IDENTIFYING AND MANAGING HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

"HBOC"

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Certified Genetic Counselor
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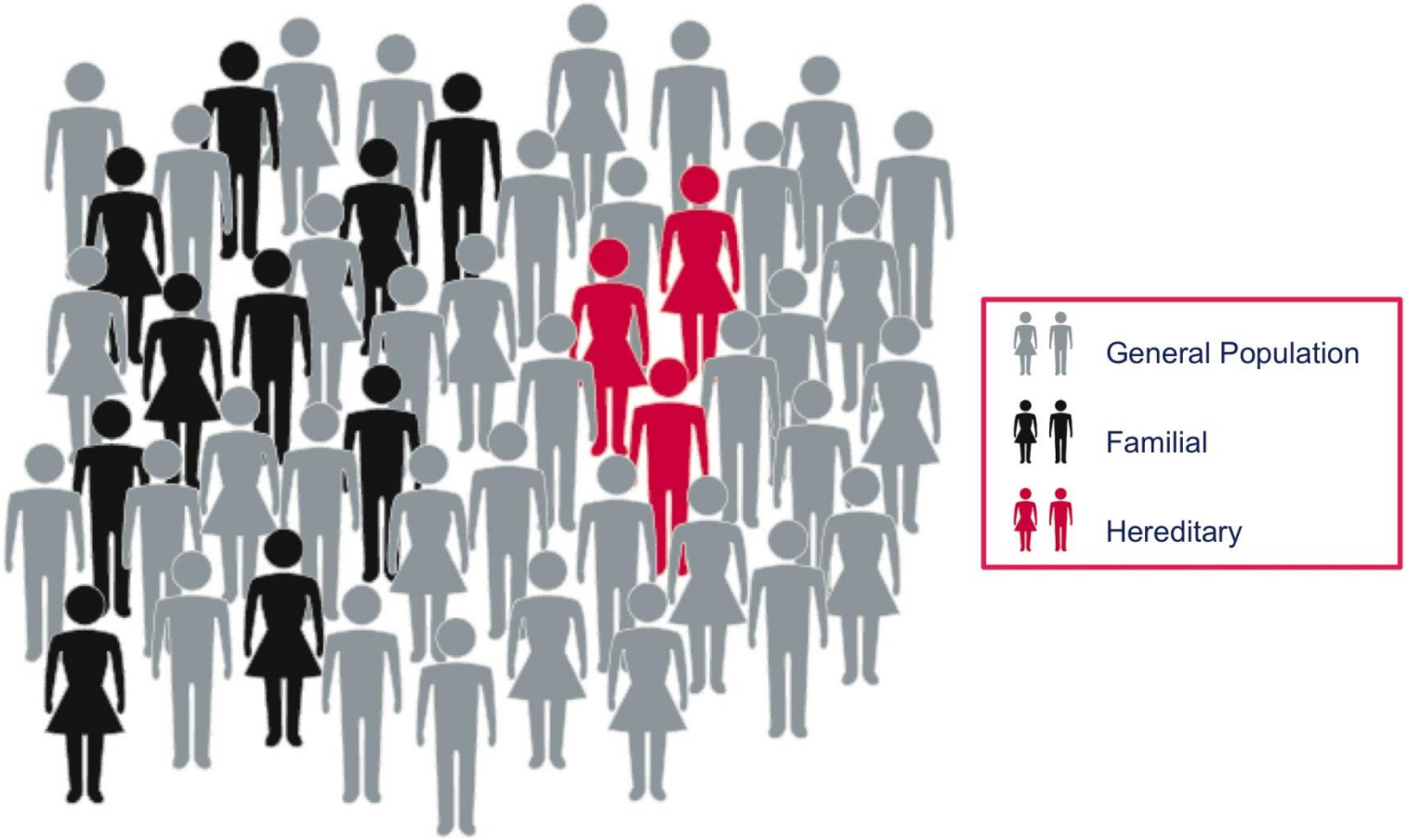
Elizabeth Wende Breast Care, LLC

HOW MANY PATIENTS ARE AT RISK OF HEREDITARY BREAST AND OVARIAN CANCER?



Elizabeth Wende Breast Care

- Internationally recognized since 1975 as a leader in the field of breast imaging and breast cancer diagnosis
- One of the largest free-standing breast imaging centers in the US
  - Nearly 200,000 patient appointments annually
- Largest single-site breast imaging center in New York State
- Classified as a Breast Imaging Center of Excellence by the American College of Radiology
- 7 Radiologists, 3 sonographers, 1 genetic counselor

EWBC-Services

Across 4 campuses:

- Digital Mammography
- 3D Digital Mammography
- Ultrasonography
- Breast MRI
- Multimodality Imaging Biopsy
- Bone Densitometry
- Massage
- Cancer Risk Assessment & Genetic Counseling*

Genetic Counseling Program

- Formal Genetic Counselor led program began in 2011
- <200 patients per year counseled by Certified Genetic Counselor
- All patients actively screened for risk factors at check-in
- Based on points system
  - 2 or more points generated a high risk (HR) letter given to patient and faxed/mailed PCP, GYN

Current GC Program

- Began in 2012
- Genetic Counselor led with 4 support staff
- ~1000 patients per year counseled by Certified Genetic Counselor
- All patient actively screened at check-in based based on NCCN guideline rubric

Current GC Program

- High Risk Letter generated when criteria met
  - "Based on the answers you supplied on your health history form today, you may be a candidate for genetic counseling, genetic testing or additional breast cancer screening. If you are interested in further cancer risk assessment, please contact…"

Current Metrics for EWBC Patients

	Daily	Weekly	Monthly	Yearly
# of Patients Served	500	2,500	10.000	120,000
# of Patients Flagged as “High Risk”	125	625	2,500	30,000
% of Patients High Risk	25%	--	--	--
# of Patients Counseled	5-8	20-25	80-100	950- 1,200
% of Patients Counseled	5%	--	--	--

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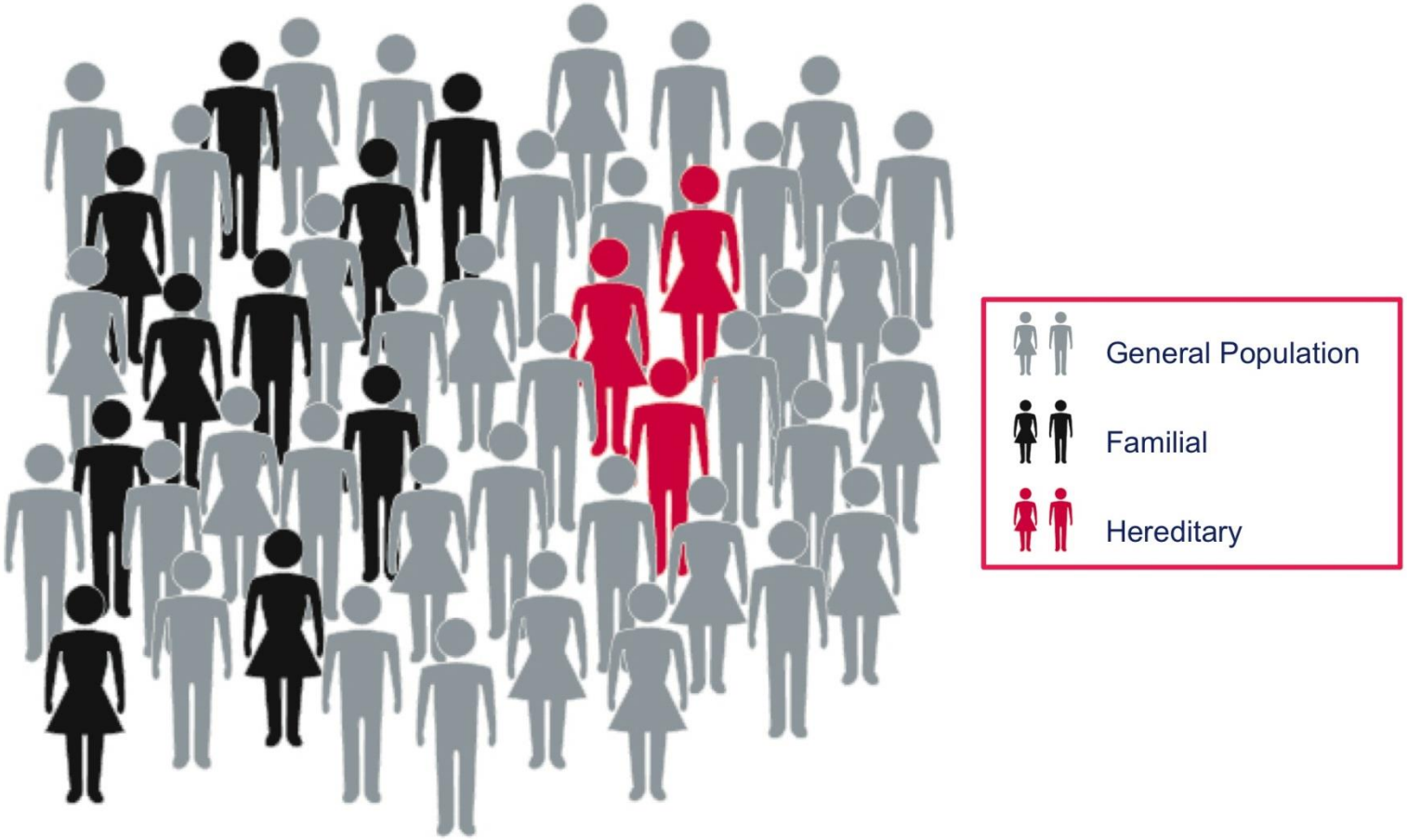



MAY 27, 2013
TIME
THE
ANGELINA
EFFECT
Angelina Jolie's double mastectomy puts genetic testing in the spotlight. What her choice reveals about calculating risk, cost and peace of mind
BY JEFFREY KLUGER & ALICE PARK
TIME.COM

THE NEW YORK TIMES

“MY MEDICAL CHOICE” MAY 14, 2013

- “MY MOTHER fought cancer for almost a decade and died at 56. She held out long enough to meet the first of her grandchildren and to hold them in her arms. But my other children will never have the chance to know her and experience how loving and gracious she was.”

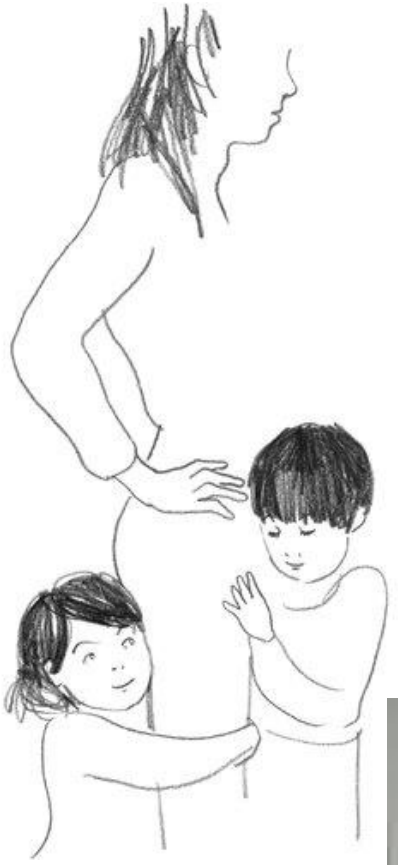
THE NEW YORK TIMES

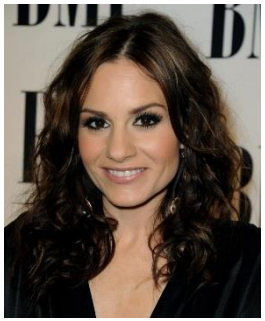
- “We often speak of “Mommy’s mommy,” and I find myself trying to explain the illness that took her away from us. They have asked if the same could happen to me. I have always told them not to worry, but the truth is I carry a “faulty” gene, BRCA1, which sharply increases my risk of developing breast cancer and ovarian cancer.”

- “But I am writing about it now because I hope that other women can benefit from my experience. Cancer is still a word that strikes fear into people’s hearts, producing a deep sense of powerlessness. But today it is possible to find out through a blood test whether you are highly susceptible to breast and ovarian cancer, and then take action.”

- “For any woman reading this, I hope it helps you to know you have options. I want to encourage every woman, especially if you have a family history of breast or ovarian cancer, to seek out the information and medical experts (*genetic counselors*!) who can help you through this aspect of your life, and to make your own informed choices.”

