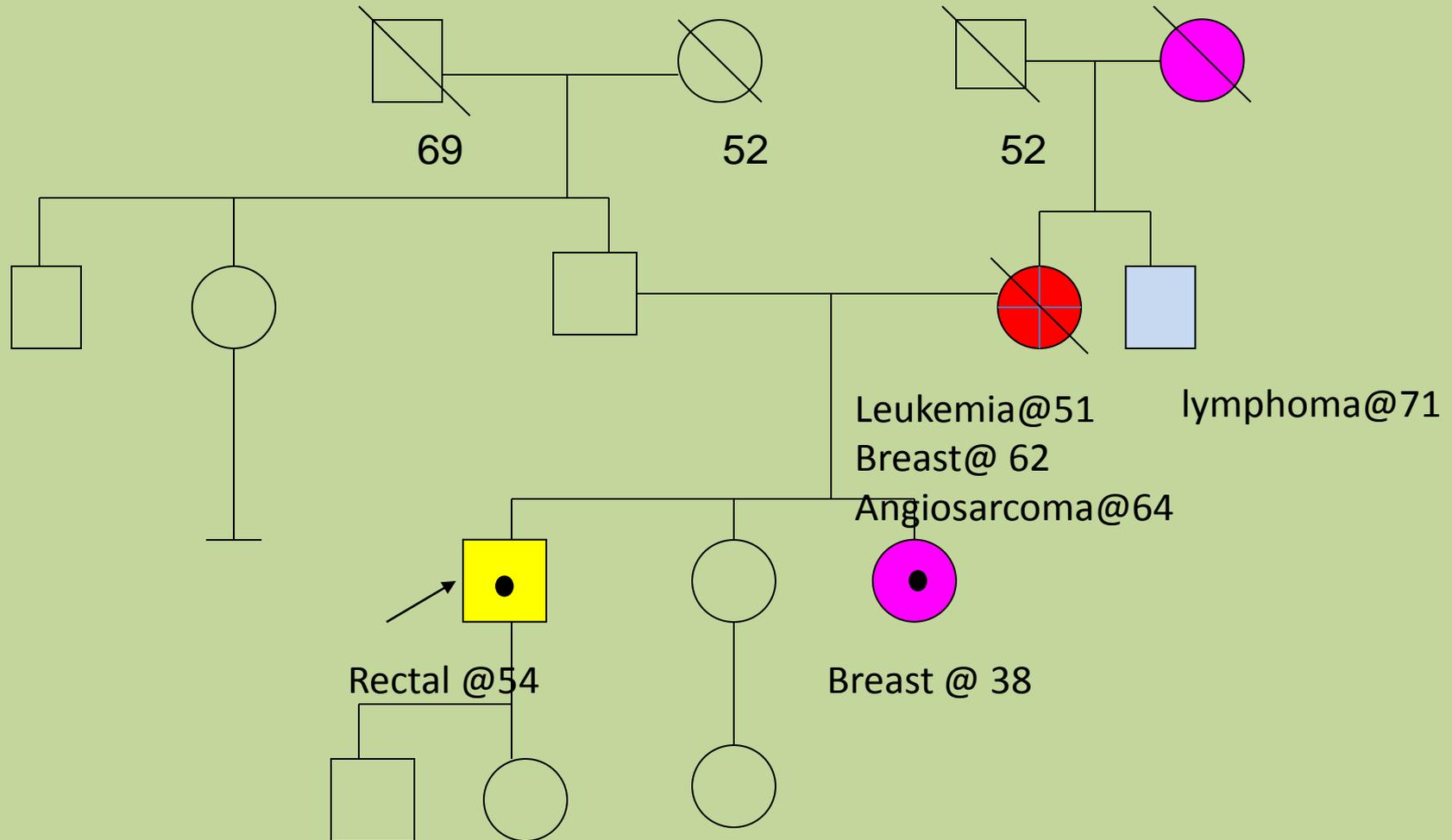
*Imagine...  
all four children have AT.*

**KIDS.  
HOPE.  
CURE.**

- Cerebellar ataxia
- Oculomotor apraxia
- Choreoathetosis
- Telangiectasias
- Immunodeficiency
- Leukemia/lymphoma
- Sensitive to ionizing radiation

