



Risk Assessment and Genetic Testing in Breast Disease

John P Smith, DO
Surgical Specialist, PA
Wichita, Kansas

Risk Assessment and Genetic Testing in Breast Disease



- Introduction
 - Gail Model
 - BRCA Testing
 - Genetic Counseling
 - OncoVue Testing
 - Summary
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Risk Assessment and Genetic Testing in Breast Disease

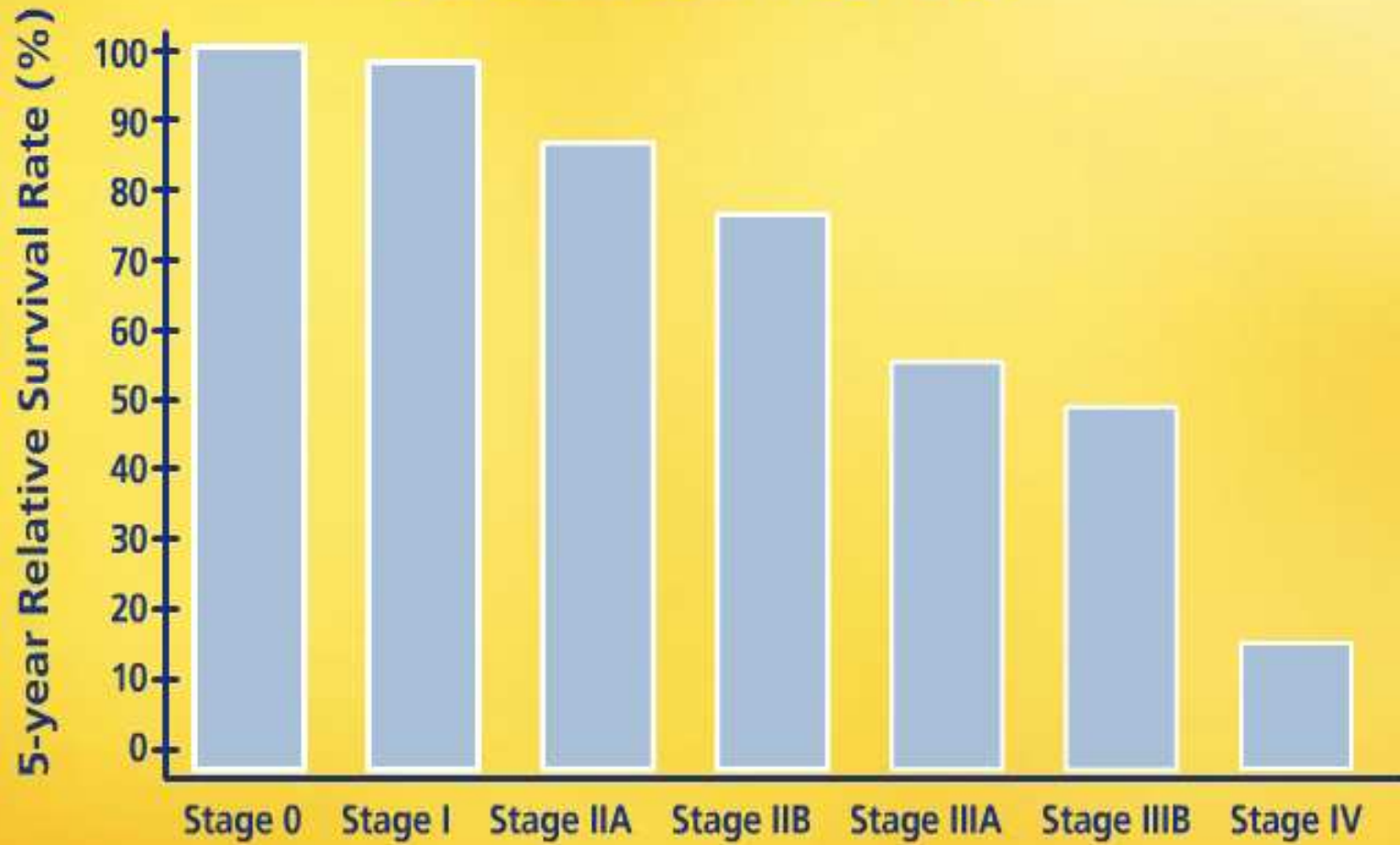
Introduction



Cancer's Devastation

- Who will get Cancer?
 - One out of every two men
 - One out of every three women
 - This year:
 - 1,445,000 will be told that they have cancer
 - 560,000 will die
 - \$206 Billion estimated by the NIH
 - \$78 Billion in direct medical expenses
 - \$18 Billion in productivity loss
 - \$110 Billion premature death productivity loss
-

Breast Cancer Survival by Stage





Risk Assessment and Genetic Testing in Breast Disease

Gail Model

Clinical Risk Assessment



- Gail model (1989)
 - Age interval and lifetime risk
 - Claus model (1994)
 - Family history/age of onset in relatives
 - *BRACAnalysis*® (1995)
 - Familial breast and ovarian cancer
-

Gail Model



- 1. Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)?
- 2. What is the woman's age?
(This tool only calculates risk for women 35 years of age or older.)
- 3. What was the woman's age at the time of her first menstrual period?
- 4. What was the woman's age at the time of her first live birth of a child?
- 5. How many of the woman's first-degree relatives - mother, sisters, daughters - have had breast cancer?
- 6. Has the woman ever had a breast biopsy?
 - 6a. How many breast biopsies (positive or negative) has the woman had?
 - 6b. Has the woman had at least one breast biopsy with atypical hyperplasia?
- 7. What is the woman's race/ethnicity?