THE NEW YORK TIMES





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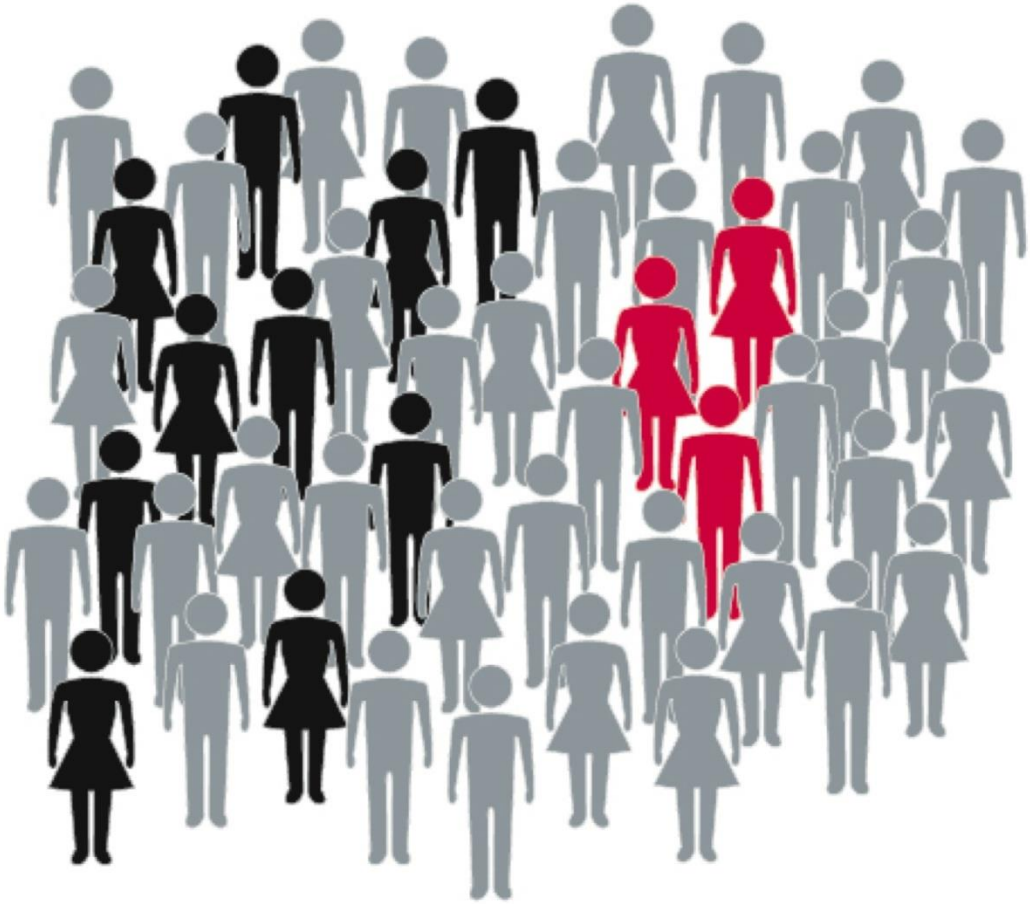
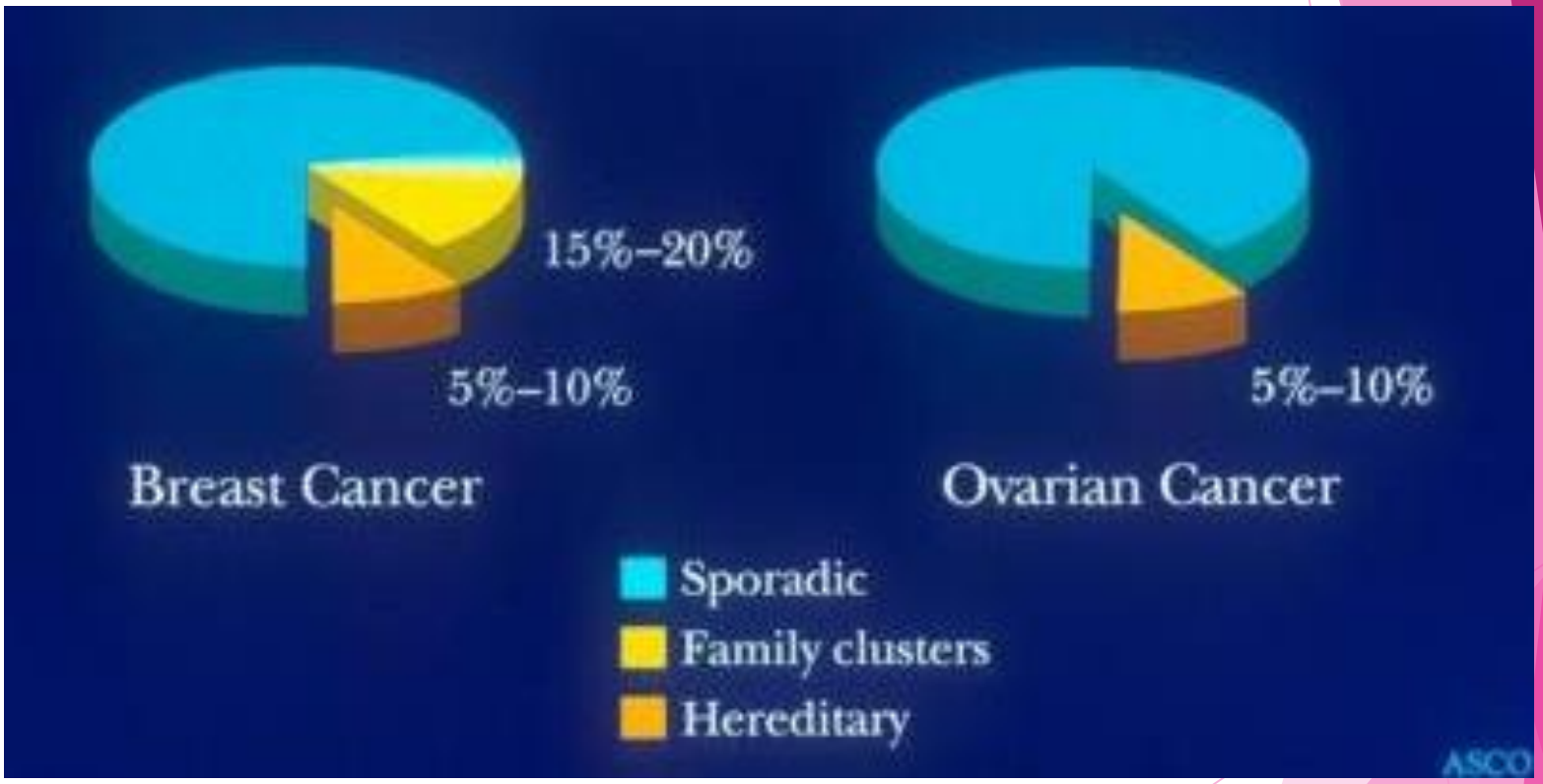


General Population

Familial

Hereditary

Most Cancer is Sporadic



Sporadic vs. Familial Cancers

Sporadic

- Cancer which occurs by chance
- Typically do not have relatives with the same type of cancer
- Cancer rate within the family matches the general population statistics
- Could be environmental or as a result of aging

Familial

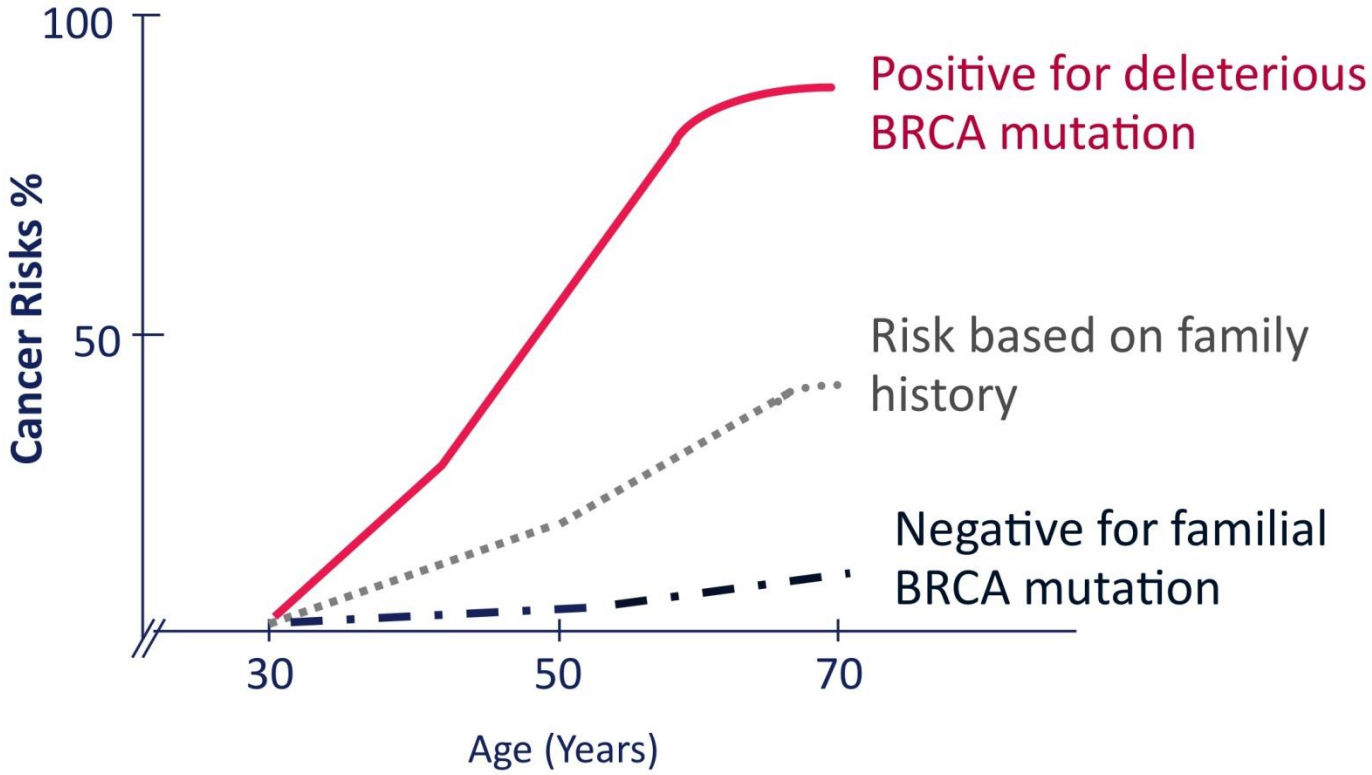
- May have relatives with the same type of cancer
- There does not appear to be a specific pattern of inheritance
- Cancer likely caused by a combination of genetic and environmental risk factors (Multifactorial)

Hereditary Cancers

Cancer that occurs when an *altered gene* is passed down in the family from parent to child

- *More* likely to have relatives with the same type of or a related type of cancer
- *May* develop more than one cancer
- Cancer *most* often occurs at an earlier than average age
- Cancer within the family *exceeds* the general population rate

FAMILY HISTORY IS NOT ENOUGH



Reprinted with permission from Ponder B: Genetic Testing for Cancer Risk. *Science* 1997; 278:1050-4.
Copyright 1997 American Association for the Advancement of Science

FAMILY HISTORY CONSIDERATIONS

- One-half of BRCA carriers inherit the mutation from their father
- Ovarian cancer is a very important factor
- Early onset breast cancer is more important than the number of affected family members
- Small overall family size, or those containing few female relatives may “mask” underlying BRCA mutations

Science 2003;302(5645):643-6
JAMA 2007;297(23):2587-95

Indicators of “HBOC”

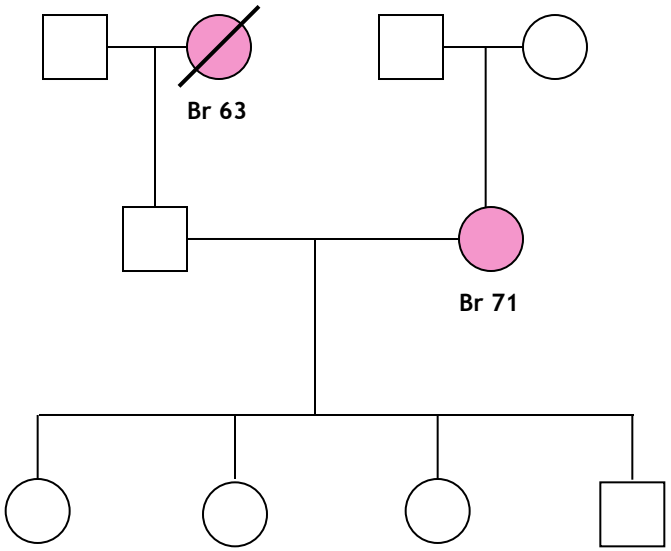
Family or personal history of

- Breast Cancer before age 45
- Premenopausal Breast Cancer
- “Triple Negative” Breast Cancer
- Ovarian Cancer
- Male Breast Cancer
- Two primary breast cancers
- Both breast and ovarian cancer in the same individual
- Two or more breast cancers in the same family, when one is under the age of 50
- Ashkenazi Jewish heritage
- A previously identified BRCA mutation in the family

Age of affected relative is **more important** than the **number** of affected relatives!

