

WHAT IS NEW IN HEREDITARY CANCER SYNDROMES?

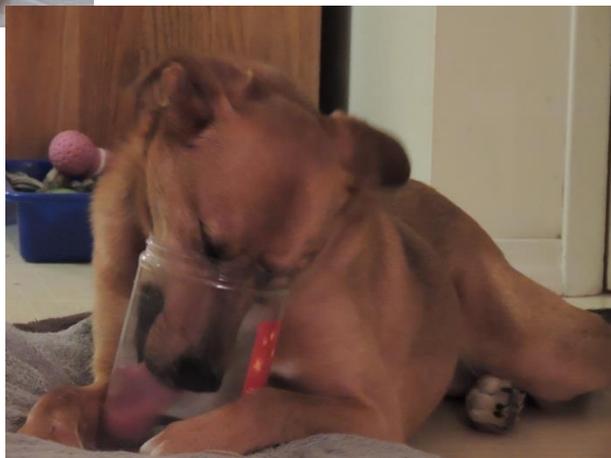
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Objectives

- Identify families who would benefit from genetic risk assessment and testing
- Describe the benefits, limitations, and challenges of genetic testing in managing families with hereditary risk
- Describe emerging trends in genetic care

No relevant financial relationships to disclose



Why should individuals be aware of their risk factors?

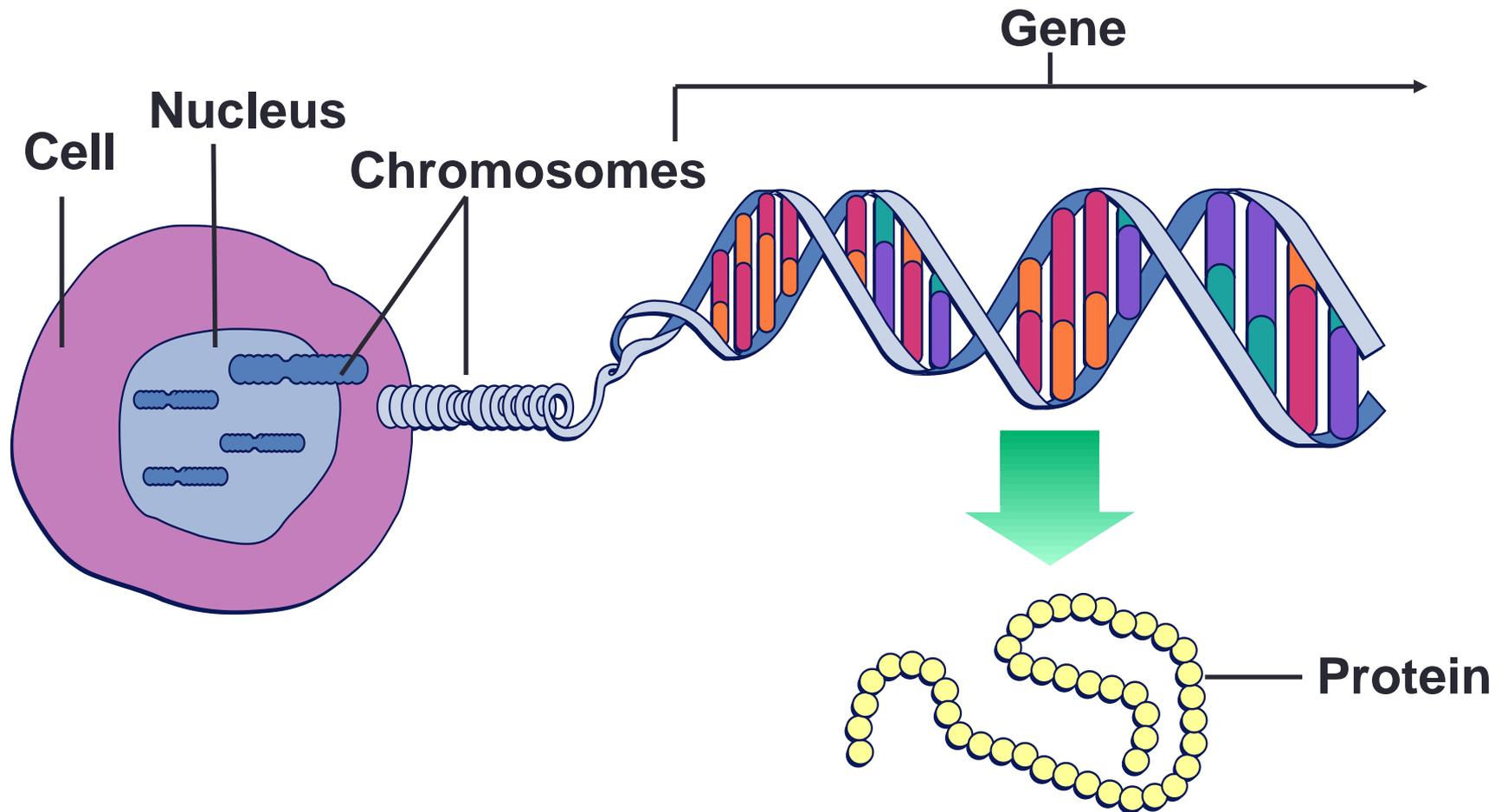
- All individuals should take steps to prevent or detect cancer whenever possible.
- Some individuals with many risk factors or hereditary risk for developing cancer may have different recommendations for the detection of cancer.