Test Results

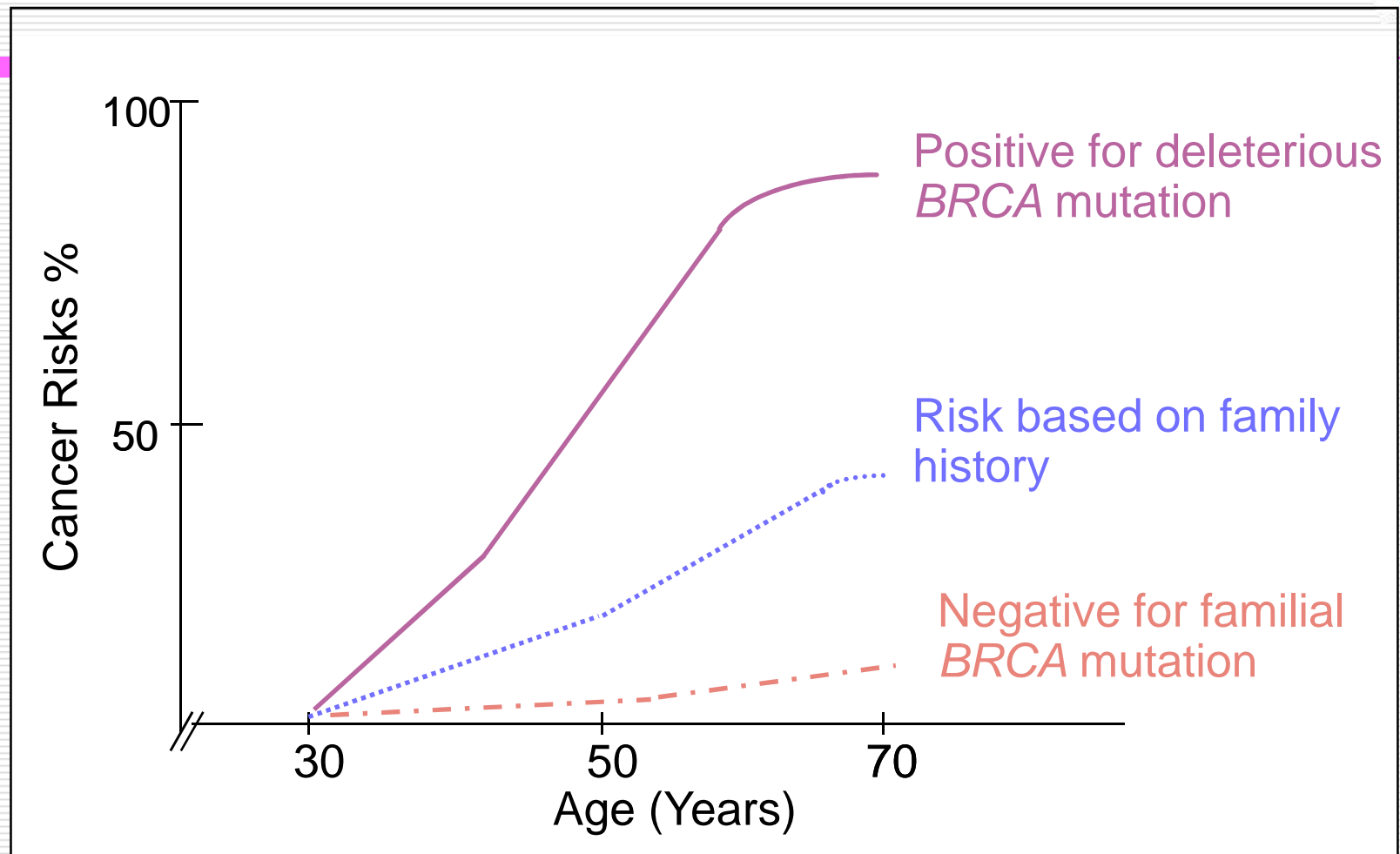
TABLE IV

SOME OTHER RISK FACTORS FOR BREAST CANCER*

- Prolonged or excessive estrogen exposure
- High fat intake/obesity
- Older ages (65-69 vs. 30-34 yr)
- Residency in North America or Europe vs Asia
- Residency in urban areas
- Higher educational status or family income
- Nulliparity or late age at first birth (≥ 30 vs. <20 yr)
- Absence of breastfeeding for long durations
- Early ages at menarche (<12 vs. ≥ 15 yr)
- Late ages at menopause (≥ 55 vs. natural menopause at <45 yr or removal of ovaries at a comparable age)
- Biopsy-confirmed proliferative breast disease
- Tallness (≥ 68 vs. <62 inches)
- Radiation to chest in moderate to high doses
- History of breast cancer in one breast
- History of primary cancer in endometrium or ovary
- Excessive alcohol consumption

**Modified from Brinton LA, Devesa S. "Etiology and Pathogenesis of Breast Cancer" in Harris JR, Lippman ME, Morrow M, Hellman S. Diseases of the Breast Lippincott-Raven Publishers, Philadelphia, 1996, p 166.*

Family History is Not Enough



Gail Model Not Valid for HBOC Families



- Will not identify testing candidates
 - No paternal history
 - No extended family- does NOT ask about 2nd degree relatives
 - No ovarian cancer history

- Incorrect estimate of HBOC cancer risks
 - Under/over estimate of breast cancer
 - Ovarian cancer not addressed

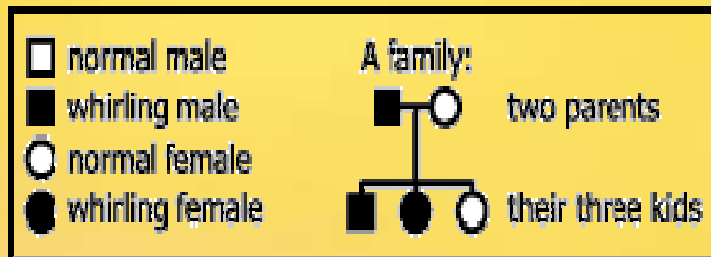
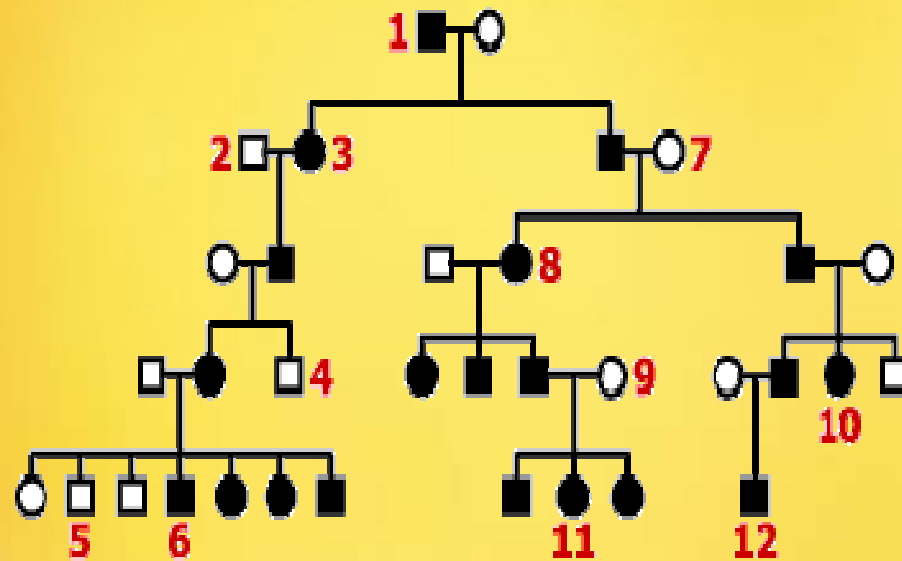