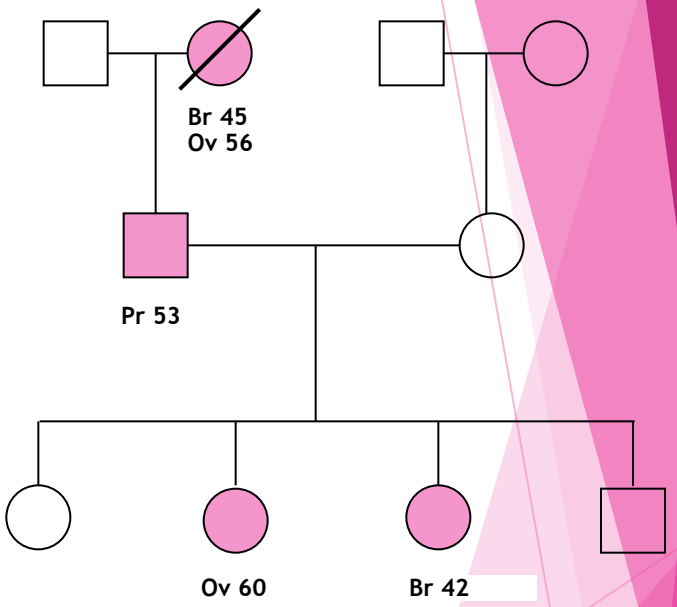
Family History: Genetic or Not?

Sporadic



- Diagnosed late in life
- No ovarian cancer
- Unilateral breast
- No clear inheritance pattern

Hereditary



- Multiple generations affected
- Individuals diagnosed before age 50
- Multiple organs and/or bilateral disease
- Male breast and/or prostate cancer

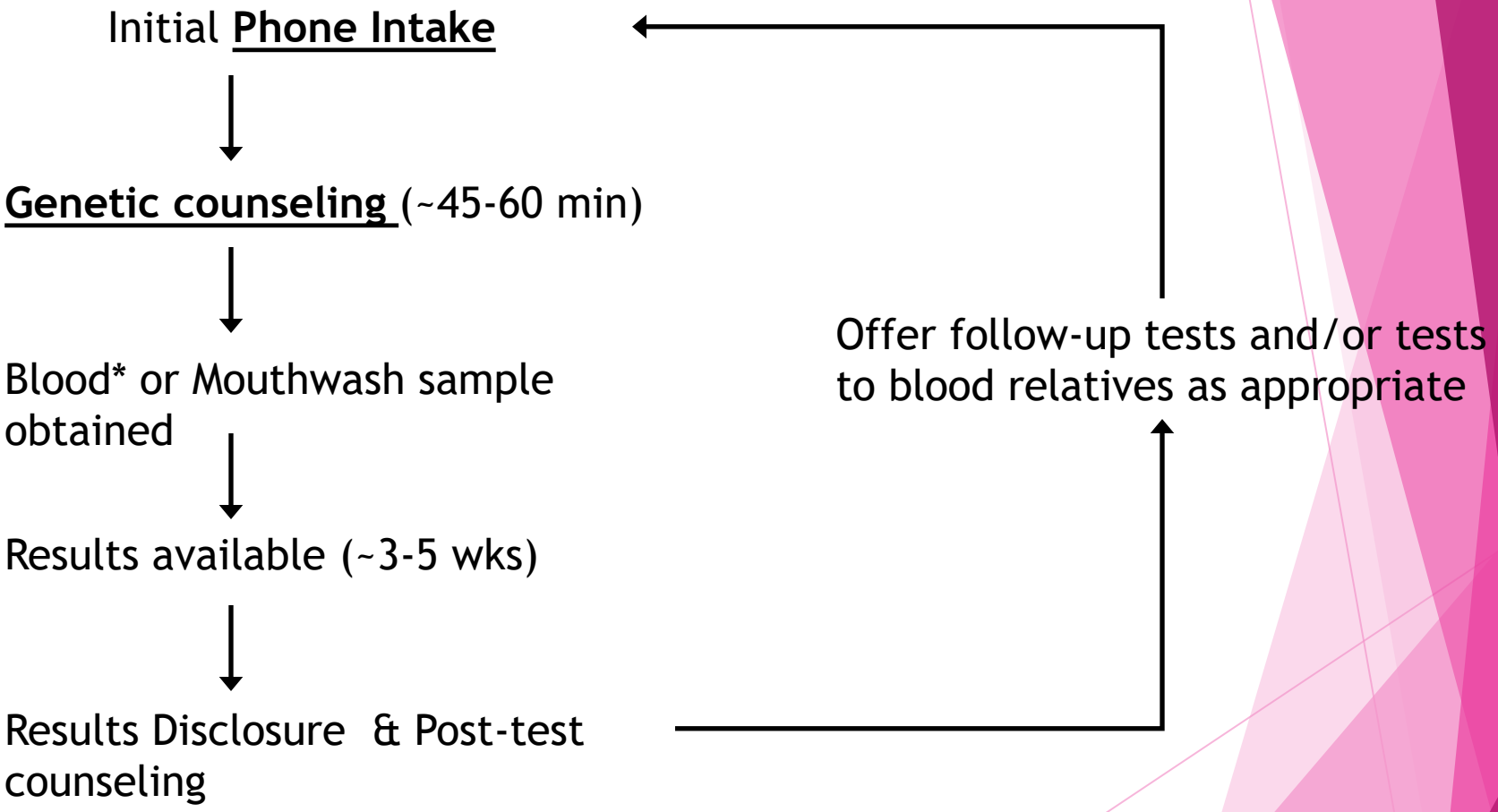
EWBC “High Risk” Letters

- Family History obtained from patients
  - At check-in
  - On-line patient portal
- **Two or more** risk factors identifies patient as potentially “High Risk”
- Letter generated to patient and physician
  - Family history indicates that the patient “may eligible for genetic counseling, genetic testing and possible additional screening via breast MRI”

BREAST AND OVARIAN CANCER			SELF	FAMILY MEMBER		Age Diagnosed
				MOTHER'S SIDE	FATHER'S SIDE	
Y	N	Breast cancer at age 45 or younger				
Y	N	2 or more breast cancers, one at age 50 or younger				
Y	N	Ovarian, Fallopian tube or Peritoneal cancer AT ANY AGE				
Y	N	Triple Negative Breast Cancer at age 60 or younger				
Y	N	**3 or more of these cancers on same side of family at any age:**				
		Pancreatic				
		Breast				
		Prostate				
		Ovarian/Fallopian Tube/Peritoneal				
Y	N	Male Breast Cancer AT ANY AGE				
Y	N	Jewish ancestry *AND* breast, ovarian or pancreatic cancer at any age on that side of the family				
Y	N	Personal or family history of colon cancer diagnosed at 50 or younger				
Y	N	Personal or family history of uterine cancer diagnosed at 50 or younger				

EWBC's Office Protocol

*After Receiving "High Risk" letter or Referral



Phone Intake

- Personal History
  - Breast or Ovarian Cancer
  - Other Cancers
  - Age of onset
  - Dense breast tissue
- Family History
  - 3 generation pedigree
  - Relationship
    - Maternal or Paternal
  - Type of Cancer
  - Age of Onset
  - Affected family members Living/Deceased

Phone Intake cont.

- Genetic Testing
  - Has anyone been tested?
  - If yes, what were the results and is a copy available?

- Risk Assessment
  - 1st Menstrual Cycle
  - Age of first child
  - Age of menopause
  - HRT use
  - Breast biopsy history

Genetic Counseling

- Family/Personal history
  - 3 generation family history
  - Review personal history
  - Is it appropriate to test?
  - Motivation for testing?

- Overview of Genetics
  - BRCA1/BRCA2
  - Genes, chromosomes

- Testing process and logistics
  - Will insurance cover the testing?
    - Who should be tested first?
      - *Affected vs. Unaffected

Genetic Counseling cont.

- Associated cancer risks
  - Cancer types
  - Possibility of another cancer syndrome
- Medical management options
  - Screening vs Surgery
- Impact on insurance
  - Medical, Life, Long-term Care
- Impact on family members
- Psychosocial

Indicators of “HBOC”

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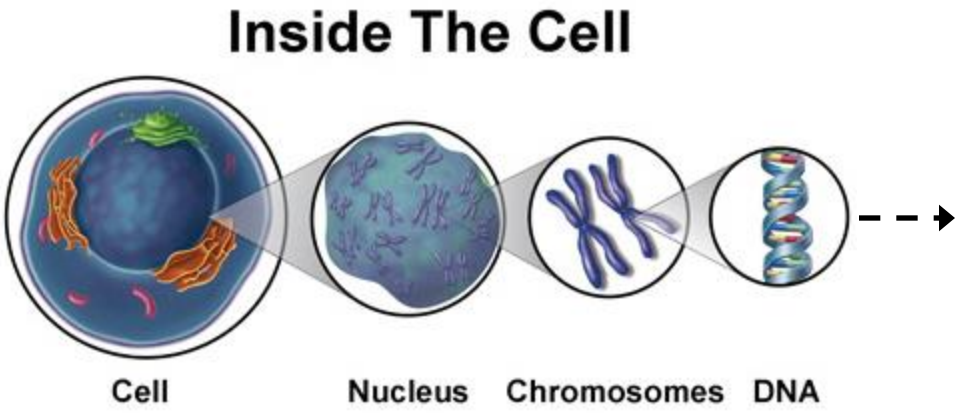
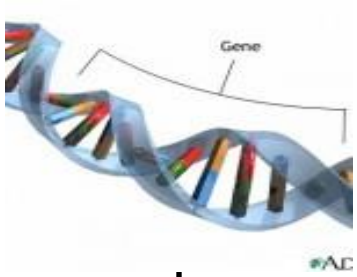
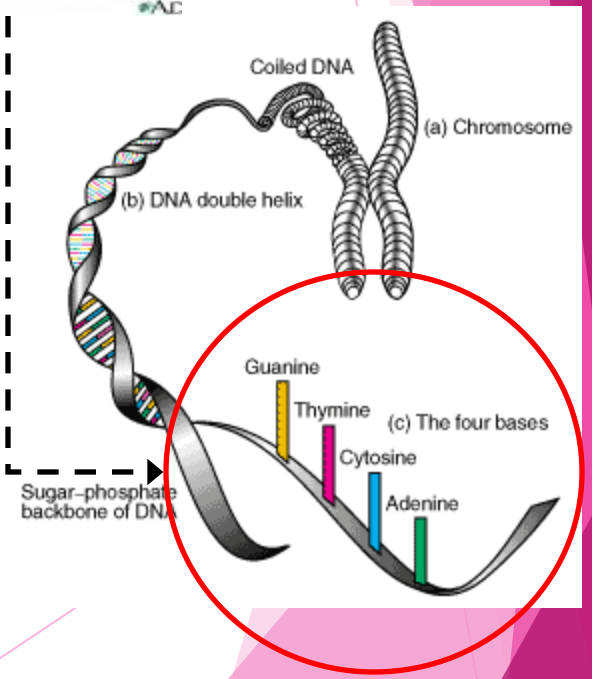
Age of affected relative is **more important** than the **number** of affected relatives!