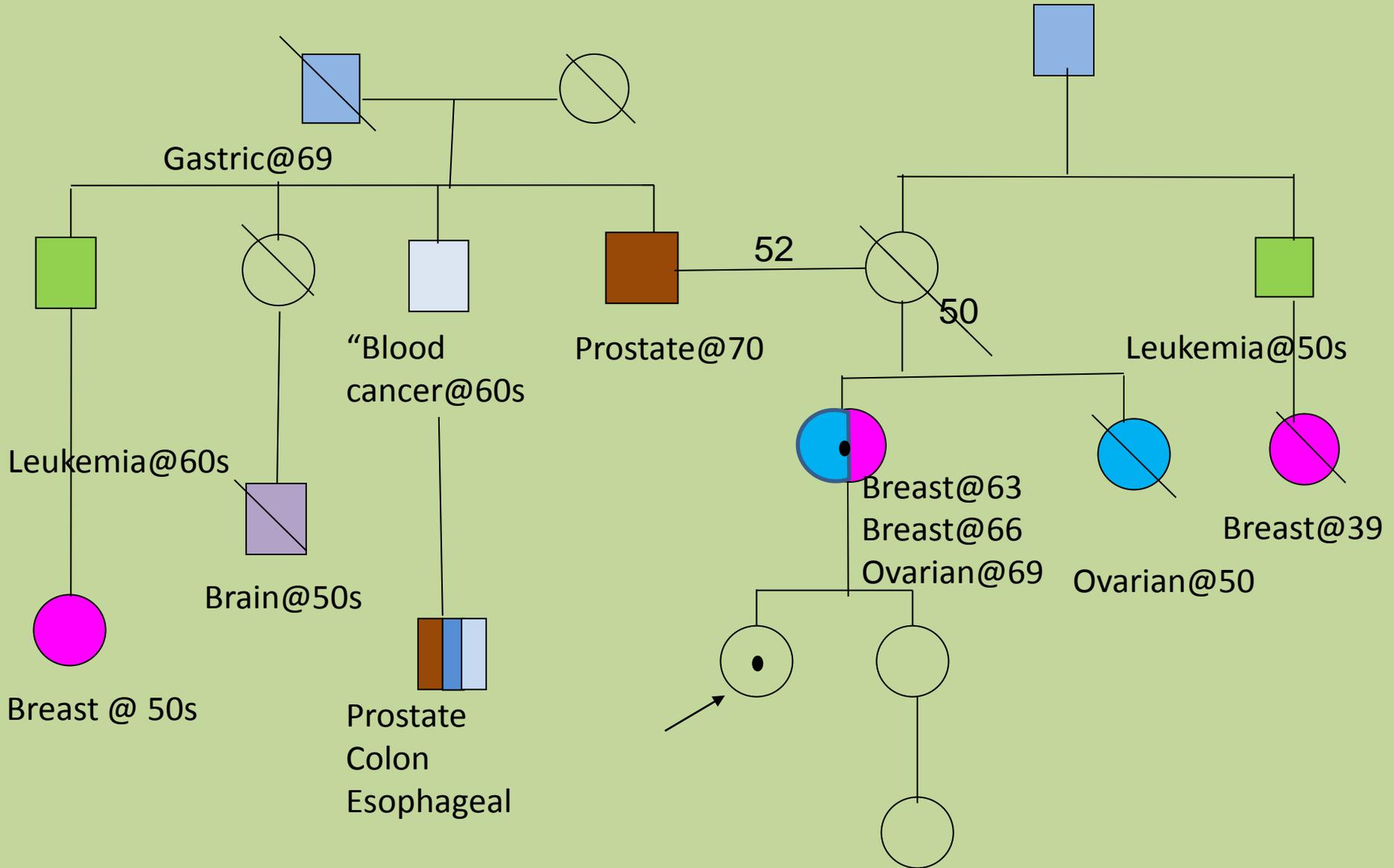


# ATM: Heterozygote

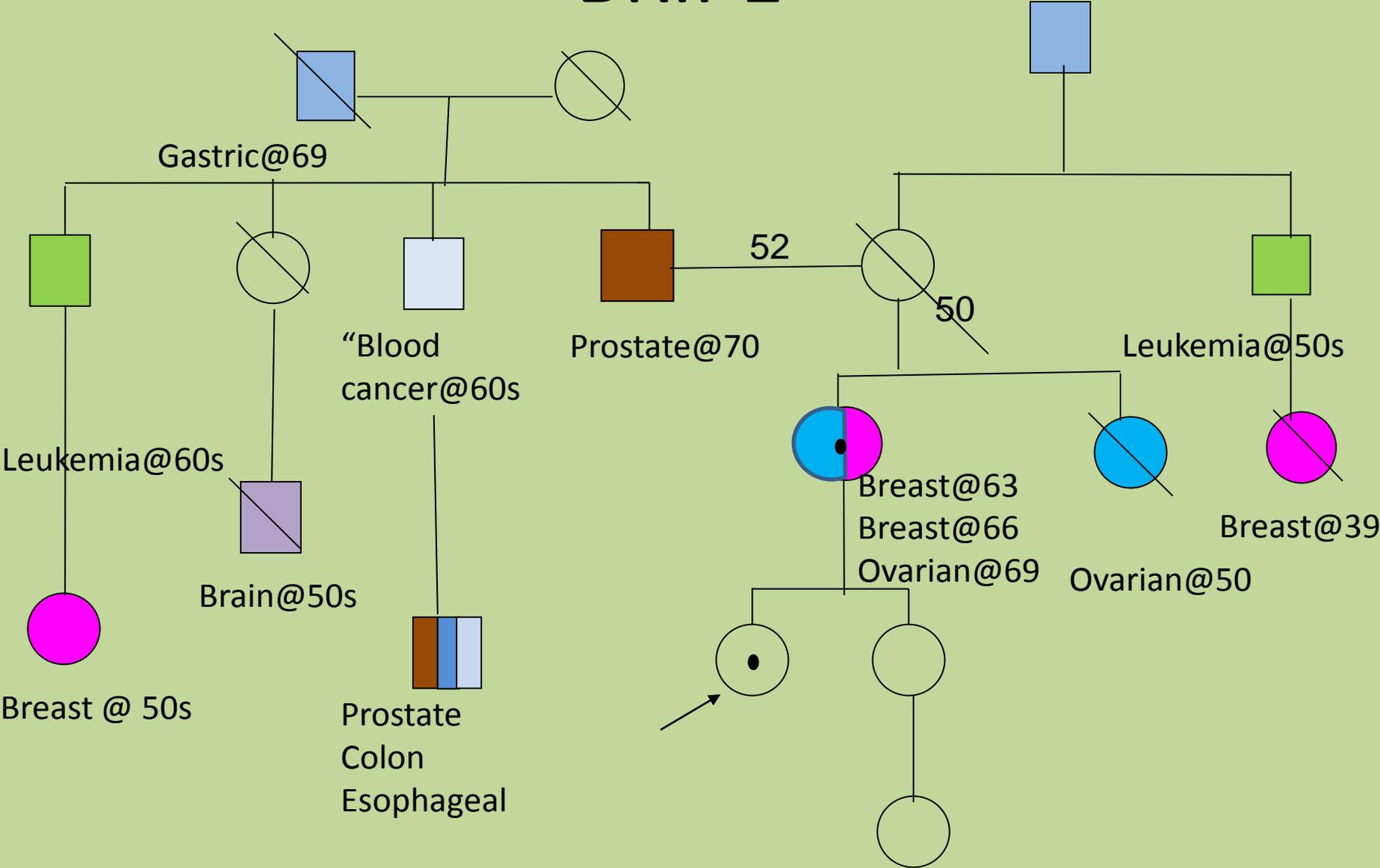


Increased risk for pancreatic, breast, leukemia/lymphoma.

Sensitive to radiation like the homozygotes?