Risk Assessment and Genetic Testing in Breast Disease

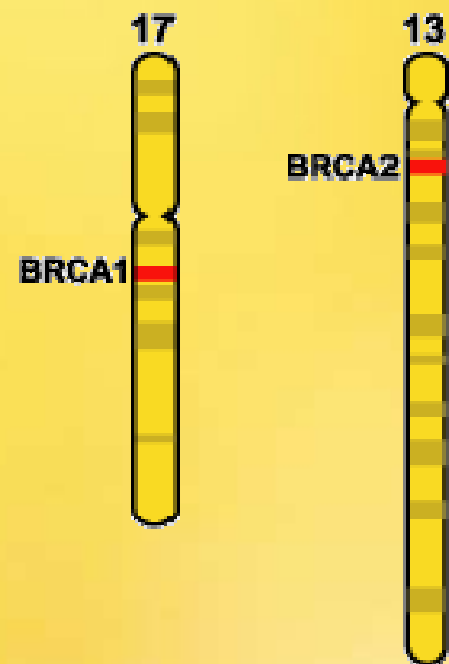
BRCA Testing

Breast Cancer Genes

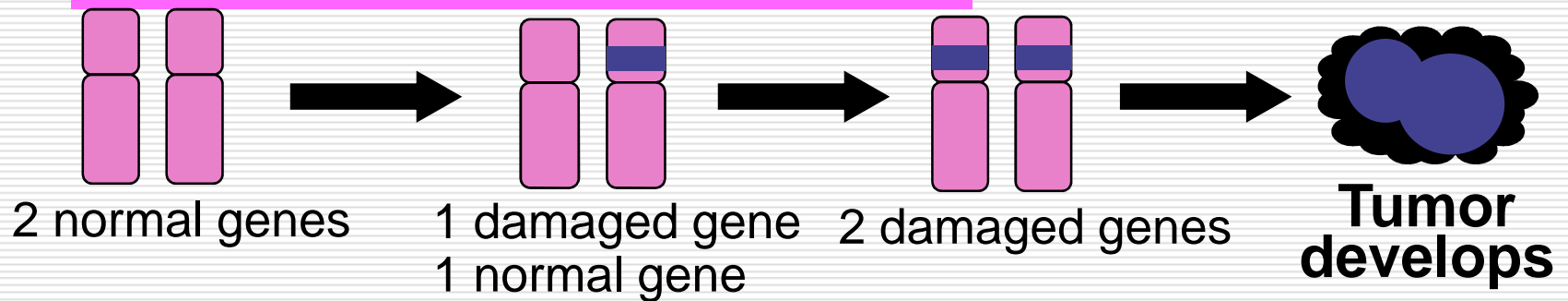
BRCA 1 and 2 Discovered 1994 and 1995



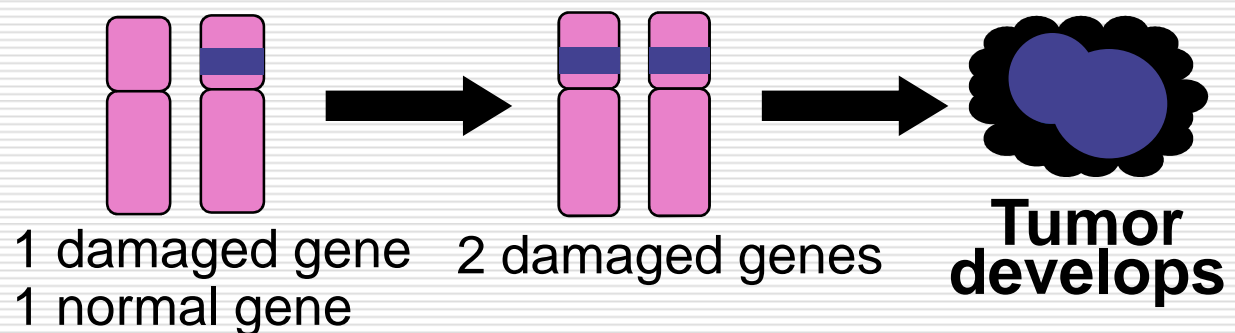
Chromosome 17 Chromosome 13



The Development of Hereditary Cancer



In hereditary cancer, one damaged gene is inherited.

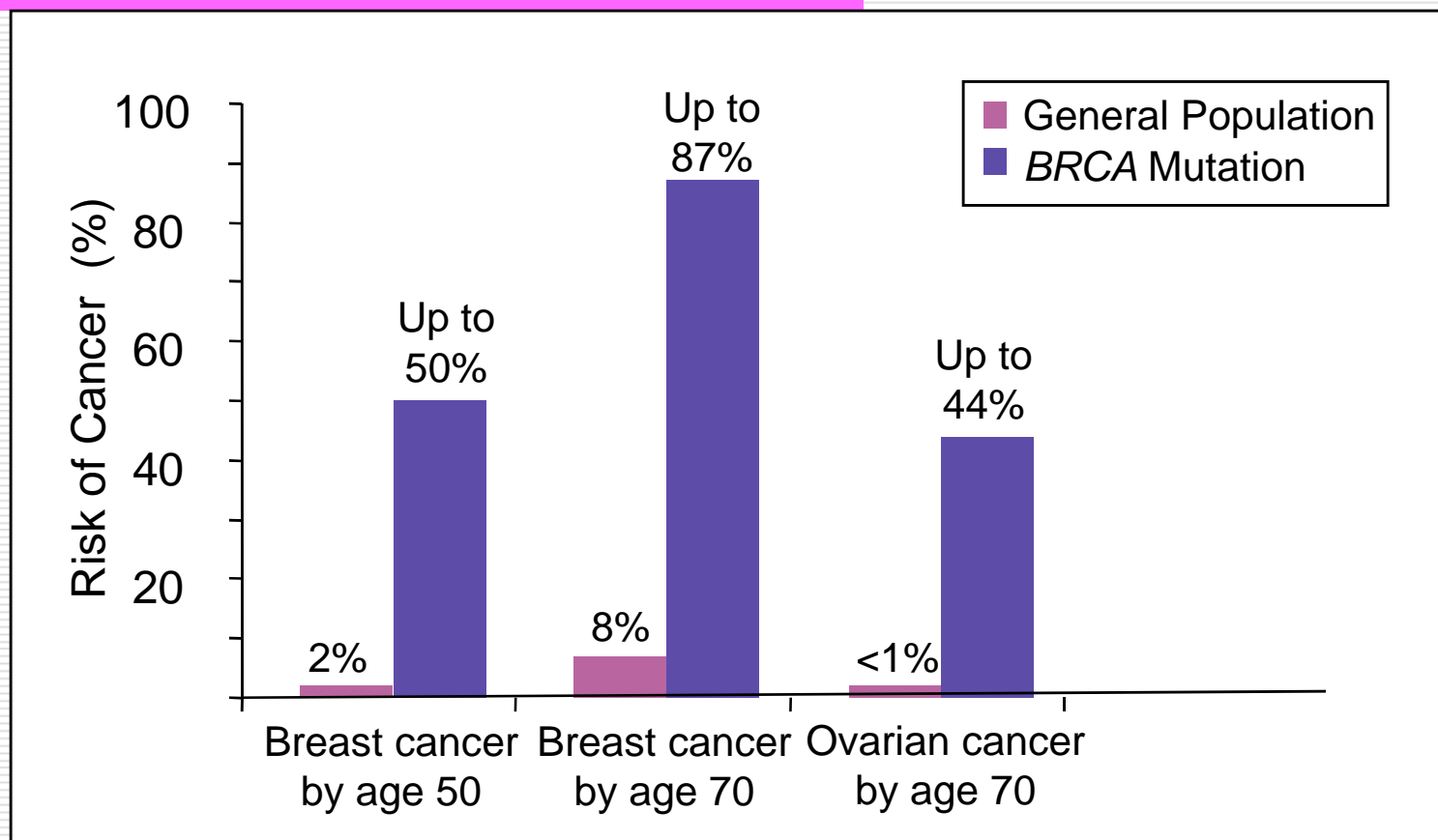


Hereditary Breast and Ovarian Cancer Syndrome



- Characterized by significantly increased risks for breast and ovarian cancer
- Most cases are caused by a *BRCA1* or *BRCA2* mutation
- Clinical testing is available to identify individuals with mutations