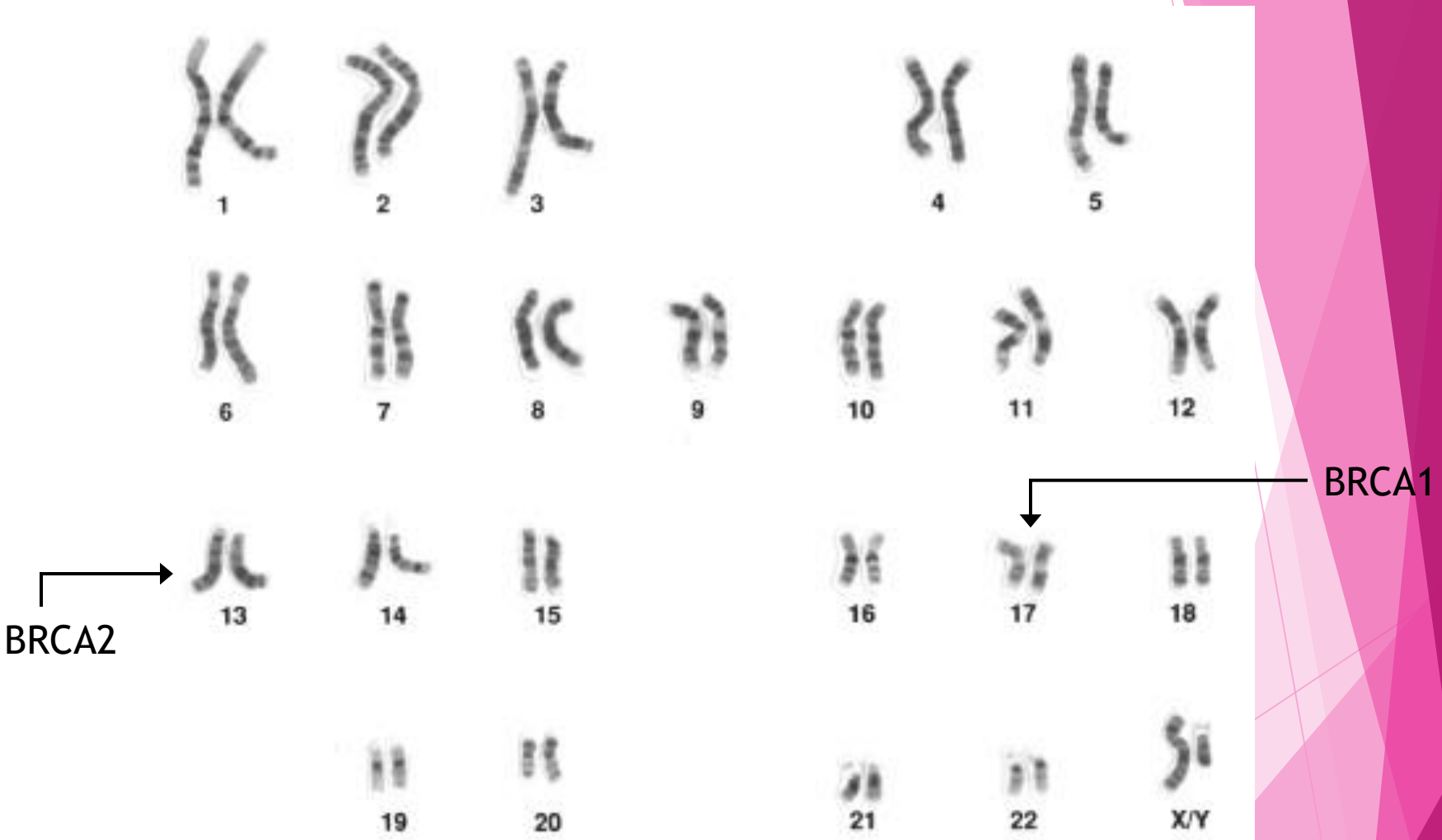
Genetics


Inside The Cell
Cell
Nucleus
Chromosomes
DNA


Gene


Coiled DNA
(a) Chromosome
(b) DNA double helix
Guanine
Thymine
(c) The four bases
Cytosine
Adenine
Sugar–phosphate backbone of DNA

Genetics



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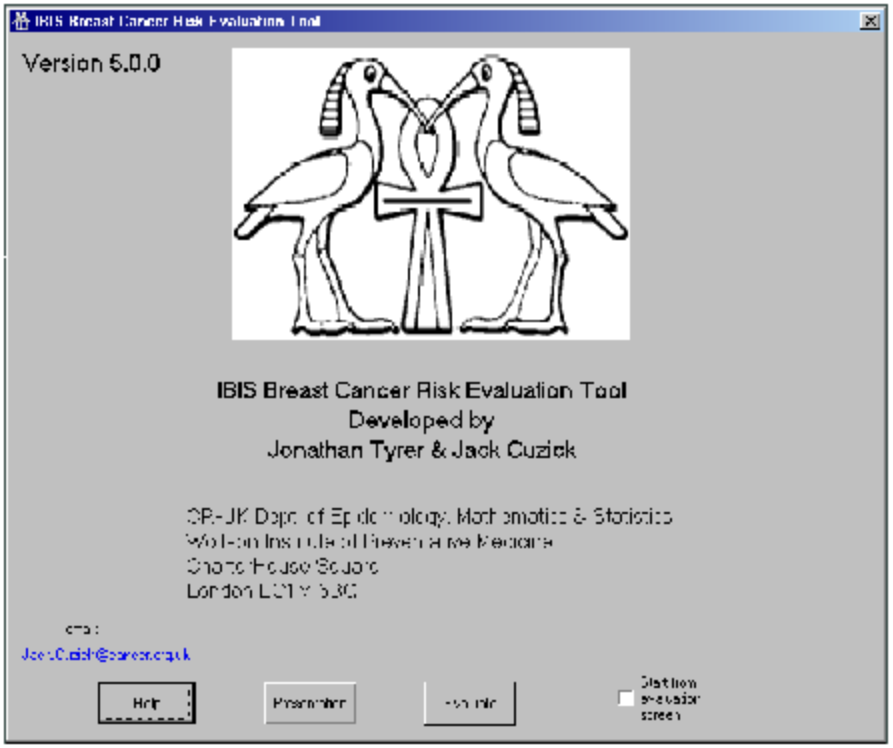
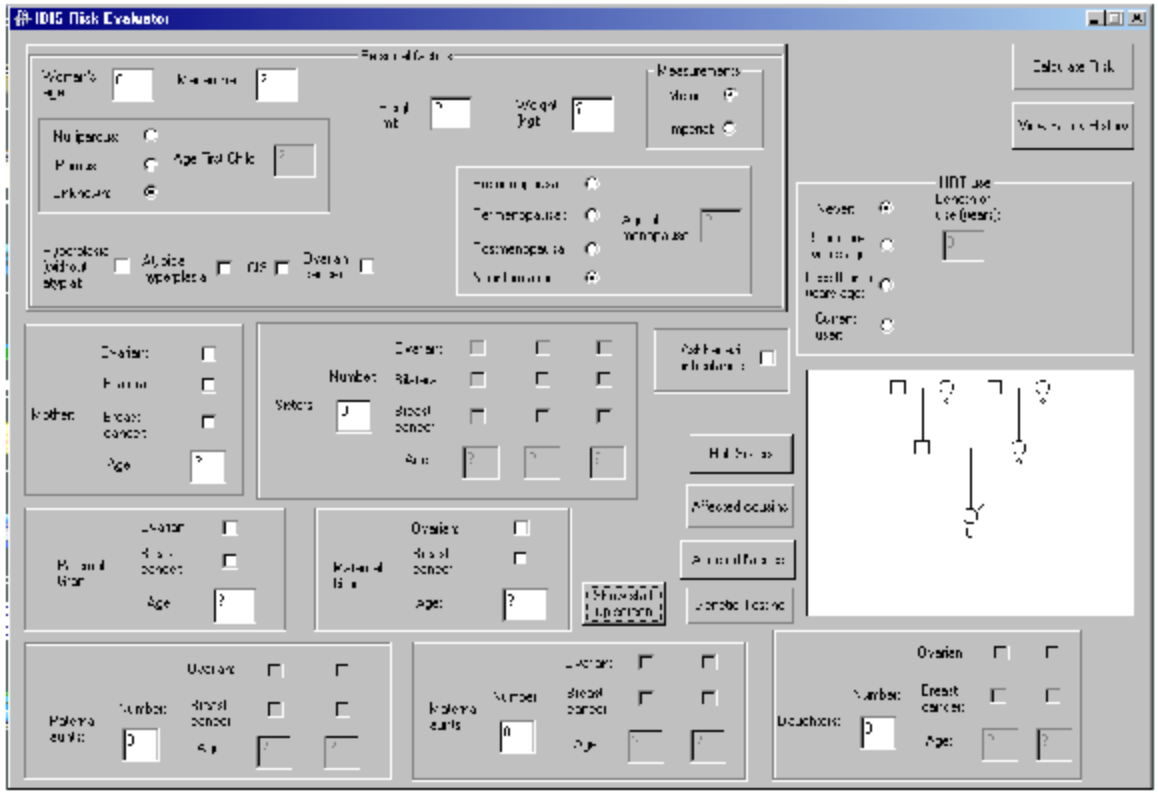
RISK ASSESSMENT SERVICES

- Tyrer-Cuzick Risk Assessment
- Determines a woman's lifetime risk of breast cancer
  - Personal risk factors
  - Family history
- If personal risk is above 20% insurance will typically cover the cost of a yearly screening MRI.
- Can be utilized in the absence of genetic testing to determine management plan
  - Also calculated post-testing for patients with a negative result

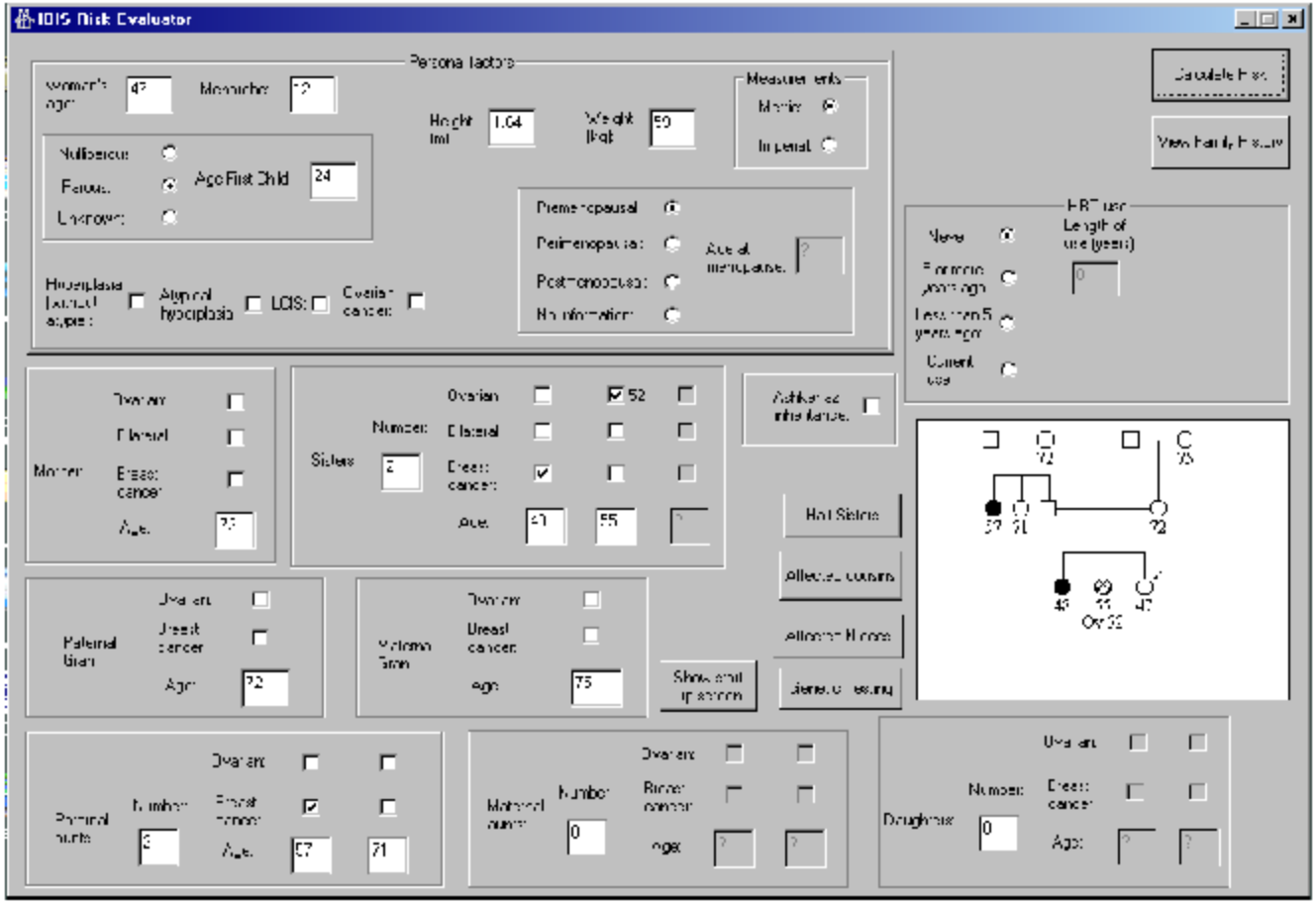
IBIS Breast Cancer Risk Evaluation Tool



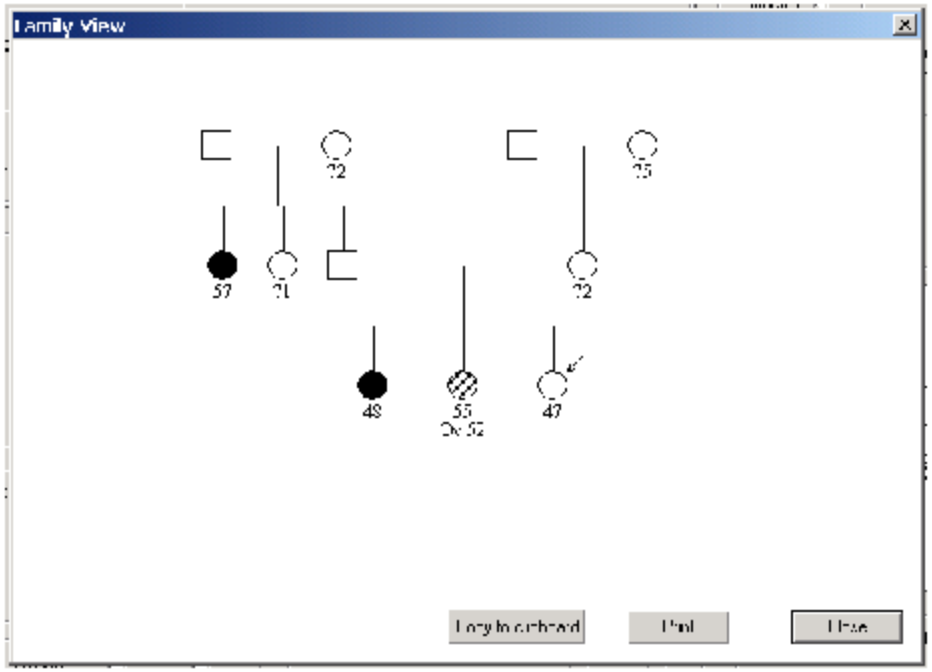
Evaluation Screen



A worked example



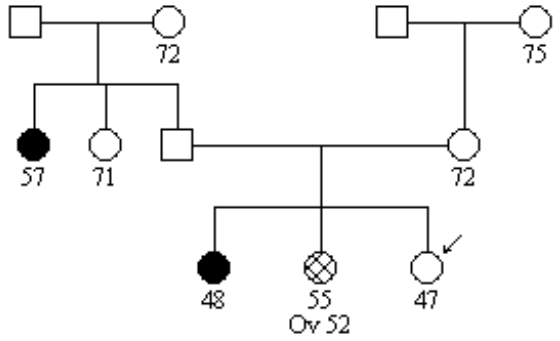
After pressing the ‘view family history’ button