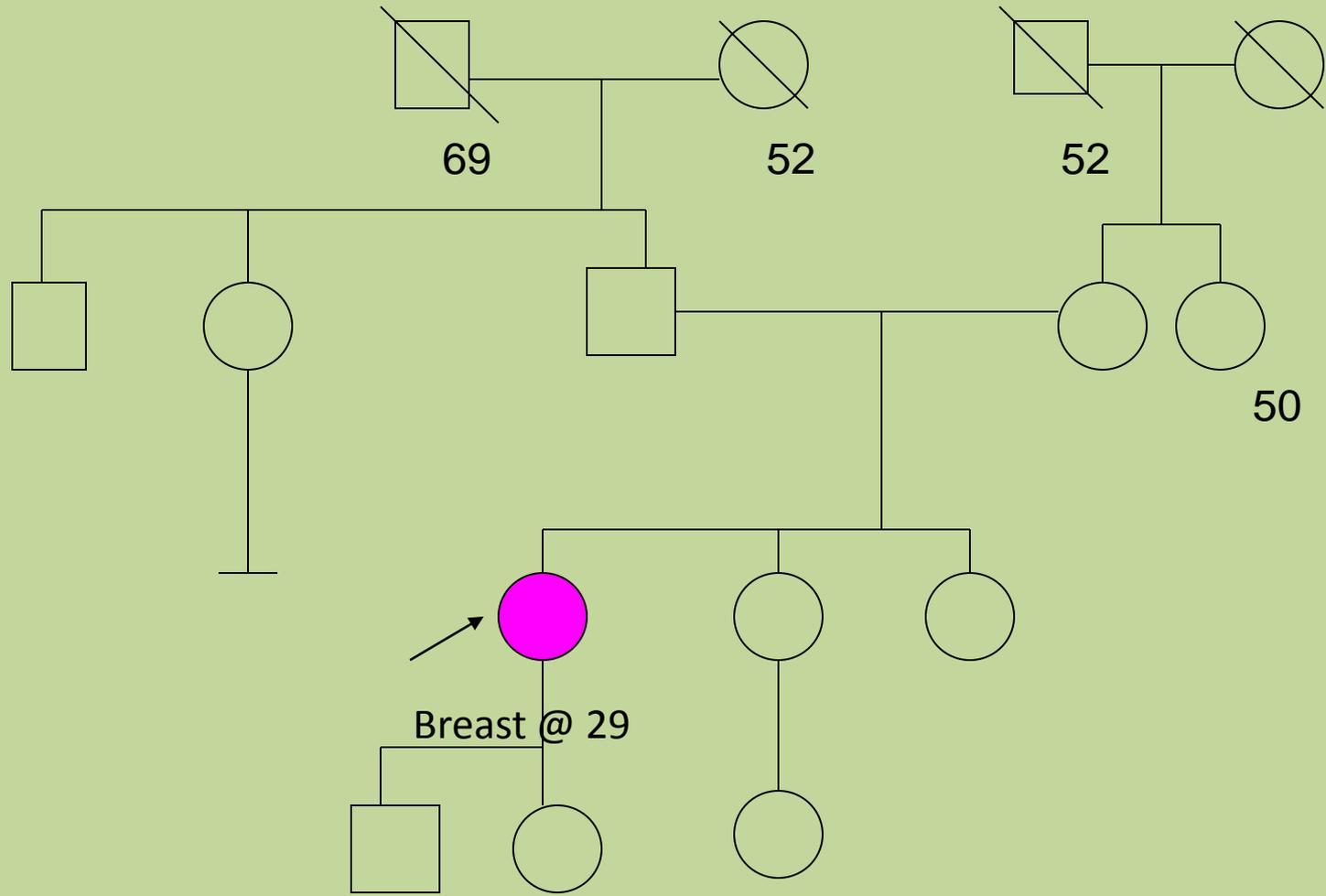


# BRIP1



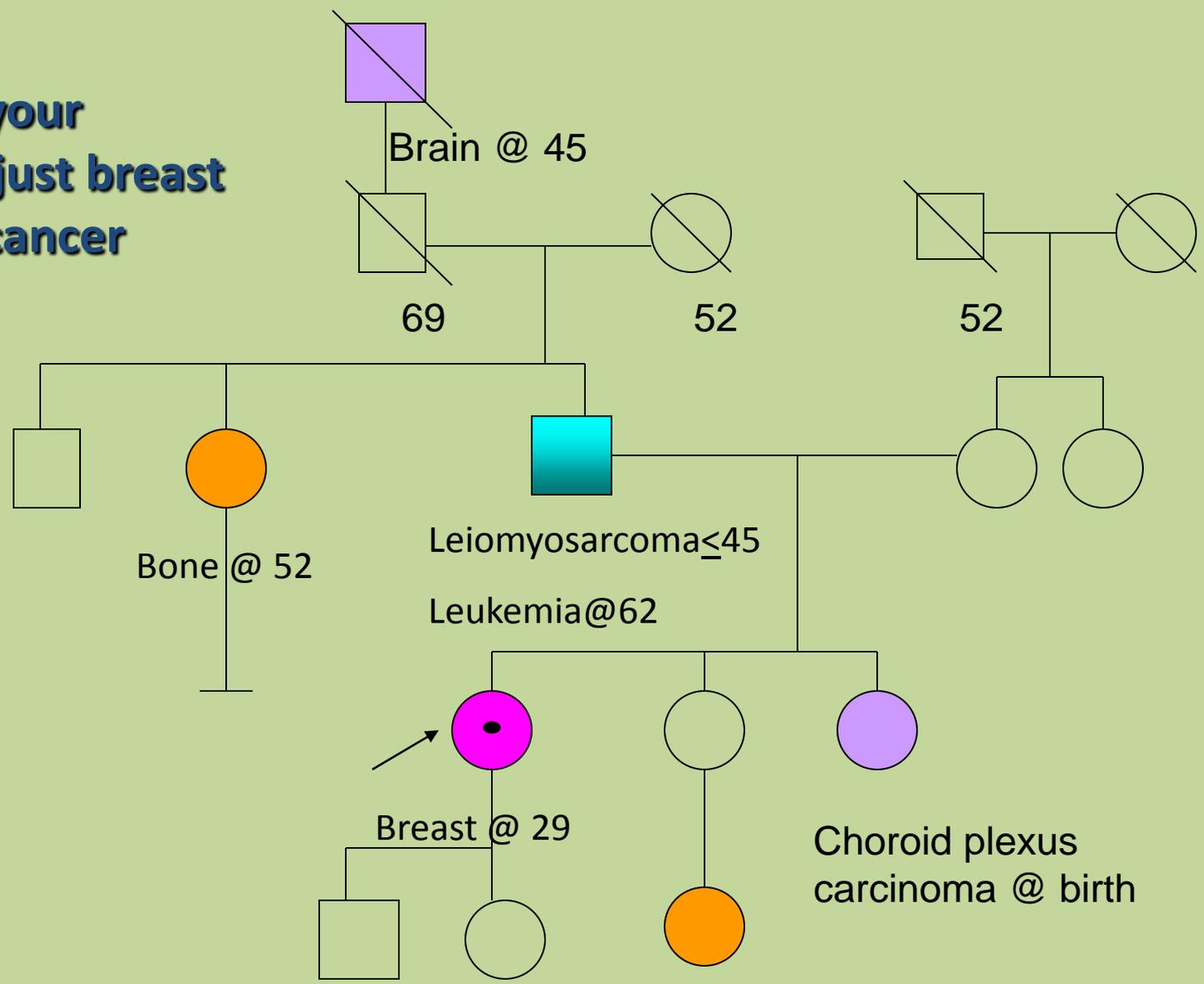


No Breast or Ovarian cancer in the family. BRCA1/2 negative.