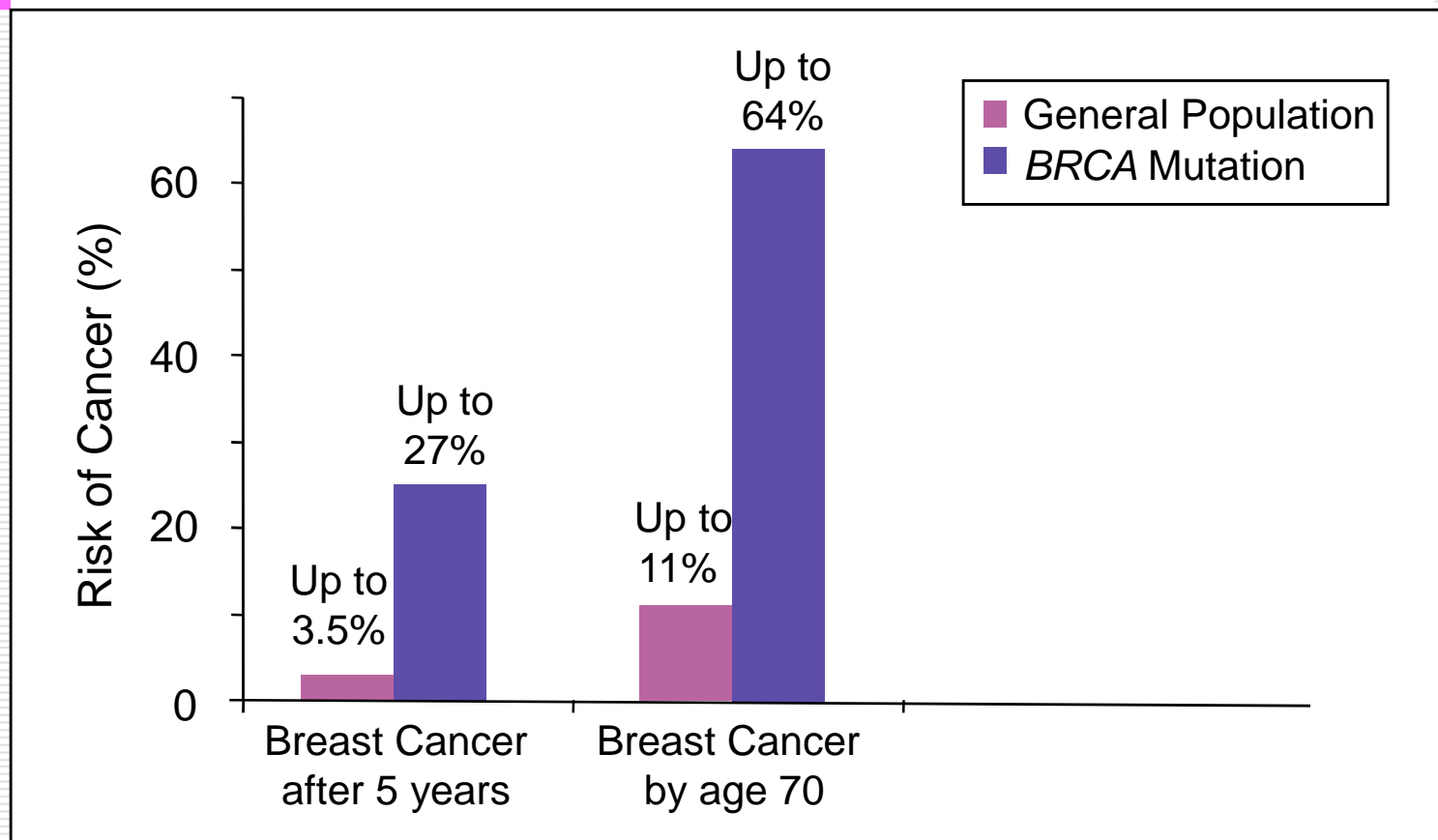
A *BRCA* Mutation Increases Breast and Ovarian Cancer Risks



Lancet 1994;343:692-695
NEJM 1997;336:1401-1408
AJHG 2003;72:1117-1130
JNCI 1999;15:1310-1316

AJHG 1995;56:265-271
Science 2003; 643-646
JCO 2005 23 (8): 1656-63
NCI (SEER) 2008

A *BRCA* Mutation Increases Risk of Second Breast Cancer



Ca Epi Biomarkers Prev. 1999;8(10):855-61

JNCI 1999;15:1310-6

JCO 1998;16:2417-25

Lancet 1998;351:316-21

JCO 2004;22:2328-35

Lancet 1994;3343:692-5

Gynecol Oncol. 2005 Jan;96(1):222-6

Ovarian Cancer AFTER Breast Cancer in *BRCA* carriers



- 10-fold increased risk compared to non-carriers
 - Limited effective ovarian cancer screening
 - Prophylactic bilateral salpingo-oophorectomy recommended

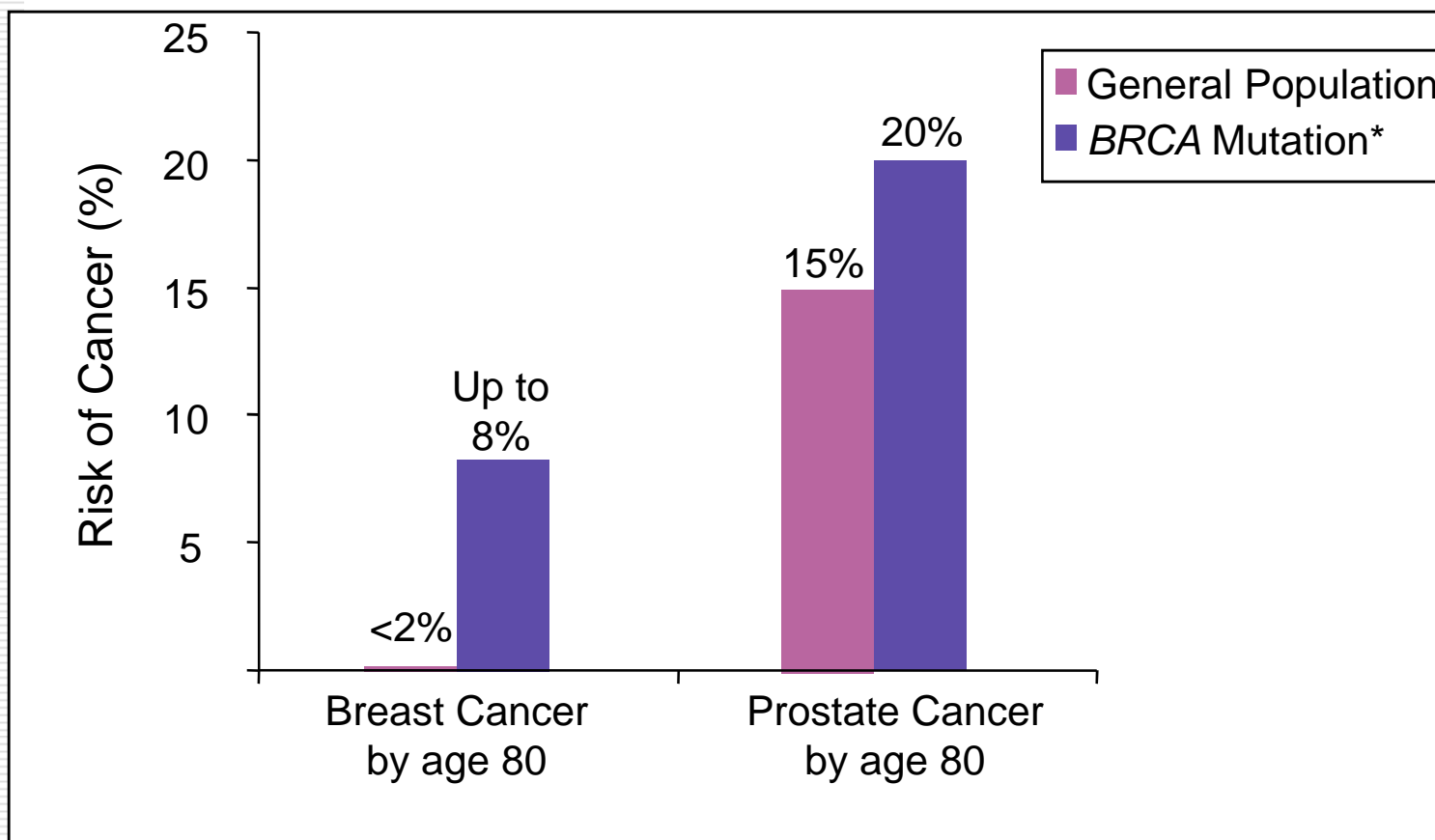
- Up to 13% risk for ovarian cancer within 10 years following breast cancer diagnosis