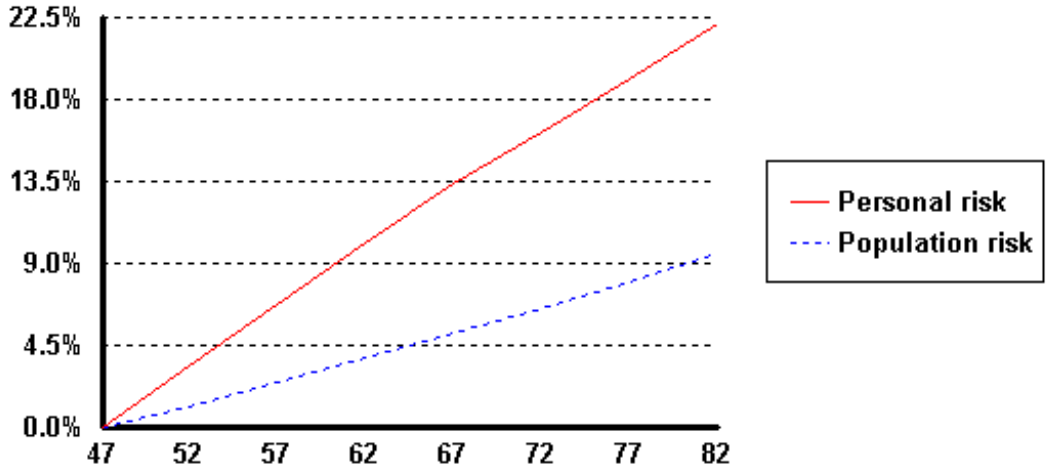


Print Preview

Age of person is 47 years.
Age at menarche was 12 years.
Age at first birth was 24 years.
Person is premenopausal.

Risk after 10 years is 6.64%.
10 year population risk is 2.389%.
Lifetime risk is 20.82%.
Lifetime population risk is 8.826%.
Probability of a BRCA1 gene is 4.468%.
Probability of a BRCA2 gene is 2.041%.





Print

Close

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Typical Guidelines used by Insurance for coverage!

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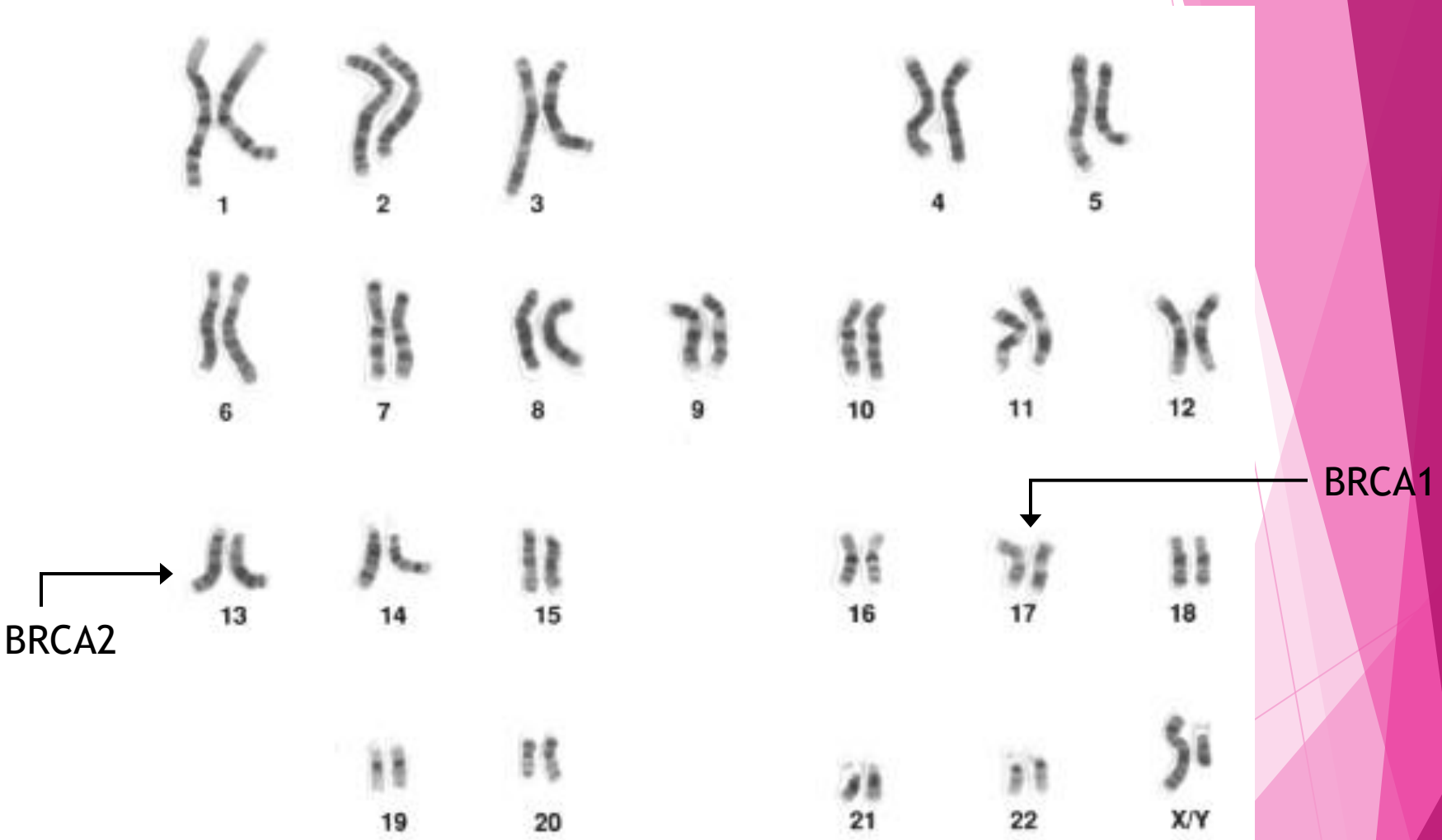
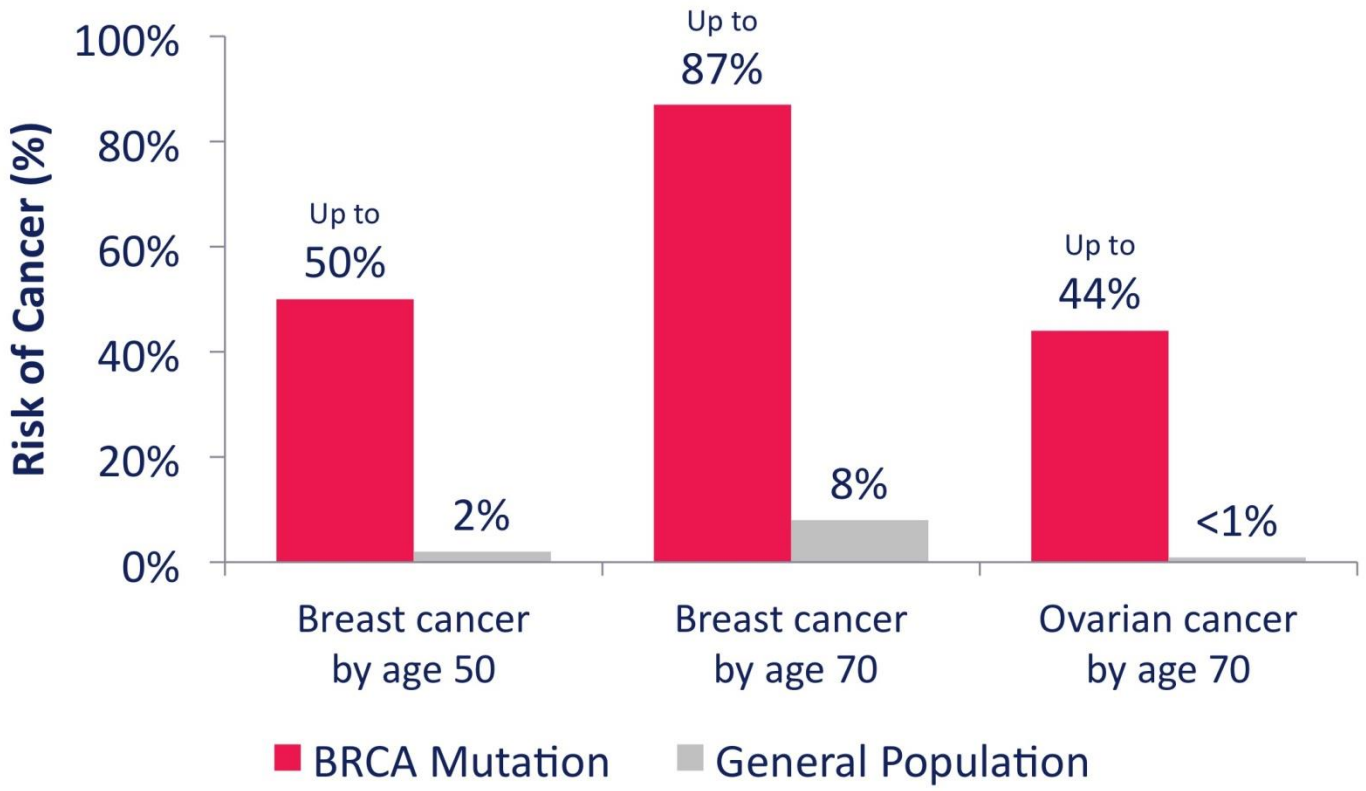


BRCA1 and BRCA2 Associated Cancers

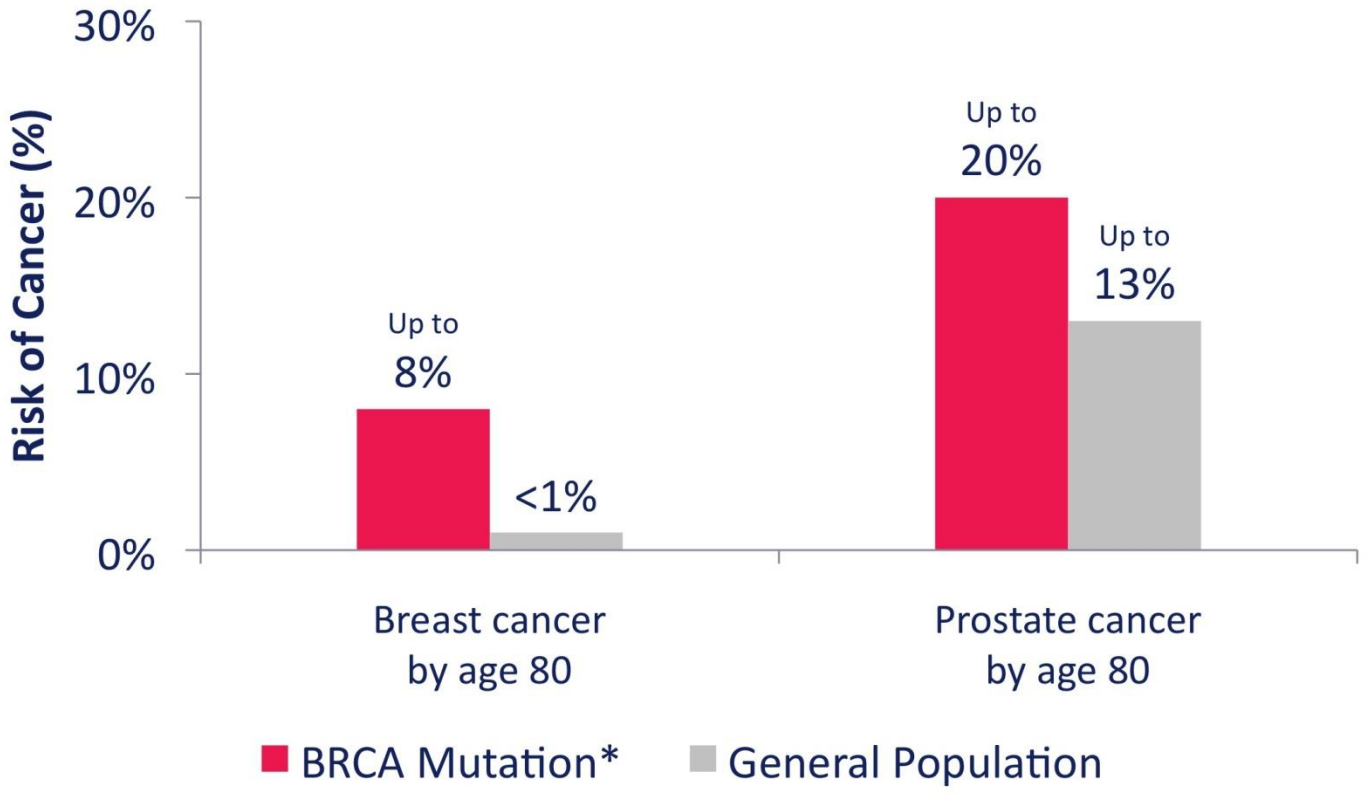
Cancer Type	General Population Risk	Mutation Carriers
Breast	12%	84-87%
Ovarian	2%	27-45%
Prostate	14%	20%
Melanoma	2%	4-5%
Pancreatic	1%	7%
Renal	<1%	3-5%

BRCA MUTATIONS INCREASE BREAST AND OVARIAN CANCER RISKS



Lancet 1994;343:692-5
NEJM 1997;336:1401-8
AJHG 2003;72:1117-30
JNCI 1999;15:1310-6
AJHG 1995:56:265-71
Science 2003;643-6
JCO 2005;23(8):1656-63
NCI (SEER) 2010

BRCA MUTATION RISKS IN MEN



*Risks refer to *BRCA2* mutation carriers.
Risks for male *BRCA1* mutation carriers are less characterized.