**Do not limit your questions to just breast and ovarian cancer**





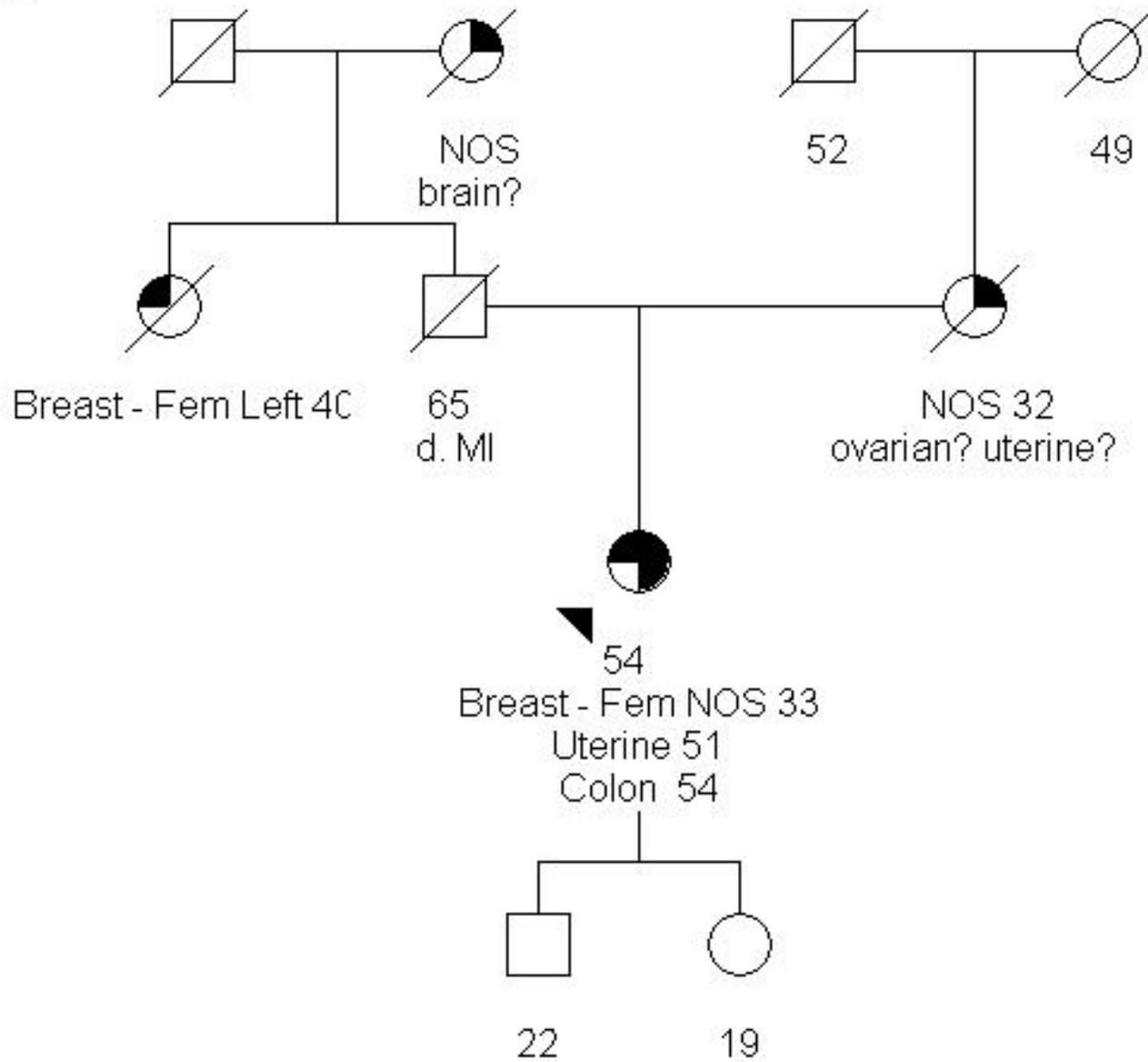
# Other syndromes: LFS

- Li Fraumeni (TP53):
  - breast, sarcoma, leukemia/lymphoma, adrenocortical tumor, brain (colon, choroid plexus carcinoma, and others)
  - LFS classic criteria: <45 with sarcoma + FDR under 45 + FDR/SDR under 45 or sarcoma at any age.
  - Management:
    - High risk breast screening similar to BRCA carriers.
    - Annual physical exam with skin and neurological exam
    - Colonoscopy every 2-5 years starting at 25
    - Full body MRI
    - Educate patients on signs/symptoms of cancer
    - Counsel about limitations of testing,
    - Sensitive to ionizing radiation?