J Clin Oncol. 1998 16:2417-242
Gynecol Oncol. 2005 Jan;96(1):222-6

Gynecol Oncol. 2007;107:159-162

www.nccn.org

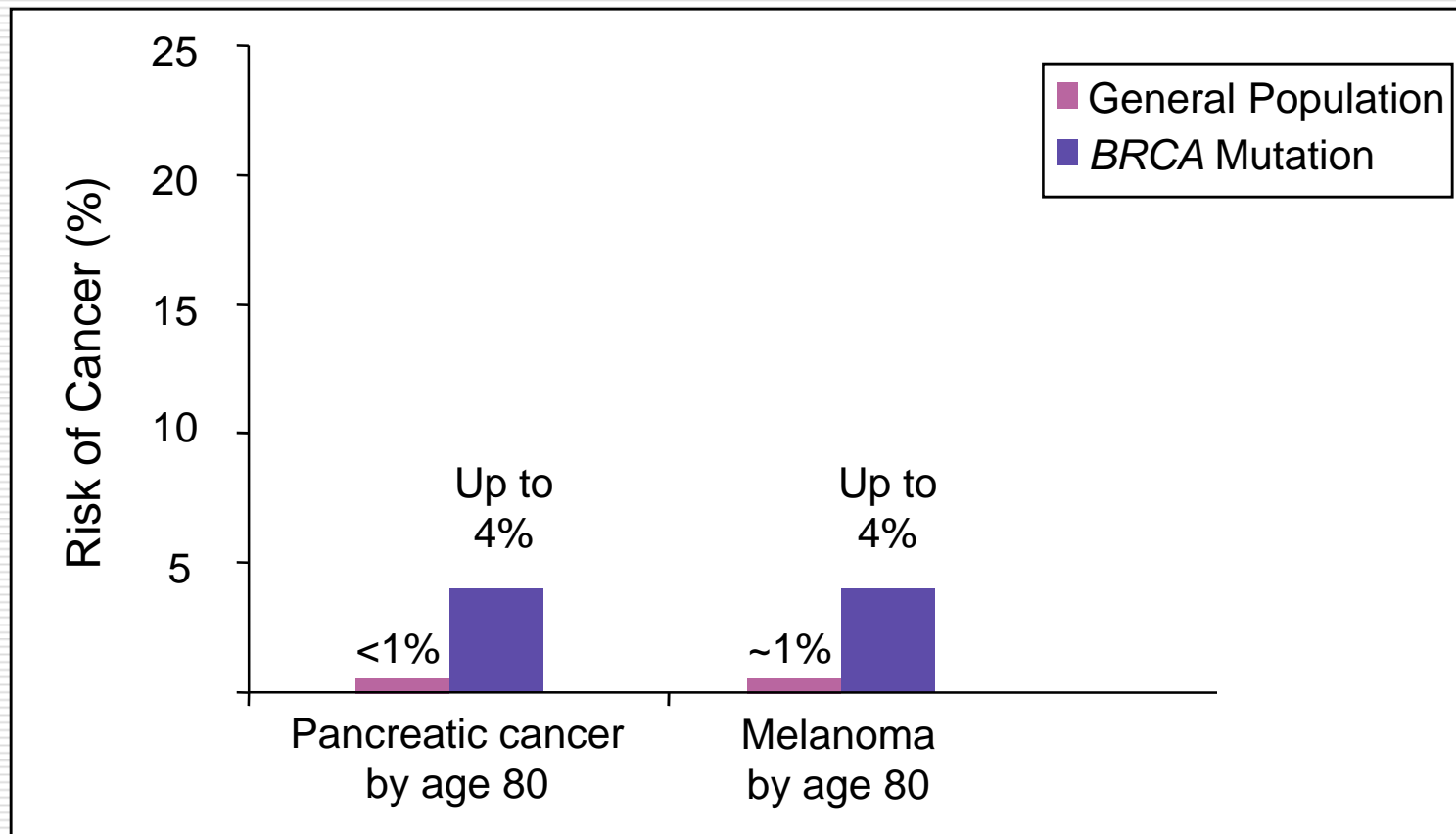
Risks in Men With a *BRCA* Mutation



Risks for male *BRCA* mutation carriers are less characterized

JCO 2004;22: 735-42
NCI (SEER) 2008
JNCI. 2007 5;99(23):1811-4

Risks of Other Cancers



JNCI 1999;15:1310-1316

JNCI 2002;94 1365-72

J Med Genet. 2005 Sep;42(9):711-9

NCI (SEER) 2008

Prevalence of *BRCA* Mutations



	Family History		
Patient's History	No breast cancer <50 or ovarian cancer	Breast cancer <50, no ovarian cancer	Ovarian cancer in one relative, no breast cancer <50
No breast or ovarian cancer	2.8%	4.5%	5.6%
Breast cancer <50	6.8%	15.8%	16.9%
Ovarian cancer, no breast cancer	8.8%	23.1%	21.1%

Prevalence of Mutations in Ashkenazi Jewish Individuals



	Family History		
Patient's History	No breast cancer <50 or ovarian cancer	Breast cancer <50, no ovarian cancer	Ovarian cancer in one relative, no breast cancer <50
No breast or ovarian cancer	6.9%	13.7%	15.6%
Breast cancer <50	12.0%	24.2%	38.8%
Ovarian cancer, no breast cancer	22.2%	37.0%	42.0%

Breast Carcinoma in situ (CIS)



Family History (Includes at least one first or second degree relative)

PATIENT HISTORY	No breast cancer <50 or ovarian cancer	Breast cancer <50 in 1 relative; no ovarian cancer	Breast cancer <50 in <1 relative; no ovarian cancer	Ovarian cancer in 1 relative; no breast cancer <50	Ovarian cancer in >1 relative; no breast cancer <50	Breast cancer <50 and ovarian cancer
CIS < 50, no invasive breast or ovarian cancer	4.3%	8.6%	16.8%	8.6%	15.7%	19.3%
CIS ≥ 50, no invasive breast or ovarian cancer	2.0%	3.8%	5.1%	3.9%	0%	10.2%

Family History Considerations



- One-half of *BRCA* carriers inherit the mutation from their father
- Ovarian cancer is a very important indicator
- 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

“Red Flags” for Hereditary Breast and Ovarian Cancer Syndrome



- Breast cancer before age 50
- Ovarian cancer at any age
- Male breast cancer at any age
- Multiple primary cancers
 - Breast and/or ovarian
- Ashkenazi Jewish ancestry
- Relatives of a *BRCA* mutation carrier

Testing for Hereditary Cancer Risk



-
- Available through healthcare providers
 - Federally-certified clinical laboratory
 - Turnaround time ~2 weeks
 - Expedited processing available
 - Insurance preauthorization services available



Risk Assessment and Genetic Testing in Breast Disease

Genetic Testing



Test Results

Components of the Genetic Counseling Process

1. Information gathering
2. Diagnosis
3. Risk assessment
4. Information giving
5. Psychological assessment and counseling
6. Help with decision making
7. On-going client support

[Modified from: AP Walker (1997)]

Interpreting Test Results



- Positive for a deleterious mutation
- No mutation detected
 - Mutation previously identified in the family
 - No known mutation in the family
- Genetic Variant of Uncertain Significance



Test Results

Potential benefits of a positive test result:

- Reduction of uncertainty
 - Opportunity for preventive measures or enhanced surveillance
 - Opportunity to alert relatives to risk
 - Opportunity to participate in clinical trials or other research
-



Test Results

Potential burdens of a positive test result:

- Anxiety
 - Depression
 - Reduced self-esteem
 - Limited effectiveness of interventions
 - Risks and costs of additional surveillance or prophylaxis
 - Strained relationships with a partner or with relatives
 - Guilt about possible transmission to children
 - Stigmatization
 - Discrimination by insurers or employers
-



Test Results

Potential benefits of a negative test result:

- Reassurance
 - Opportunity to avoid unnecessary surveillance and prophylaxis
 - Reduced costs
-



Test Results

Potential burdens of a negative test result:

- False reassurance
 - Survivor guilt
-



Test Results

Potential burdens of an alteration of uncertain significance:

- Adverse psychological impact
 - Need for continued surveillance
 - Need for testing of family members to determine significance
-



Test Results

COMMON MISCONCEPTIONS:

- A positive result means cancer is present.
 - A positive result means cancer is certain to develop.
 - A positive result means improved detection, prevention, treatment or survival.
 - A negative result means cancer is not present.
 - A negative result means cancer will not develop.
 - A negative result means an inherited cancer susceptibility is not present.
 - Mutations conferring a susceptibility to breast or ovarian cancer are transmitted only by women.
-