JCO 2004;22:735-42
NCI (SEER) 2010
JNCI 2007 5;99(23):1811-4

Possible Outcomes of Testing

- **Positive Result**
  - Increased cancer risk
- **Negative Result**
  - If previously identified mutation within the family, no increased risk
    - "True negative"
  - If pt is the first person tested: Cancer risk remains unknown
    - Use individual risk estimates
    - Tyrer-Cuzick Risk Assessment

Possible Outcomes Cont.

- **Variant of Unknown Clinical Significance**
  - Occurs in about 1% of our patient population
  - Not enough data to determine the impact of the variant
  - Additional family studies are necessary to determine the significance
  - **Recommendation to screen as if the patient is "positive"**

  OR

  - **Ignore the result until more data becomes available**

Historic Testing Strategies

2012-2014

- **Integrated BRACAnalysis ($4000)**
  - Both Comprehensive and BART

2010-2012

- **BRACAnalysis Rearrangement Testing ($600)**
  - Identifies an additional 5% of BRCA mutations

1998-2010

- **Comprehensive BRACAnalysis** ($3300)
  - Identified 95% of BRCA mutations

1998-Current

- **Multi-site Analysis- for Ashkenazi Jewish pts** ($700)
  - Tests for the three most common Ashkenazi mutations

- **Single Site** ($400)
  - Family member has tested positive
  - AKA “Known Familial Mutation” Analysis

Current Testing Strategy

BRCA, only

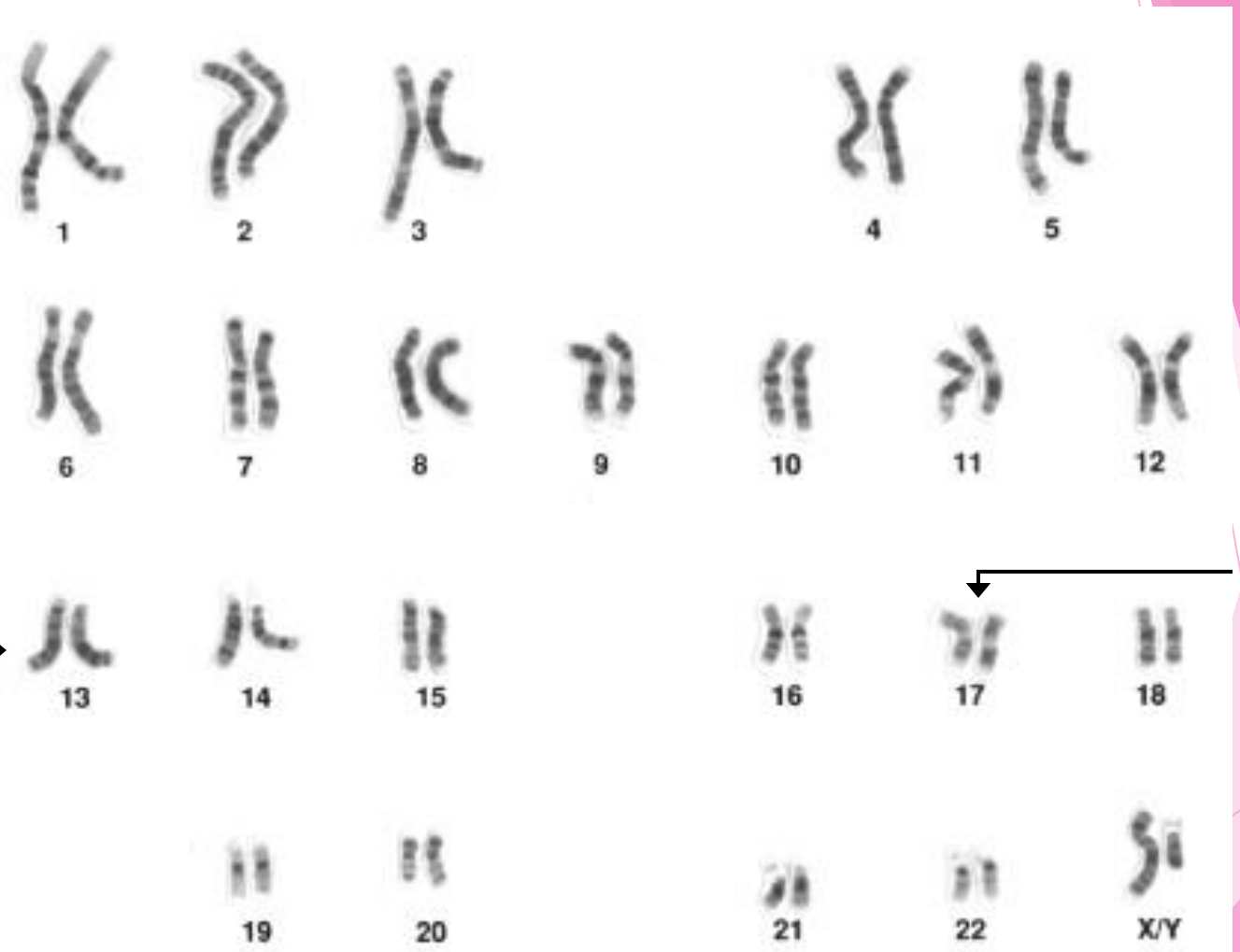
- **If Jewish**
  - AJ Panel- Multisite 3 BRACAnalysis
- **If previously negative via Comprehensive Analysis**
  - Sequencing
  - Can reflex to BART
- **If no previous testing**
  - Sequencing and BART - Integrated Analysis
- **If known familial mutation**
  - Single site analysis

Current Testing Strategy

Consider Cancer Gene Panels

- **If BRCA was previously negative**
- **If family history is consistent with another cancer gene**
- **Provides more information in a more cost effective fashion**