# Family E

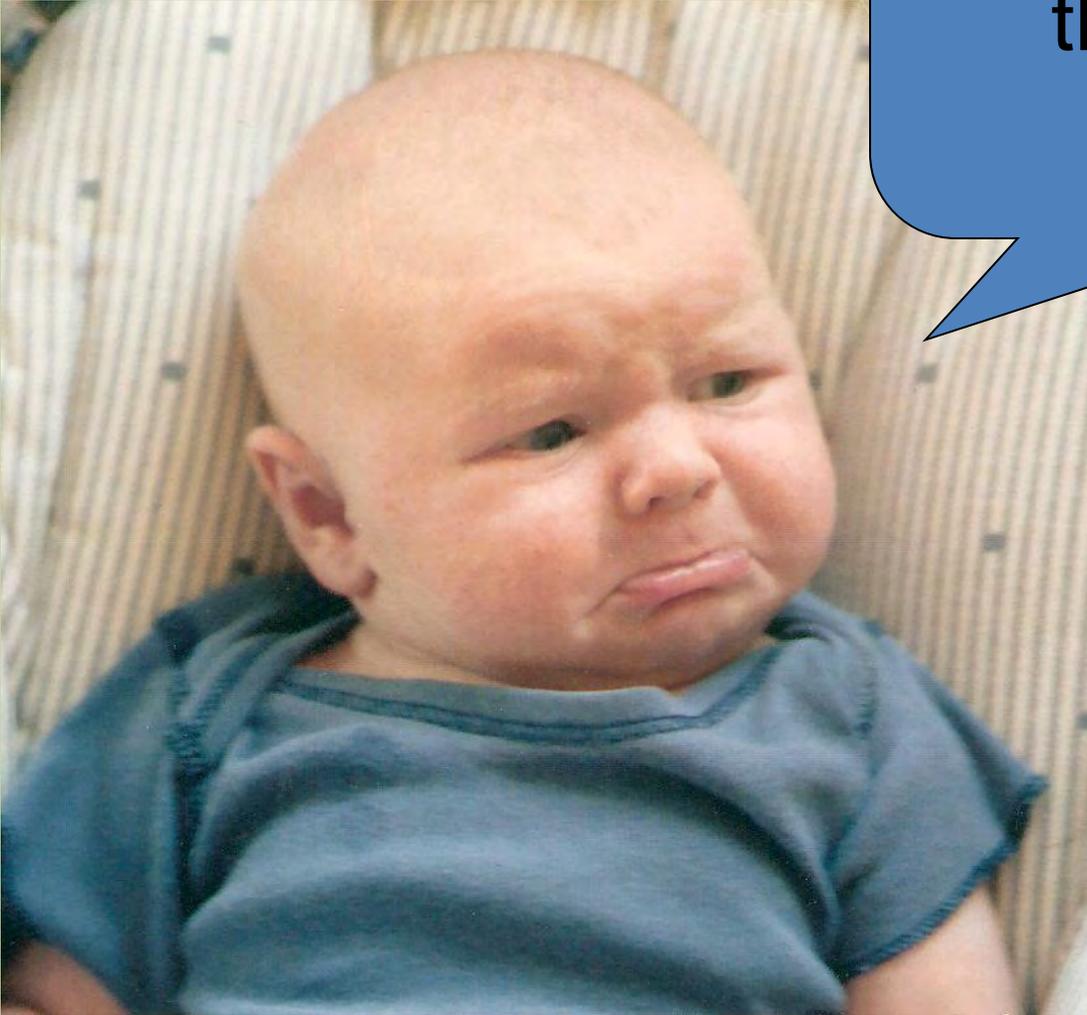
3/15/2009



# Lynch Syndrome Cancer Risks

Cancer	Lynch Syndrome Risk by Age 70	General Population Risk by Age 70
Colorectal	80%	5%
Uterine	60%	2.7%
Ovarian	12%	1.4%
Stomach	12%	1%
Small Bowel	1-4%	<1%
Ureter/Renal Pelvis	4%	<1%
Brain (glioblastoma)	4%	<1%
Pancreatic/Biliary	2%	<1%

“I don't wanna do  
the prep doc?”



# Lynch Syndrome Surveillance

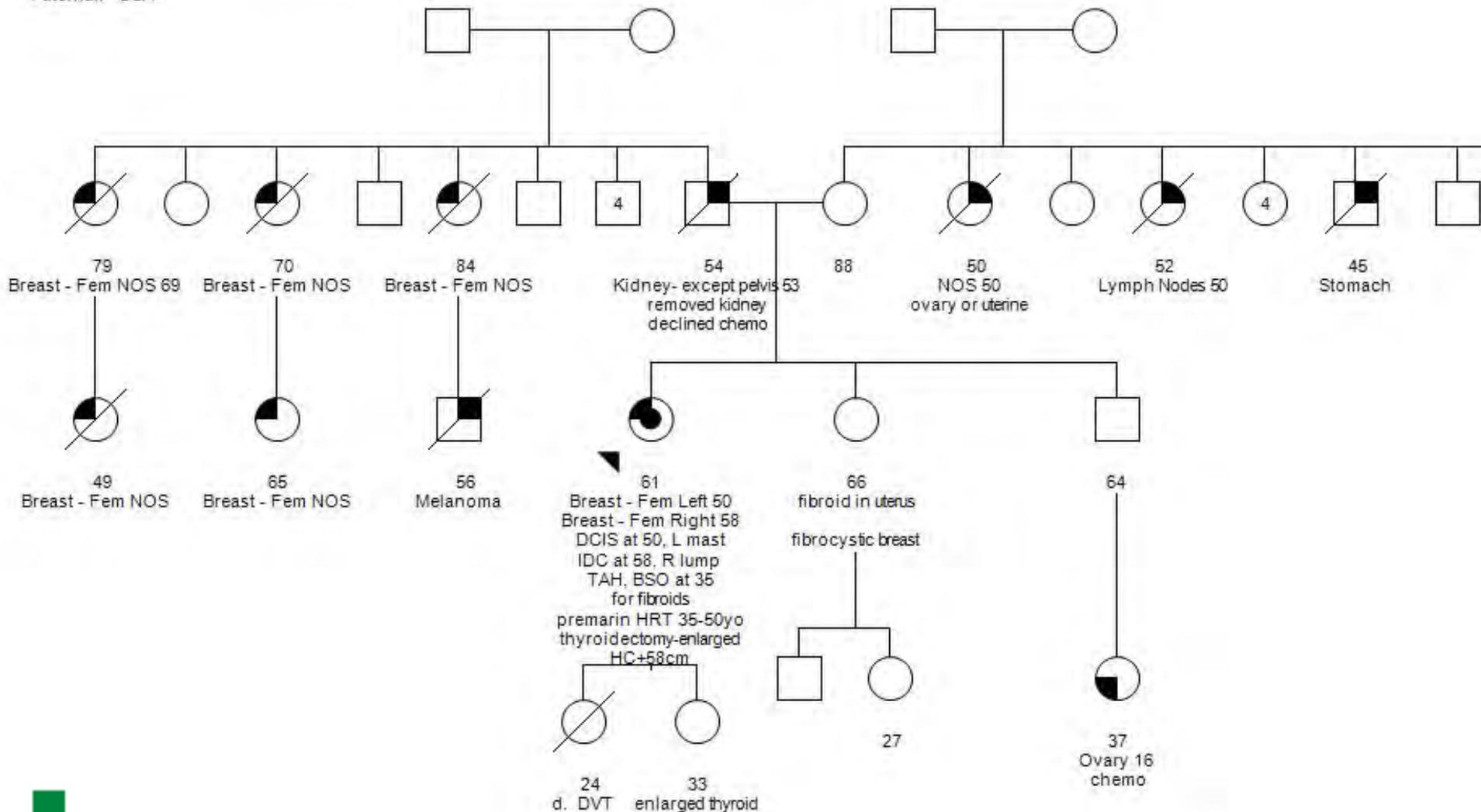
Site	Procedure	*Begin at	How often?
Colon	colonoscopy	20-25*	1-2 years
Stomach/ sm. bowel	Upper EGD/capsule	30-35	1-5 years

\*Or 5-10 yrs prior earliest dx in family, whichever comes first

- Consider annual urinalysis
- Yearly physical exam

-  Cancer Table.CancerDiagnosis = Breast - Fem Right
-  Cancer Table.Cancer Diagnosis = Lymph Nodes
-  Cancer Table.Cancer D
-  Cancer Table.CancerDiagnosis = Breast - Fem Left
-  Cancer Table.Cancer Diagnosis = Stomach
-  Cancer Table.CancerDiagnosis = Kidney- except pelvis
-  Cancer Table.Cancer Diagnosis = Breast - Fem NOS

ANCESTRY:  
Maternal: USA  
Paternal: USA





# Other Syndromes: Cowden

- Cowden Syndrome (PTEN)
  - Breast, uterine, thyroid (papillary, follicular)
  - Criteria: 2 major or 1 major + 2 minor
    - Major: breast/uterine/thyroid cancer, mucocutaneous lesions, macrocephaly (>97<sup>th</sup> percentile), multiple GI hamartomas/ganglioneuromas
    - Minor: RCC, fibroids, lipomas, fibroma, MR, autism, thyroid nodule/goiter/adenoma, single hamartoma/ganglioneuroma