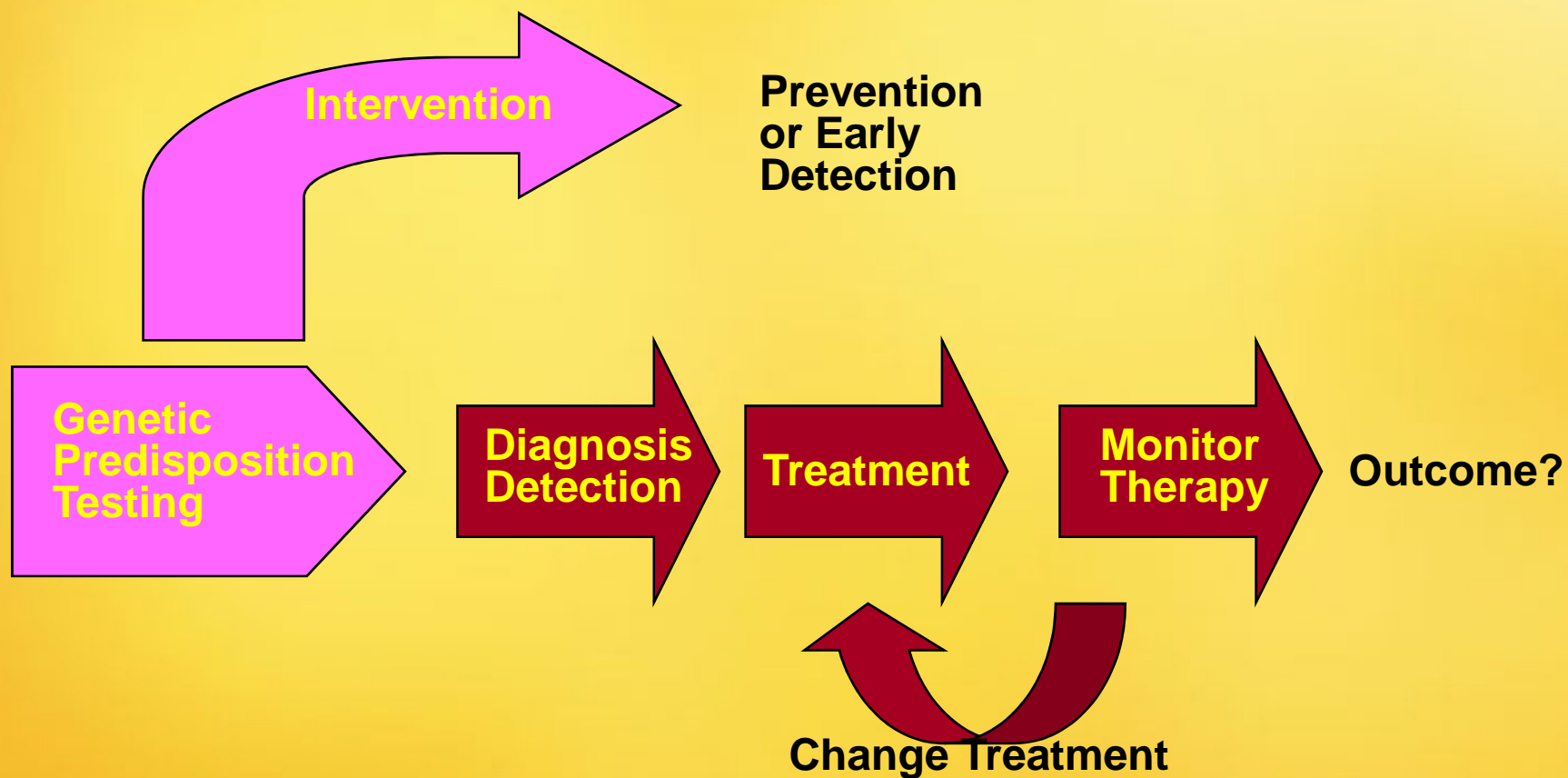


Risk Assessment and Genetic Testing in Breast Disease

OncoVue

Breast Cancer Risk Test

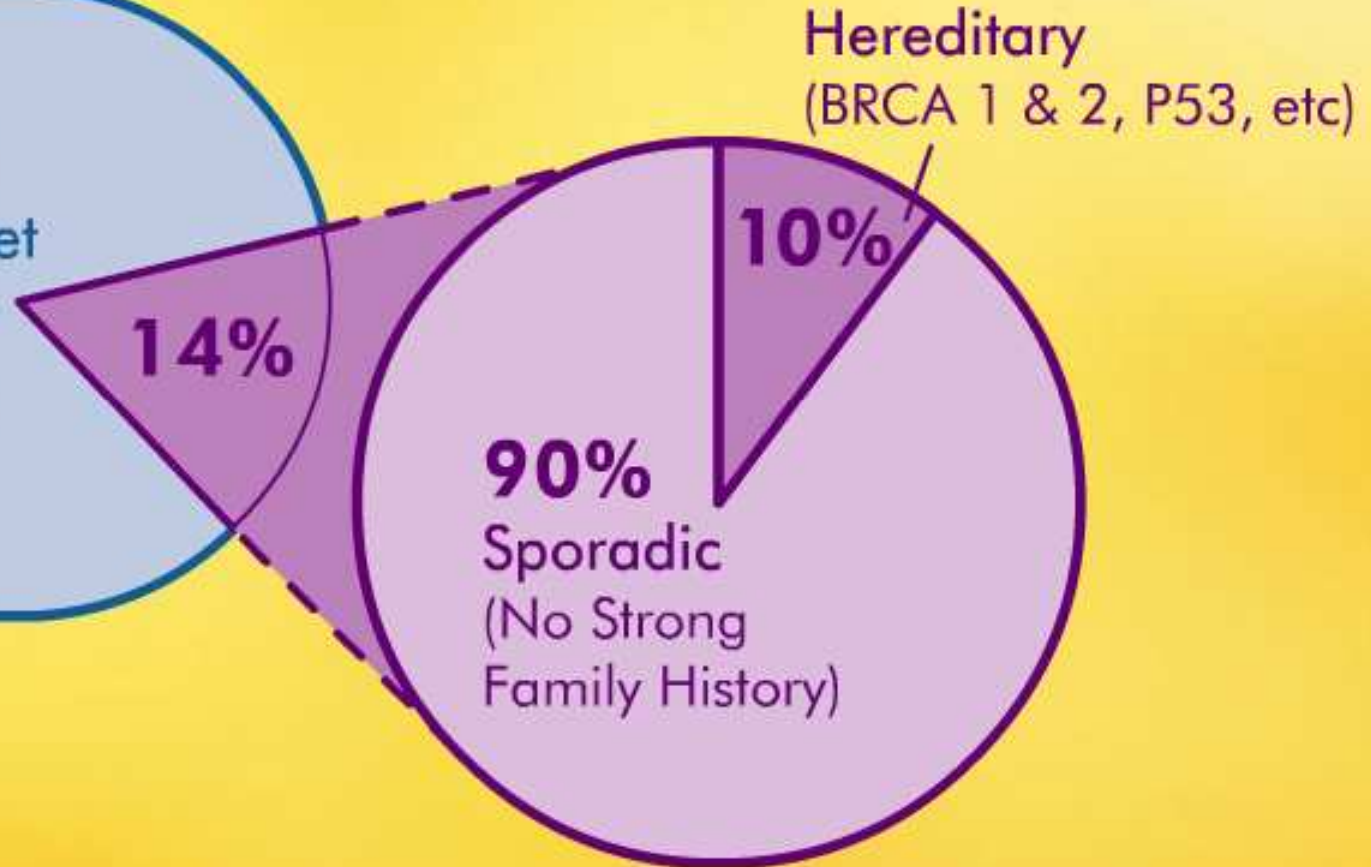
Changing Health Care Model



All Women



Women with Breast Cancer



2005, American Cancer Society

Genetics 101

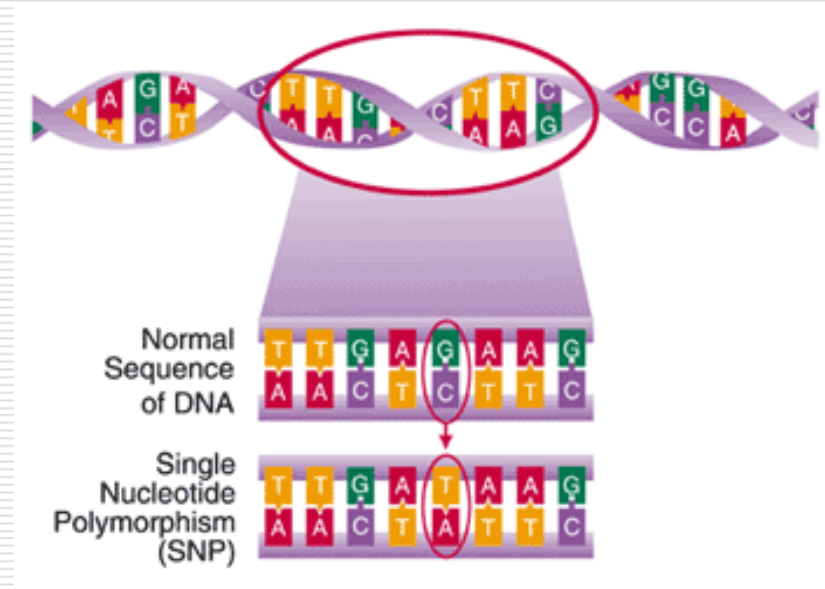


“Genetically, all individuals are 99.9% the same.”



SNP Genomics

- GENOME: The total DNA content of all genes on the chromosomes of individuals
- GENOMICS: the study of genes and their function
- 3 billion base pairs in the human genome
- All individuals have 99.9% identical sequence
- Single Nucleotide Polymorphism: (SNP) Single Base Pair Change. Our inherited differences and susceptibility to disease



117 SNPs in Diverse Pathways



- ❑ Steroid Hormone Receptors/Metabolism (22)
- ❑ DNA Damage/Repair (30)
- ❑ Xenobiotic/Conjugation/Detoxification (14)
- ❑ Cell Cycle and Apoptosis (14)
- ❑ Growth Factors and Signaling (11)
- ❑ Immune Modulation/Cytokines (8)
- ❑ Invasion/Metastasis (7)
- ❑ Lipid Metabolism (5)
- ❑ Free Radical Scavengers (3)
- ❑ Angiogenesis (3)

Gene Criteria for Selection



- **Multiple Common Polymorphisms over multiple genes**
 - **Mostly Single Nucleotide Polymorphisms**
 - **13 genes show significance for age dependence**
 - **Some genes that indicate high risk pre-menopausal become “protective genes” post-menopausal**
 - **Pathways**
 - **Steroid Hormone Metabolism (6)**
 - **DNA Repair (6)**
 - **Growth Factors (3)**
 - **Cell Cycle and Apoptosis (Programmed Cell Death) (1)**
 - **Extracellular Matrix (1)**
 - **Free Radical Scavengers (1)**
 - **Xenobiotic Metabolism (1)**
 - **22 SNPs on 19 genes located on 13 different chromosomes**
-



OncoVue®

breast cancer risk test



Company History



- ❑ **Originated in 1993 at Samuel Roberts Noble Foundation**
 - ❑ **Transferred to Oklahoma Medical Research Foundation and spun out in 1999**
 - ❑ **Located in the PHF Research Park, Oklahoma City, OK**
-

InterGenetics' Mission



“To identify individuals who are unknowingly predisposed to potentially fatal diseases and provide medical intervention to change their outcome”

OncoVue®...different from other Genetic Tests

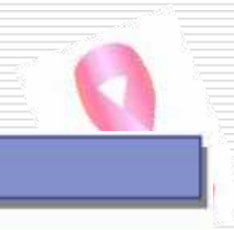


- Looks at combinations of genes and epistatic interactions
 - DNA Repair
 - Cell cycle control
 - Steroid hormone metabolism

- In combination with personal history and lifestyle factors

= Risk for sporadic breast cancer

Jane Doe was 31 when she took the test

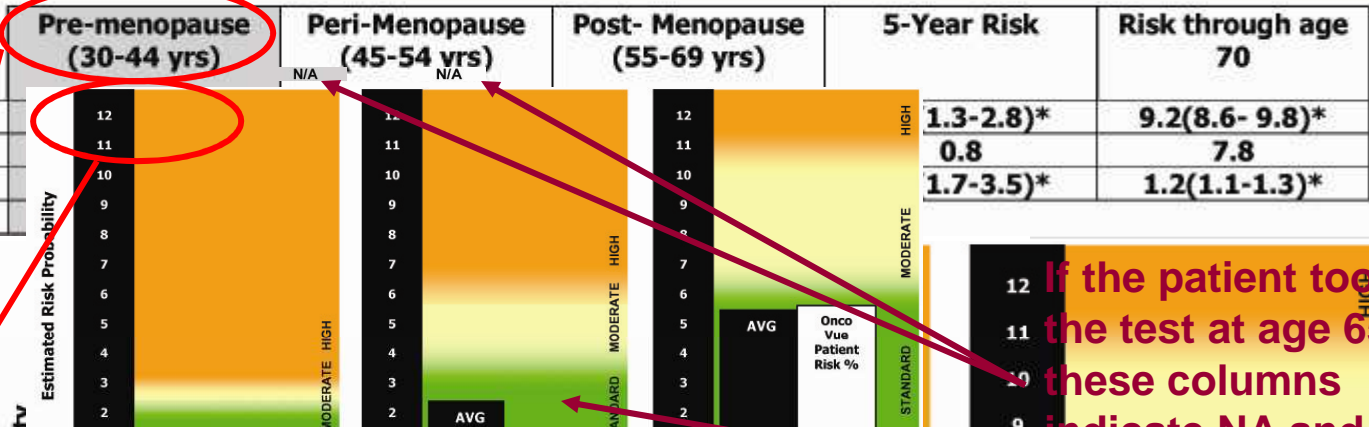


PATIENT REPORT

Patient Name: Sample Patient Date of Receipt: January 6, 2007
 Date of Birth: October 23, 1975 Date Reported: January 9, 2007