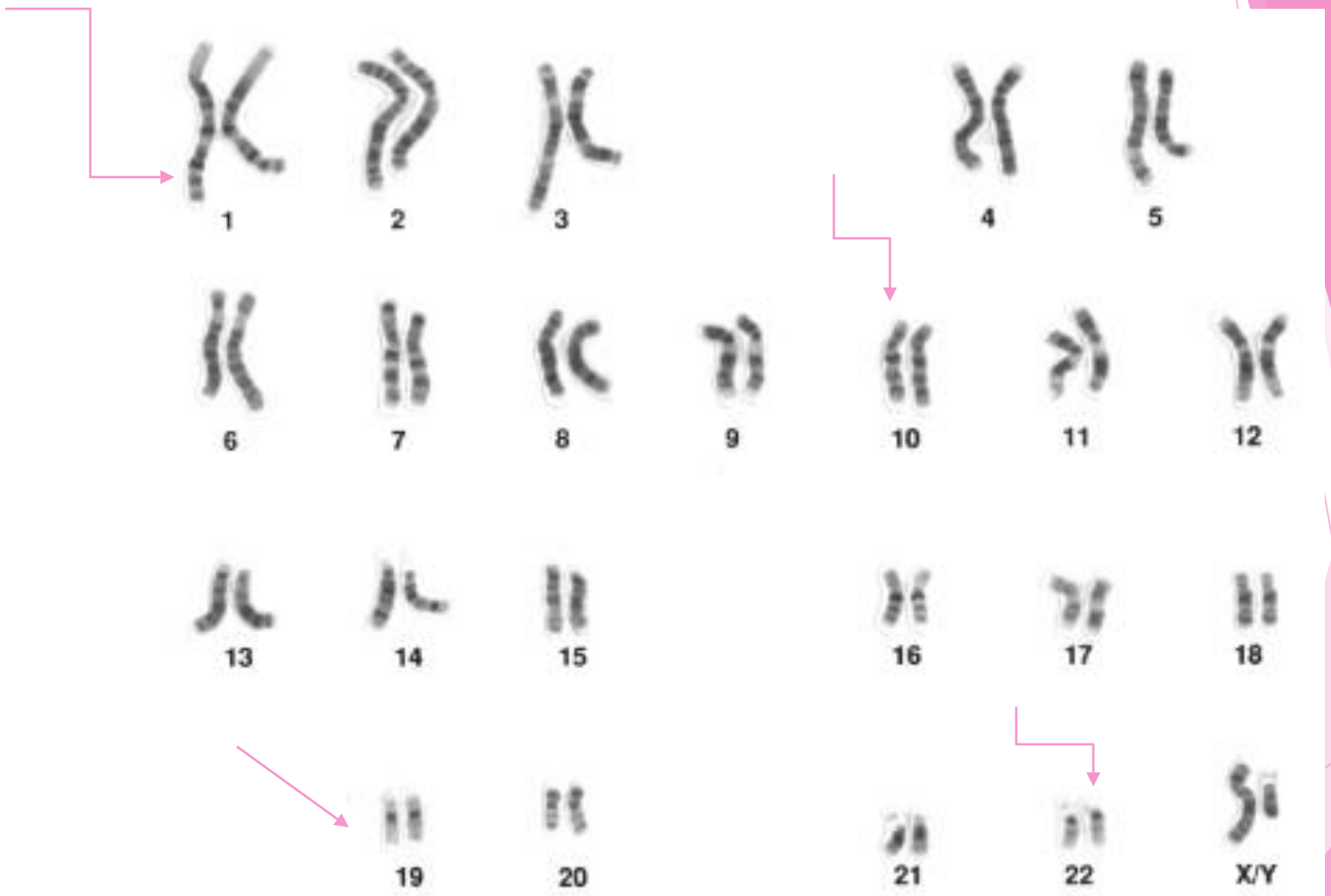
Genetics



BRCA1 NEGATIVE

BRCA2 NEGATIVE

Genetics



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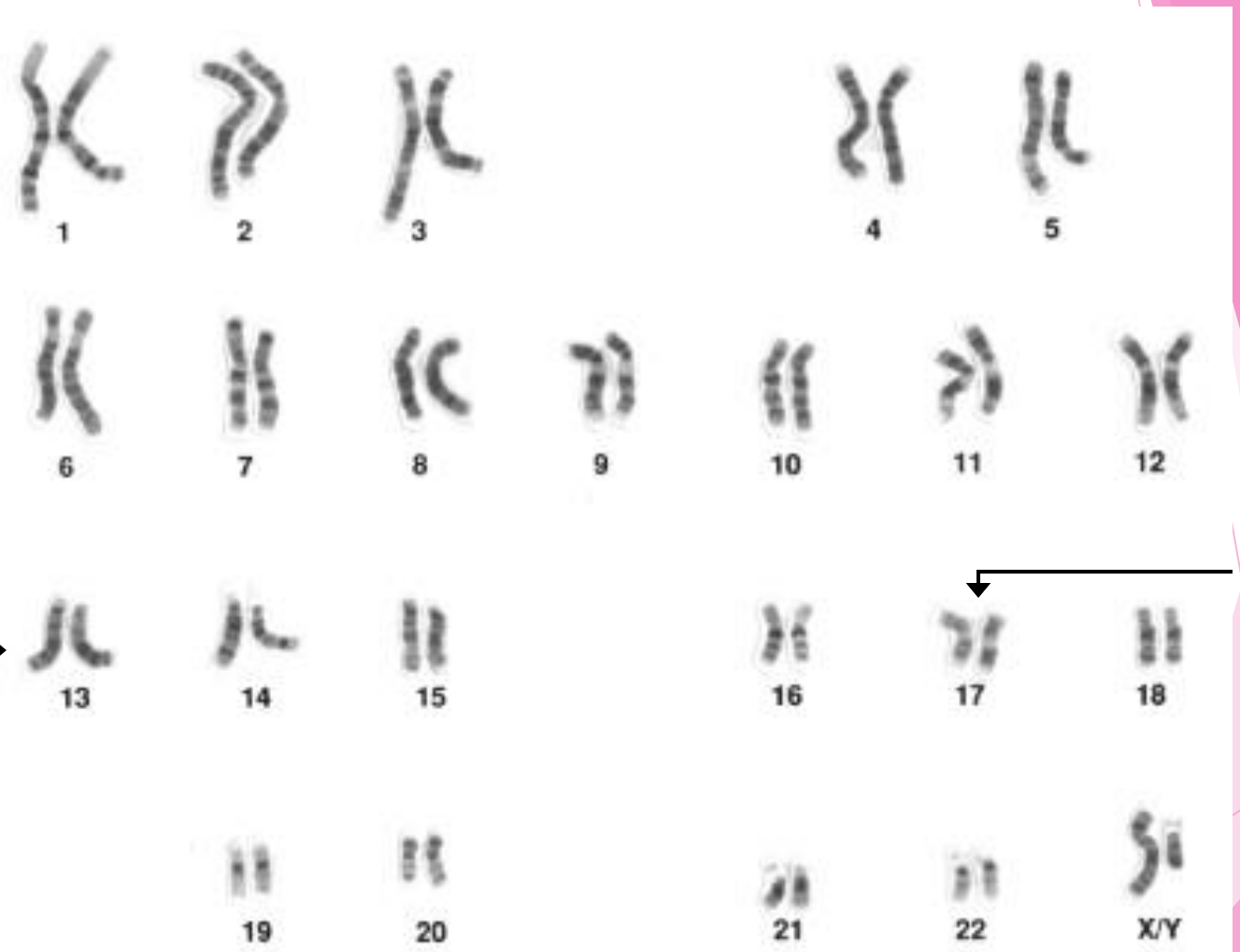


BRCA1 NEGATIVE

BRCA2 NEGATIVE

Cancer gene panels

Current Panel Options

- BreastNext
  - Ambry Genetics
  - 18 gene panel
  - ~8 week turn-around time

- **myRisk***
  - **Myriad Genetics**
  - **25 gene panel**
  - **~4-6 week turn-around time**

- GeneDX
  - New 43 gene panel

Cancer gene panels

Pros and Cons

- Longer turn-around time
- High variant rate
- Reveals the cause of cancer in previously unsolved families
- Allows for healthy individuals to screen early and often
  - Currently no widely accepted clinical management guidelines outside of BRCA1/2 and a few additional genes

“What should I do with this information?”

- An affected individual might seek testing for surgical decision making
- A healthy individual might seek testing to determine the best management protocol for their risk level
- Both types of patients may seek testing to help their family members especially siblings and children
- A positive result leaves an individual wondering……

Options after Positive Results

Increased Surveillance vs Surgery

(*Early Detection*) (*Risk Reduction*)

Possible Options after Positive Results

Increased Surveillance

(*Early Detection*)

- Breast
  - Mammogram
  - MRI
  - Clinical Breast Exams
- Ovarian
  - Ultrasound
  - CA-125

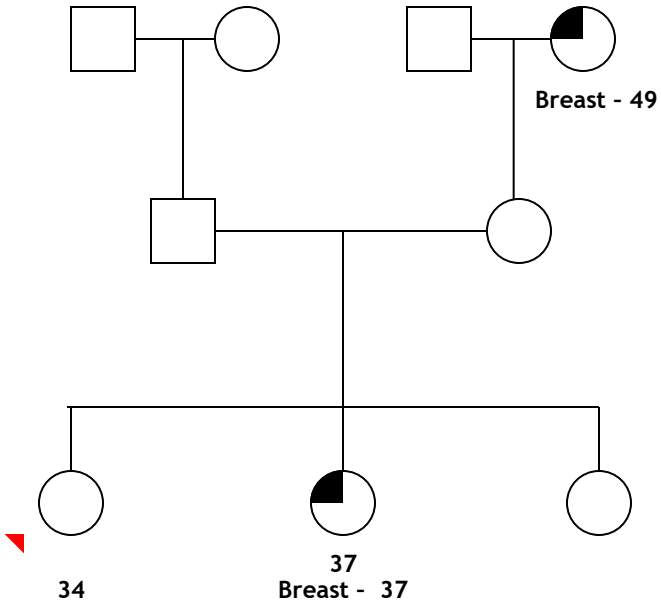
Possible Options after Positive Results

Surgery
(*Risk Reduction*)

- Breast
  - Mastectomy

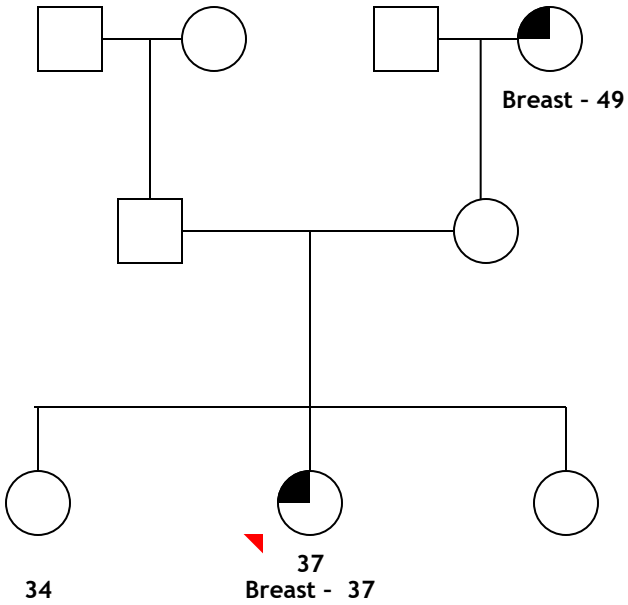
- Ovarian
  - Oophorectomy
  - Hysterectomy

Typical Family History



Breast Cancer

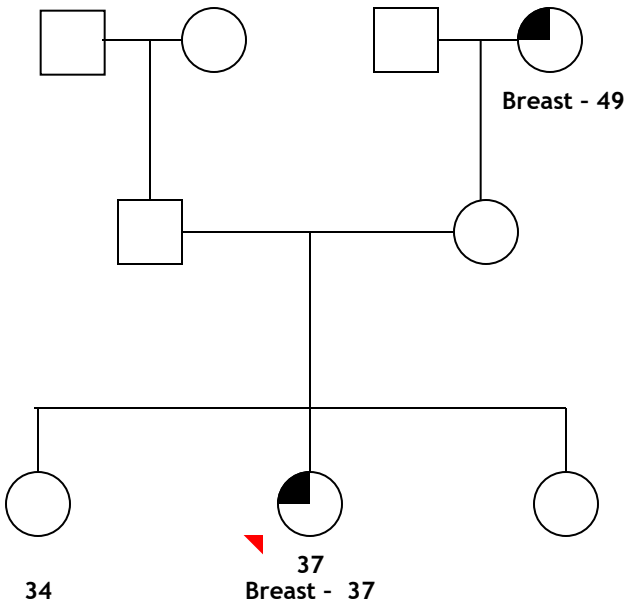
Ideal Patient



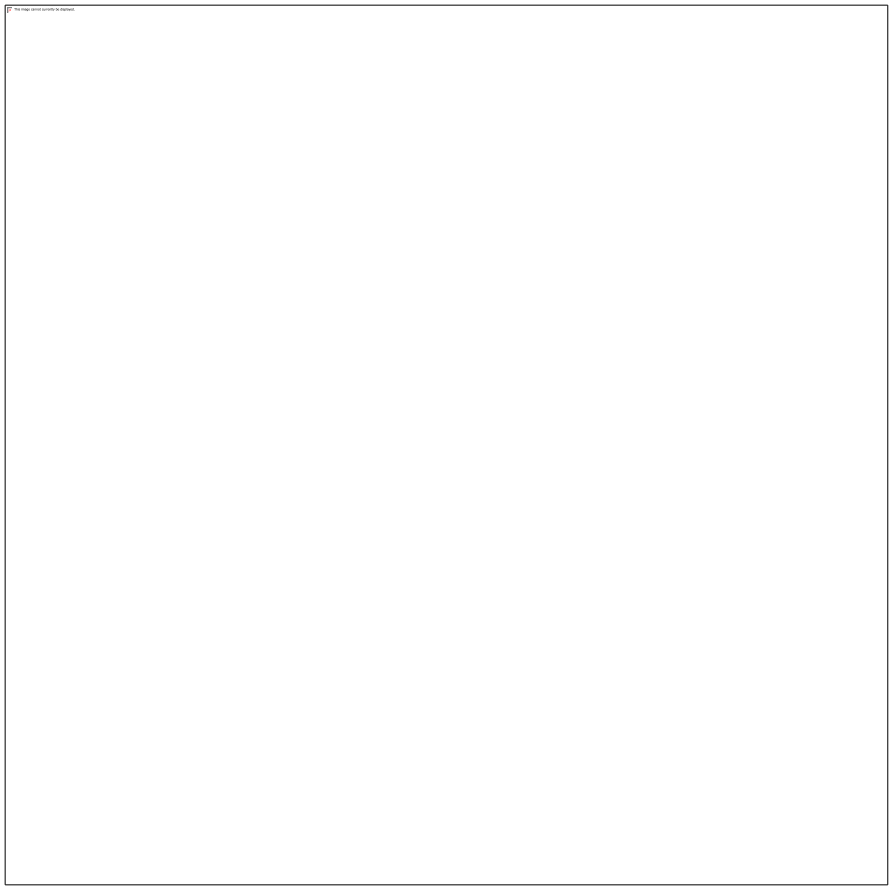
Breast Cancer

Patient Outcome

Positive for a BRCA1 mutation



Breast Cancer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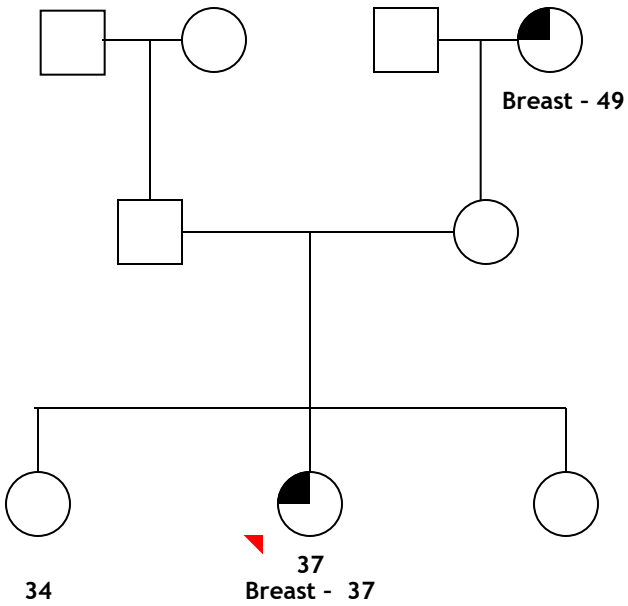
Examples of additional genes

Gene	BR	OV	CRC	MEL	PANC	PROS	GAST	END	OTH
BRCA	X	X		X	X	X			
Lynch		X	X		X		X	X	X
FAP			X		X		X		X
LFS	X	X	X	X	X	X	X	X	X
PHTS	X	X	X					X	
PJS	X	X	X		X		X	X	X
CHEK2	X		X			X			