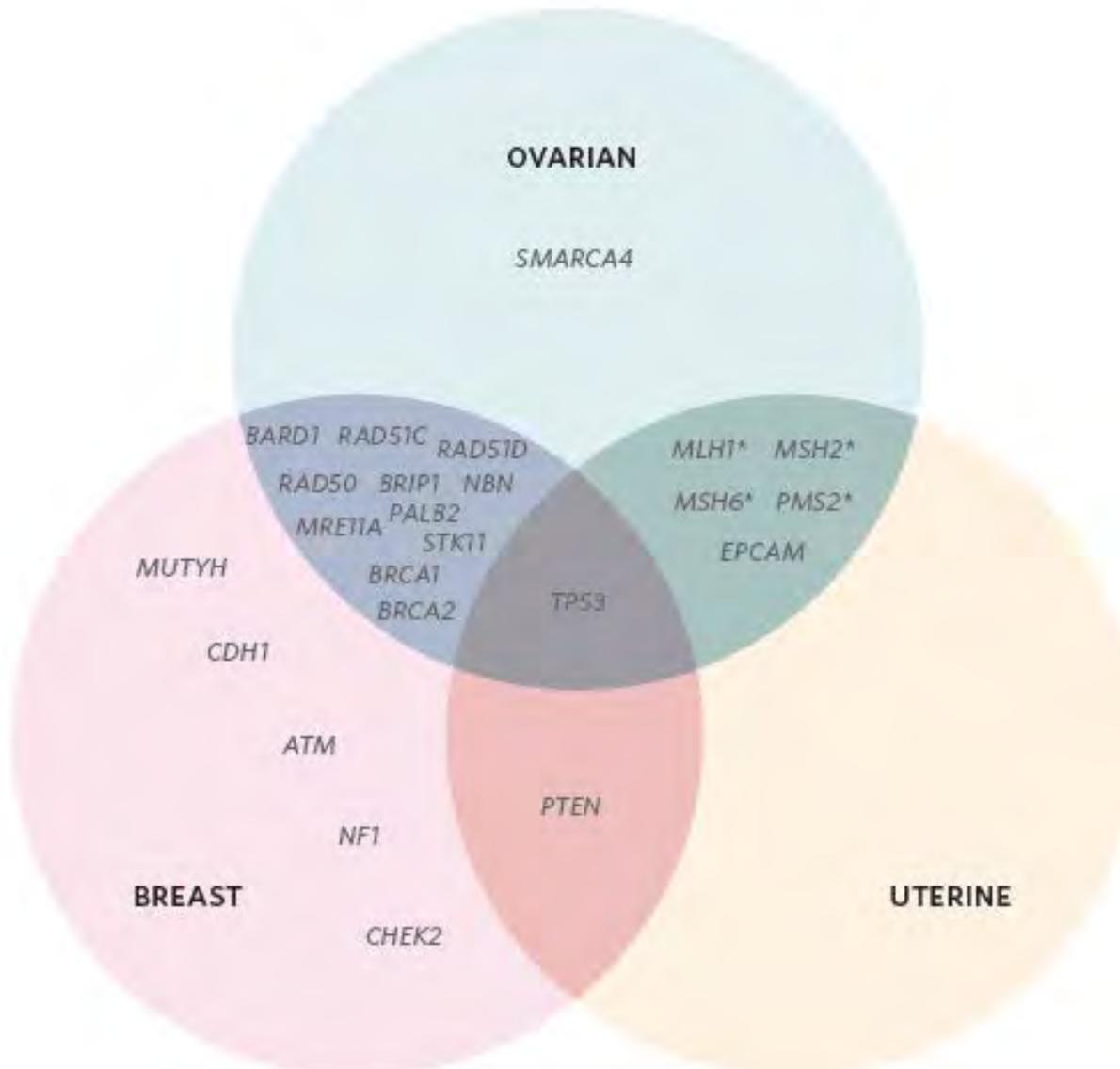


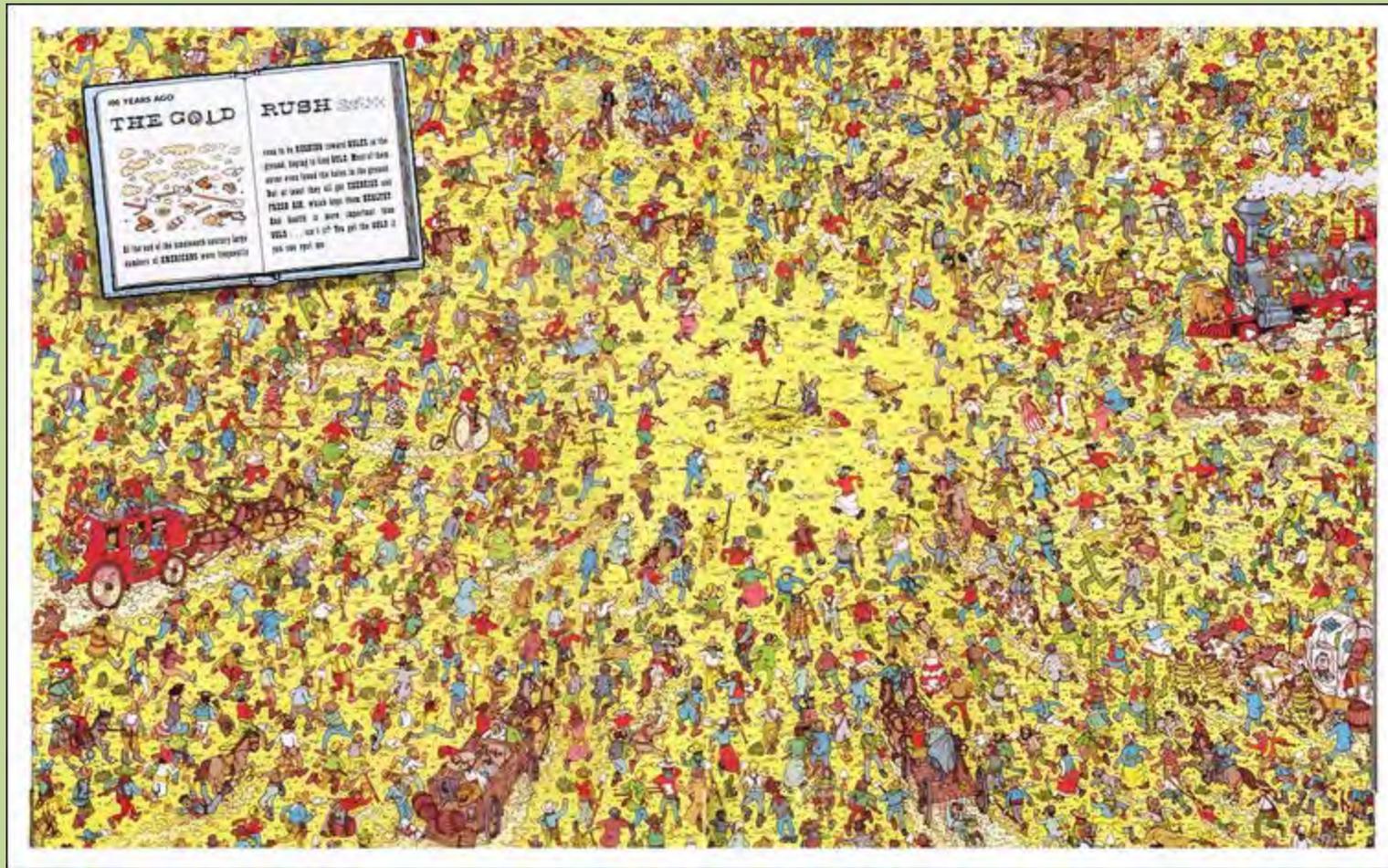
# Management for Cowden Disease

– Management:

- Mammo/MRI starting 30-35
- BSE at 18/ Clinic breast exam at 25 1-2 times per yr
- Endometrial cancer screening (efficacy unknown)
- Risk reducing agents/surgery
- Annual physical with attention to associated tumors/cancer begin at 18 (skin, thyroid)
- Baseline thyroid ultrasound at 18
- Colonoscopy starting at 35 or 5-10 years earlier if symptoms or polyps found.

# Genes linked to GYN cancers





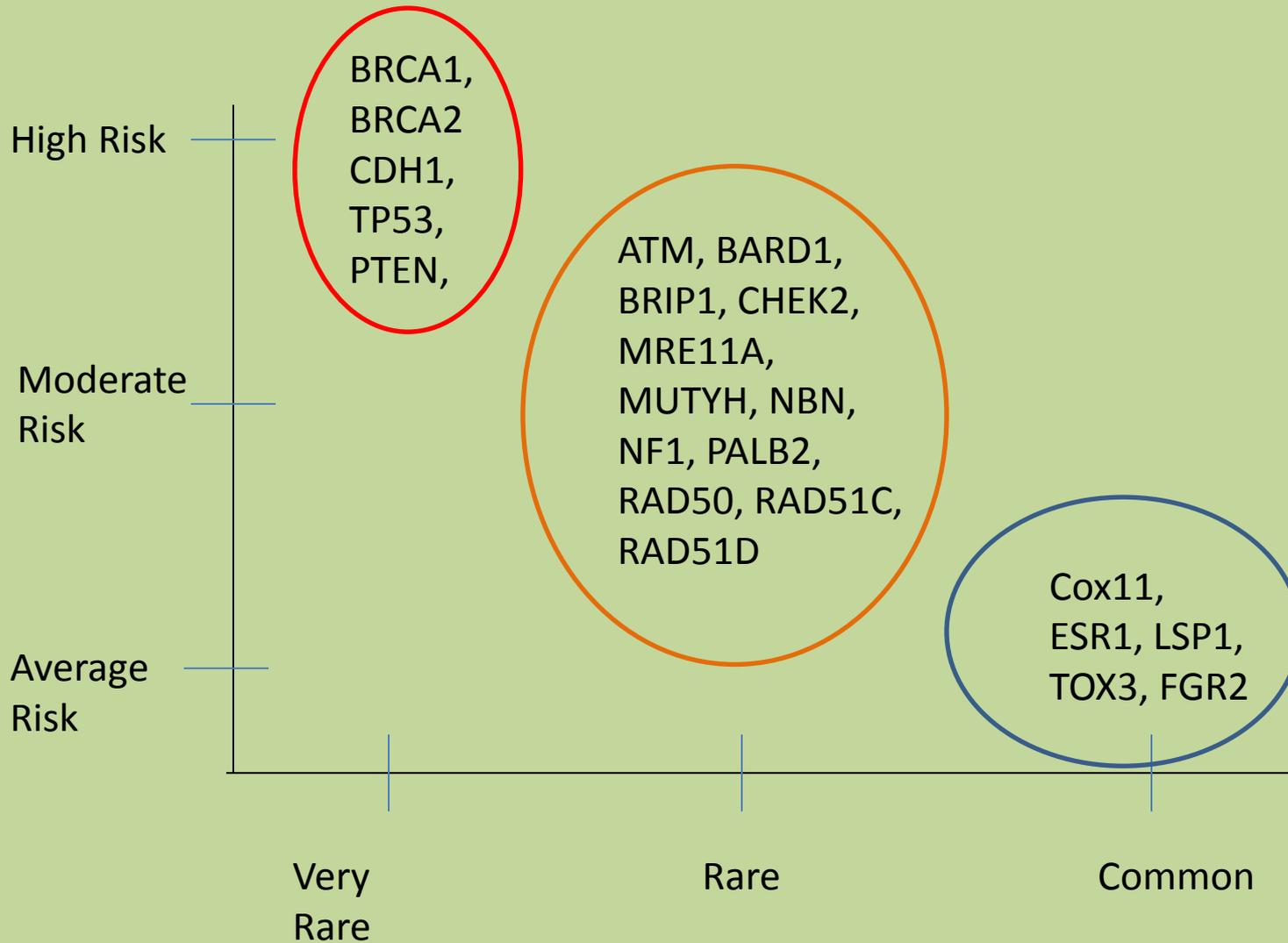


# Gene Panel testing

- Test multiple genes linked to cancer with one sample.
- Advantage
  - Lower cost
  - Ability to test multiple rare genes for lower cost
  - Decrease need for additional testing in future
  - Identify gene mutations that were not expected
- Disadvantage
  - More uncertain variants
  - Incidental findings
  - Emotional impact
  - Complex answers



# Penetrance vs. Prevalence of hereditary susceptibility genes



# Highly Penetrant Genes

Syndrome	Gene(s)	Cancer Spectrum/Risks
FAMMM	CDKN2A, CDK4	CDKN2A: 28-76% melanoma, ≤17% pancreas, others CDK4: 74% melanoma, pancreas, breast, others
FAP/AFAP	APC	Up to 100% CRC, ≤12% duodenum, ≤5% thyroid, pancreas, small bowel, gastric, liver
HBOC	BRCA1, BRCA2	41-84% breast, 11-54% ovarian, 30% prostate, 3-7% pancreas/male breast
HDGC	CDH1	40-83% diffuse gastric, 39-52% lobular breast, CRC
JPS	BMPR1A, SMAD4	40-70% CRC, 21% gastric
LFS	TP53	73% for male carriers and nearly 100% for female carriers; breast cancer, sarcoma, brain, osteosarcoma, adrenal
Lynch	MLH1, MSH2, MSH6, PMS2, EPCAM	20-80% CRC, 15-60% uterine, ≤20% ovarian, ≤8% urothelial, ≤7% gastric, ≤4% small bowel, ≤3% brain, sebaceous tumors, breast, pancreas, prostate
MAP	MUTYH	≤80% CRC, ~4% duodenum, endometrial, ovarian, bladder, breast, and skin
PJS	STK11	32%-54% breast, 39% CRC, 11-36% pancreas, 29% gastric, 21% ovarian tumors, 15% lung, 13% small bowel, 10% cervical/uterine, 9% testicular tumors
PTHS	PTEN	25-50% breast, 10% thyroid, ≤10% uterine, melanoma, renal, CRC
VHL	VHL	70% renal, ≤17% pancreas (neuroendocrine), pheos