SUMMARY OF RISKS IN THIS REPORT

	Pre-menopause (30-44 yrs)	Peri-Menopause (45-54 yrs)	Post-Menopause (55-69 yrs)	5-Year Risk	Risk through age 70
OncoVue® Patient Risk %	12	N/A	N/A	1.3-2.8)*	9.2(8.6- 9.8)*
Average Woman's Risk %	12	12	12	0.8	7.8
Relative Risk	1.0	0.8	0.8	1.7-3.5)*	1.2(1.1-1.3)*
OncoVue Risk Category	High	High	High		



and her risk of developing breast cancer

The **OncoVue® Patient Risk** is an estimated percent probability which takes into account the patient's genetic contribution for risk and certain personal history measures to determine her individual risk of developing breast cancer based on the patient's age on the date of the test. ***95% confidence interval**, shown as the numbers in parentheses following the OncoVue Patient Risk, indicates that there is a 95 percent probability that the true risk percentage lies within the specified range. The **Average Woman's Risk** reflects the average woman's probability of developing breast cancer within each age category and is calculated using the National Cancer Institute's Devcan program (<http://srab.cancer.gov/devcan>). **Relative Risk** refers to the risk of the patient compared to the average woman. If the OncoVue Patient Risk and the Average Woman's Risk were the same, the relative risk would be 1.0. The **OncoVue® Patient Risk Category** is provided as an additional reference and does not replace the computed estimated risk probabilities. Standard, Moderate, and High risk levels on the graphs are presented as a general guide based upon the computed risk for the patient. The risk categories for the specified age intervals are shown in the following table:

OncoVue Risk Category	Pre-menopause (30-44years)			Peri-menopause (45-54 years)			Post-menopause (55-69 years)		
	Standard	Moderate	High	Standard	Moderate	High	Standard	Moderate	High
Estimated Risk Probability	<2%	2%-3%	>3.0%	<3.6%	3.6%-6.3%	>6.3%	<6%	6.0%-10.8%	>10.8%

The **Five-Year OncoVue Patient Risk Category** represents the patient's risk in the next five years based on the patient's age on the date of test. The **Risk through age 70** represents the patient's cumulative risk from the age of the patient on the date of the test through age 70. The **Average Woman's Risk through Age 70** represents the average woman's risk of developing breast cancer from the age of the patient on the date of the test through age 70. The **Age Interval Risk** is based on the patient's age on the date of the test and includes her risk for the entire age interval.

performed pursuant to an agreement for use of the test for clinical or research purposes only. This test is not intended for use in a clinical setting.