Patient Outcome

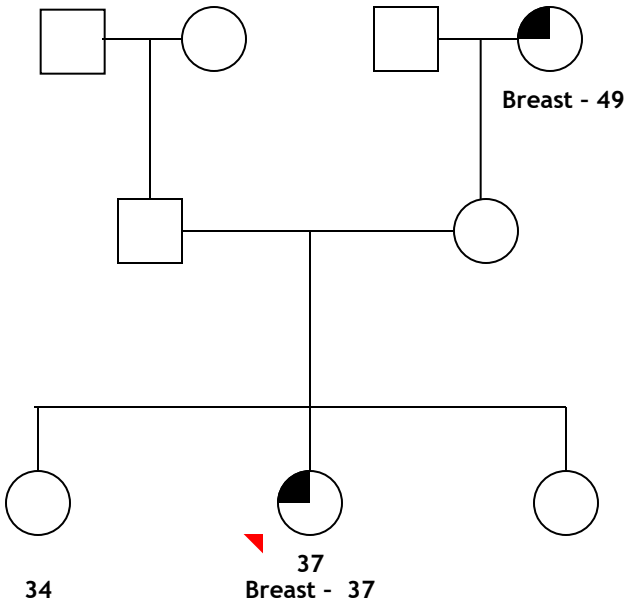
Positive for a PTEN mutation



Breast Cancer

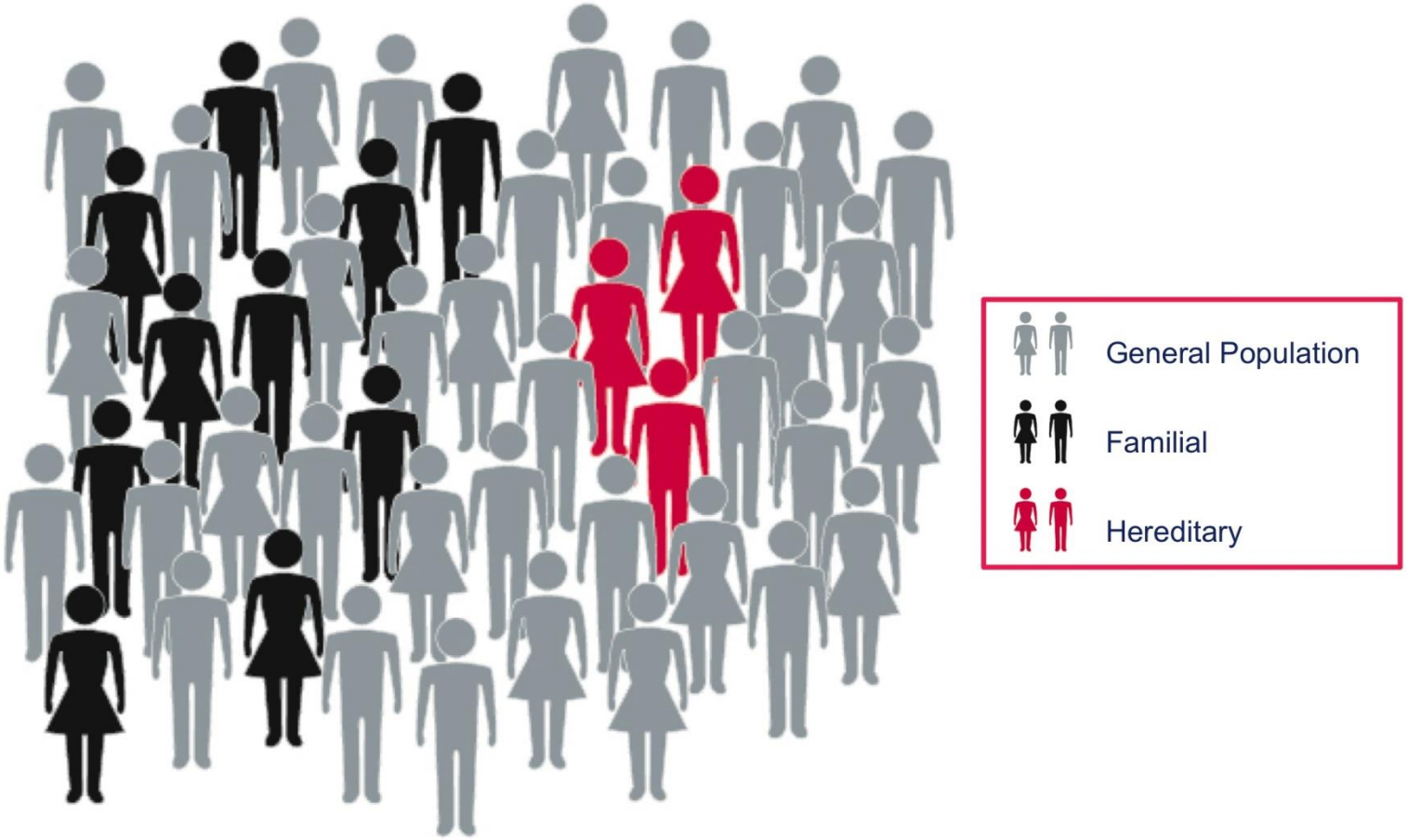
Patient Outcome

Positive for a BARD1 mutation



Breast Cancer

HOW MANY PATIENTS ARE AT RISK OF HEREDITARY BREAST AND OVARIAN CANCER?



Current Metrics for EWBC Patients

	Daily	Weekly	Monthly	Yearly
# of Patients Served	500	2,500	10.000	120,000
# of Patients Flagged as “High Risk”	125	625	2,500	30,000
% of Patients High Risk	25%	--	--	--
# of Patients Counseled	5-8	20-25	80-100	950- 1,200
% of Patients Counseled	5%	--	--	--

Current Volume Related Concerns

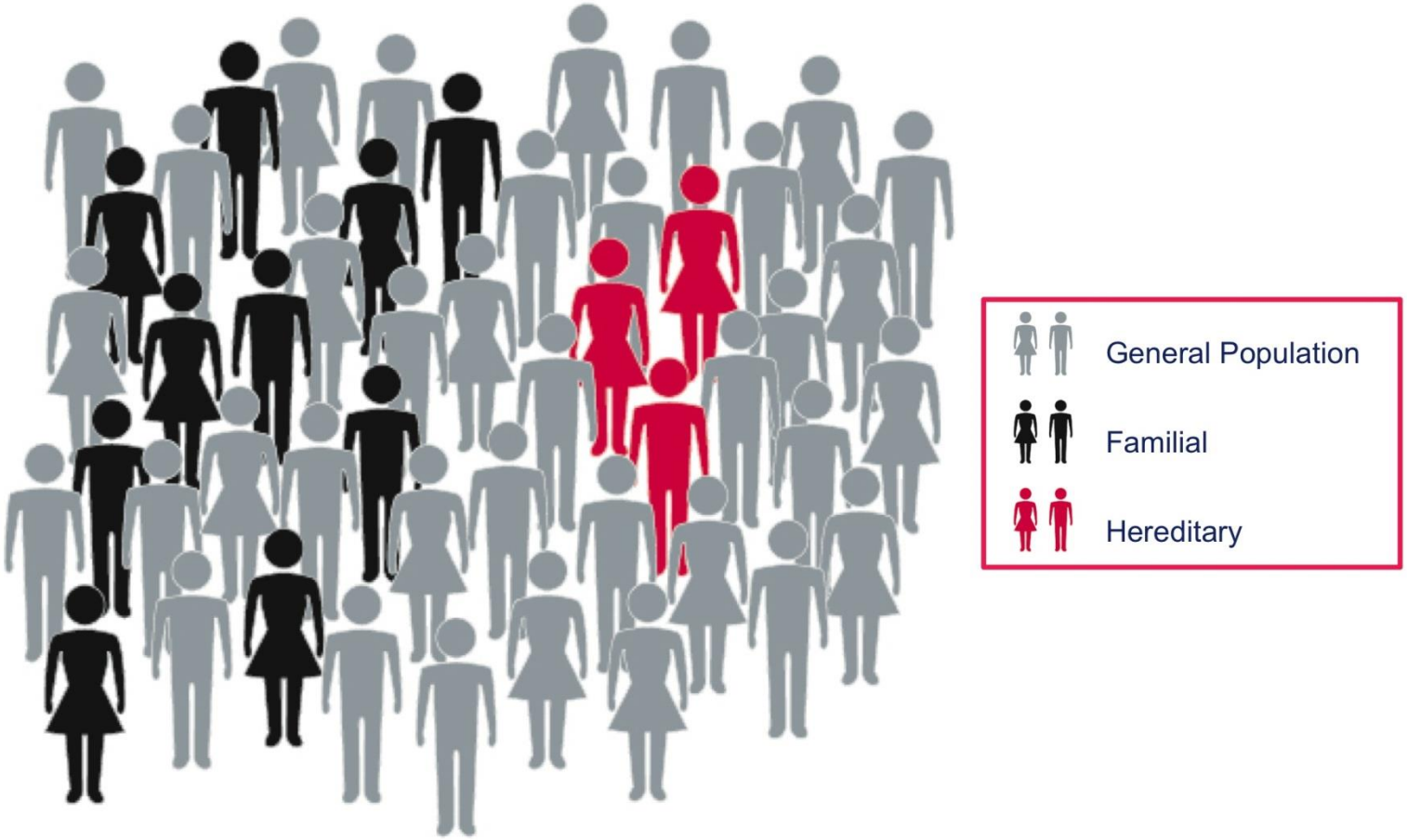
- 25% of patients identified as High Risk
  - Too many?
  - Criteria too broad?
  - May not be capturing the “most” at risk patients
- Less than 10% of patients call the Genetic Counseling and Cancer Risk Assessment Office
  - Why?
  - Barriers?
  - Should we be more proactive?

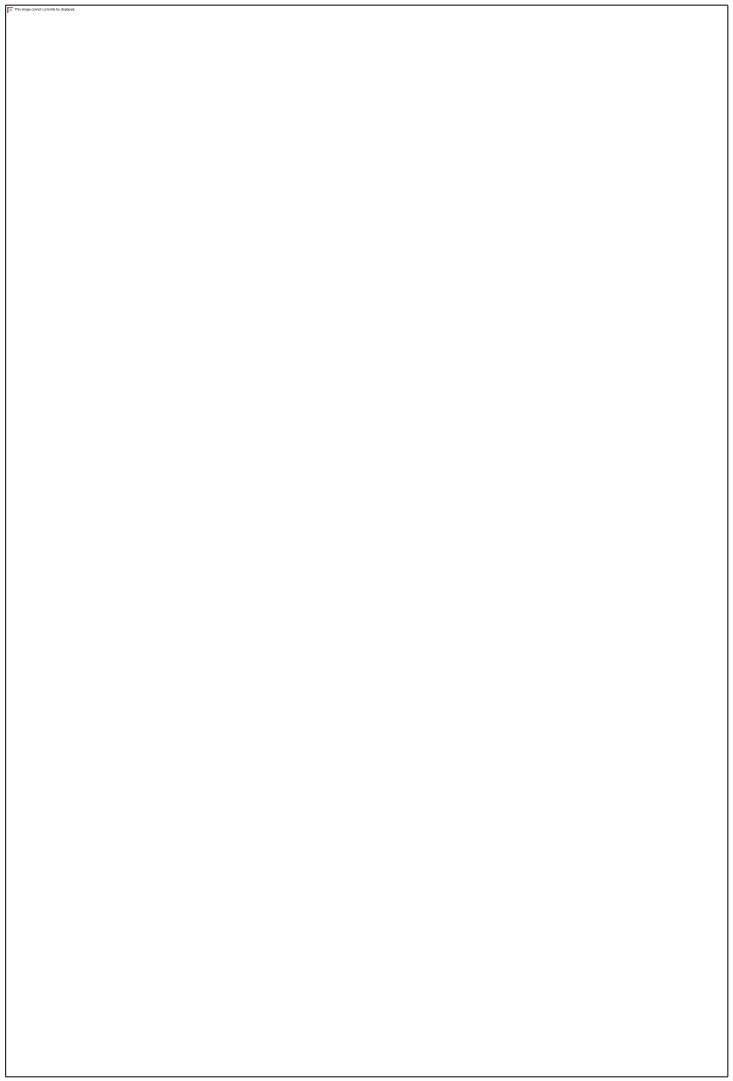
Additional Response

Monthly Community Lectures

- “For additional information, please consider attending an upcoming community lecture when our certified genetic counselor will discuss the differences between genetic/familial and sporadic breast cancer, EWBC’s protocol for genetic testing, insurance coverage criteria and how testing may impact your future management.”
- Average 45-50 attendees
- Staff available to answer questions and complete intake process

HOW MANY PATIENTS ARE AT RISK OF HEREDITARY BREAST AND OVARIAN CANCER?





Decoding Annie Parker.

- Based on true events, Decoding Annie Parker tells the life affirming story of two remarkable women; the irrepressible Annie Parker, a three time cancer survivor and the geneticist Mary-Claire King whose discovery of the breast cancer BRCA gene mutation is considered one of the most important discoveries of the 20th century.

New England Journal of Medicine

"*Breast-Cancer Risk in Families with Mutations in PALB2*"

- Cohort of 362 individuals with deleterious mutations were studied
- The absolute life-time risk of breast cancer for a woman with a PALB2 mutation and a family history of two or more first degree relatives with breast cancer was reported to be as high as 58%
- News traveled quickly about the identification of another important cause of hereditary breast cancer.

New England Journal of Medicine

"*Breast-Cancer Risk in Families with Mutations in PALB2*"

- Women with PALB2 mutations have a high risk (33%-58% by age 70) of breast cancer
- PALB2 also confers an elevated risk of both male breast cancer and pancreatic cancer
- While there are currently no widely-accepted guidelines for the medical management utilizing guidelines established for other conditions which similarly increase the risk for these cancers is commonplace
- The increase in risk warrants consideration of modification of standard population screening by starting younger and performing the screening at a greater frequency.

EWBC's Genetic Counseling and Cancer Risk Assessment Office
Jessica Salamone, ScM, CGC

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Fax: (585) 758-7089

"I choose not to keep my story private because there are many women who do not know that they might be living under the shadow of cancer. It is my hope that they, too, will be able to get gene tested, and that if they have a high risk they, too, will know that they have strong options."

"Life comes with many challenges. The ones that should not scare us are the ones we can take on and take control of."

- New York Times-Angelina Jolie