# Moderate Risk Genes

Syndrome/Pathway	Gene	Cancer Spectrum/Risks
Ataxia-Telangiectasia	<b>ATM</b>	25-30% breast, CRC, pancreas
DNA Repair	<b>CHEK2</b>	28-38% breast, ≤50% prostate, thyroid, CRC, male breast, ovarian, uterine
Fanconi Anemia	<b>PALB2</b>	25-50% breast, ≤10% pancreas, ovarian

# What to ask your patients

- Who has cancer in your family?
- What type of cancer was it?
- How old were they when they got cancer?
- Does your patient have risk factors for cancer?
  - Atypical ductal hyperplasia, LCIS, other precancerous lesions
  - Dense breast
  - Hormone, oral contraceptive use
  - Menarche < 12, breastfeeding history, age of first child, etc



## Who should see a genetic counselor?

- Breast, colon, uterine cancer under 50 (triple negative breast cancer <60)
- Ovarian cancer at any age
- Ashkenazi Jewish with breast or ovarian
- Multiple PRIMARY cancers in one individual
- $\geq 3$  (or  $\geq 2$  if premenopausal) family members in same lineage
- Male with breast cancer
- Rare cancers: Medullary thyroid, paraganglioma, pheochromocytoma, adrenocortical carcinoma, choroid plexus carcinoma
- polyposis >20 polyps

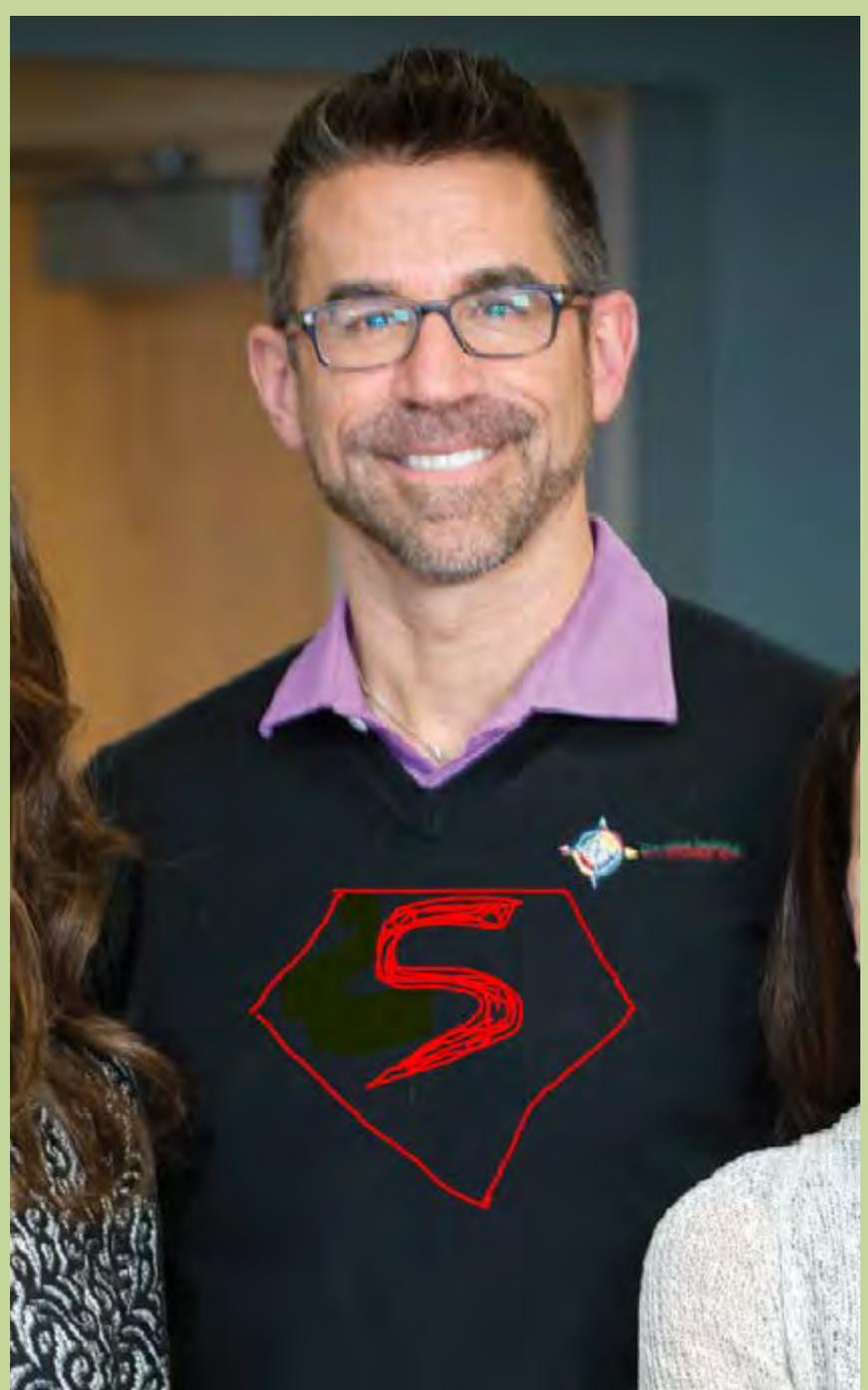
(Breast cancer includes invasive and DCIS)

# Risk Assessment in the doctor's office

- Online or tablet based questionnaire patient completes
  - Hughes RiskApps, My Family Health Portrait, MeTree, Progeny
- Online risk programs you input yourself
  - Gail, CaGene, Tyrer Cuzick (IBIS), BRCAPRO



Dr. Schroeder  
to the rescue!





# High Risk Breast Clinic

- Breast C.A.R.E. Program (Comprehensive Assessment and Risk Evaluation)
- Determine risk for breast and/or other cancer:
  - Recommendations prevention and early detection
  - diet, exercise, Vitamin D, stress reduction, smoking cessation
  - for chemoprevention and MRI screening
- Risk for Hereditary Predisposing Gene
  - Offer genetic testing when appropriate

# Psych-social issue

- Worry about self
- Worry about family
- Pressure for the young
- Genetic guilt/survivor's guilt
- Pre-viver: where do I belong?
- Emotional versus logical decision
- Coping strategies
- Financial
- Family reactions
- Dealing with intensive screening, risk reducing surgeries

# Logistics



# Summary

## Hereditary causes of cancer

- Earlier onset
- Higher risk
- At risk for more than one type of cancer

Note: You can be high risk but gene negative



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