Number: 37D1047365. Joseph M. Quashnock, Ph.D., HCLD (ABB), FACB- Laboratory Director, Clinical Testing- Rev. 11/12/07

OncoVue® Performance



- ❑ Evaluate with informative measures that reflect improvement in individual risk estimation
- ❑ Not a traditional diagnostic test
- ❑ Gail Model is current clinical tool for risk estimation for the majority of women especially those without a strong family history

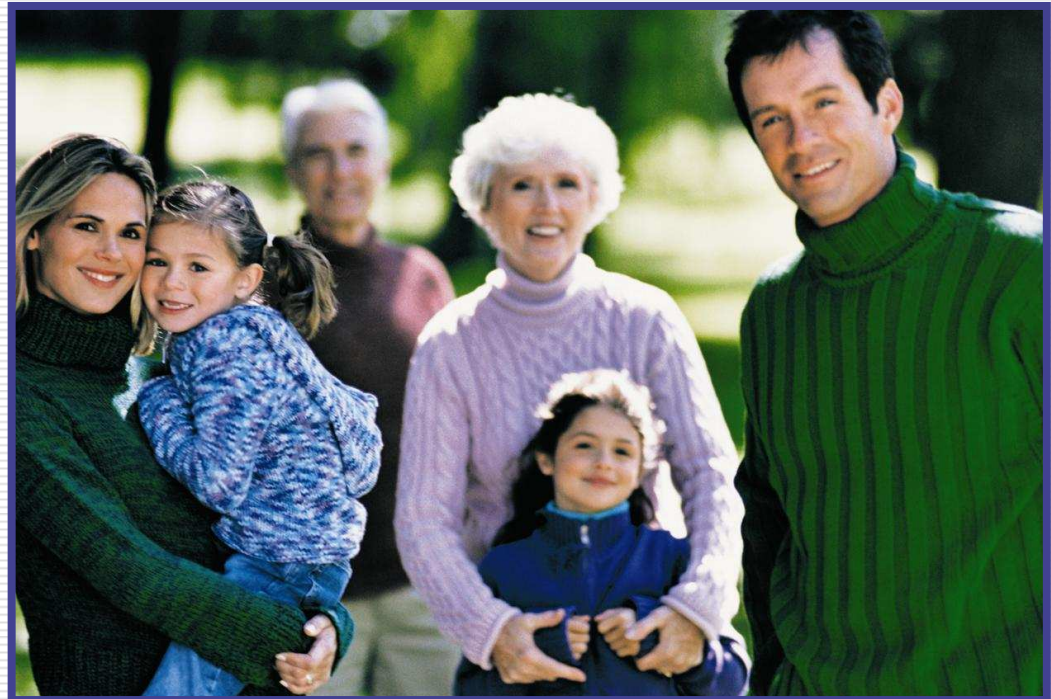


Risk Assessment and Genetic Testing in Breast Disease

Summary



Knowledge
is Power
and Hope





Supplemental Slides

Managing Hereditary Cancer Risk

improved outcomes with proven medical interventions*



-
- Surveillance
 - Chemoprevention
 - Prophylactic surgery

**Individual risk reduction may vary based on personal health history*

Surveillance for Breast Cancer



Procedure	Age to begin	Frequency
Breast self-exam	18 yrs	Monthly
Clinical breast exam	25 yrs	Twice a year
Mammography	25 yrs	Yearly
MRI	25 yrs	Yearly

Chemoprevention of Breast Cancer



Tamoxifen:

- Affected *BRCA* carriers: up to 53% decrease for contralateral breast cancer
- Unaffected *BRCA2* carriers: 62% decrease*
- Unaffected high-risk: 45% decrease

Raloxifene:

- Raloxifene is as effective as Tamoxifen in reducing the risk of invasive breast cancer
- No data specifically for *BRCA* mutation carriers

Aromatase Inhibitors:

- Currently under investigation

* Not statistically significant

Int J Cancer. 2006;118(9):2281-4
Lancet 2000;356:1876-81
JAMA 2001;286:2251-6
JNCI 1998; 90:1371-88
JAMA 2006;295(23):2727-41

Prophylactic Mastectomy



≥ 90% breast cancer risk reduction in *BRCA* carriers

- Total (simple) mastectomy more effective than subcutaneous mastectomy

Surveillance for Ovarian Cancer



-
- CA-125
 - Pelvic exams
 - Transvaginal ultrasound

Additional screening techniques under investigation due to limited efficacy of current options

Chemoprevention of Ovarian Cancer

Oral Contraceptives



- Up to 60% risk reduction for ovarian cancer
- Current literature supports there is **no evidence** that current low-dose oral contraceptive formulations increase the risk of early onset breast cancer for mutation positive individuals

NEJM 1998; 339:424-8
NEJM 2001;345:235-40
JNCI 2002;94:1773-9
Ca Epi Biomarkers Prev. 2005 Feb;14(2):350-6
JCO. 2007 ;112(S3):700-709
Cancer Epidemiol Biomarkers Prev. 2006;15(10)

Prophylactic Oophorectomy

Recommend bilateral salpingo-oophorectomy (BSO)
at age 35 or after childbearing is complete



- Up to 96% ovarian cancer risk reduction in *BRCA* carriers
- Can reduce **breast** cancer risk by up to 68% for both *BRCA1* and *BRCA2* carriers

Occult Cancers in *BRCA* carriers at BSO



- Prevalence of occult tumors: up to 23.5%
 - fallopian tube
 - ovarian cancer

- Removal of both ovaries and fallopian tubes is recommended

- Careful pathological examination after BSO
 - even if gross pathology is normal

Gynecol Oncol. 2002;87(1):52
Br J Cancer 2004; 90:1492-7
NEJM 2002;346:1616-22
Am J Surg Pathol 2001;25:1283-9
JCO. 2005 1;23(1):127-32
Gynecol Oncol. 2005 Aug;98(2):179-81

Medical Management in Male *BRCA* Carriers



Site	Procedure	Frequency
Breast	Clinical breast exam	Yearly
	Breast self-exam	Monthly
	Mammography	Based on Clinical Findings
Prostate	Prostate-specific antigen testing	Yearly
	Digital rectal exam	Yearly

Impact of HBOC in Your Practice



- Up to 22% of breast cancer patients are at-risk for hereditary breast and ovarian cancer syndrome
- Mutations in *BRCA1* and *BRCA2* dramatically increase the risks for breast and ovarian cancer
- Specific medical management options are available to reduce cancer risks

Hormone Replacement Therapy (HRT)



- Option after prophylactic oophorectomy
 - No significant increase in breast cancer risk for mutation carriers

- Recommend to discontinue HRT use ~ 50 years of age
 - Approximate time of expected natural menopause