Risk factor assessment is important for all nurses regardless of practice setting

What do families share?



Chromosomes, DNA, and genes

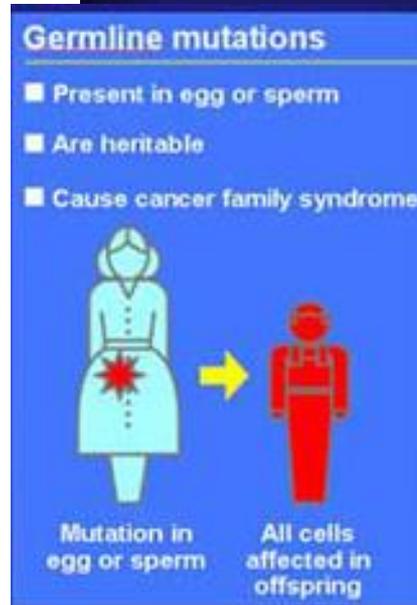
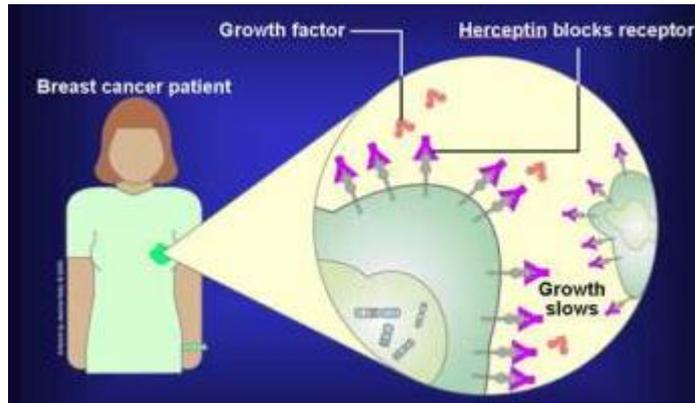


Cancer is a result of uncontrolled cell division

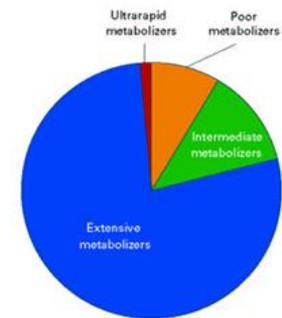
- ✓ Occurs when there is an alteration in the genes. This is called a **mutation**.
- ✓ Gene mutations may be a result of exposure to environmental **carcinogens**.
- ✓ Gene mutations could also be **inherited** from a parent.

How does genetic/genomic information affect clinical oncology practice?

- Somatic mutations in tumors that guide personalized treatment decisions
- Germline mutations in families that guide prevention and early detection decisions
- Pharmacogenomics to guide medication choices



Variations in CYP2D6 drug metabolism in a Caucasian population



Patients need accurate information



“More and more patients are going to the Internet for medical advice. To keep my practice going, I changed my name to Dr. Google.”

Refer to a genetics professional

- MD with a fellowship in genetics
- Board certified Masters prepared genetics counselor www.nsgc.org
- Credentialed advance practice nurse through American Nurses Credentialing Center - Advanced Genetic Nursing credential (AGN-BC)



Who is at high risk for hereditary cancer?



Hereditary cancers account for only a small proportion of all cancer

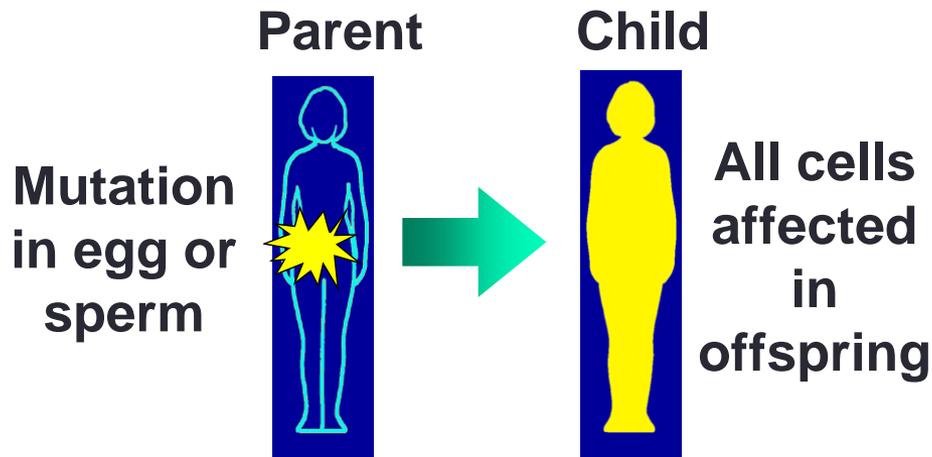
An accurate family history is the key to:



- Accurate risk assessment
- Effective genetic counseling
- Appropriate medical follow-up

Cancer arises from gene mutations

Germline mutations



- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Somatic mutations

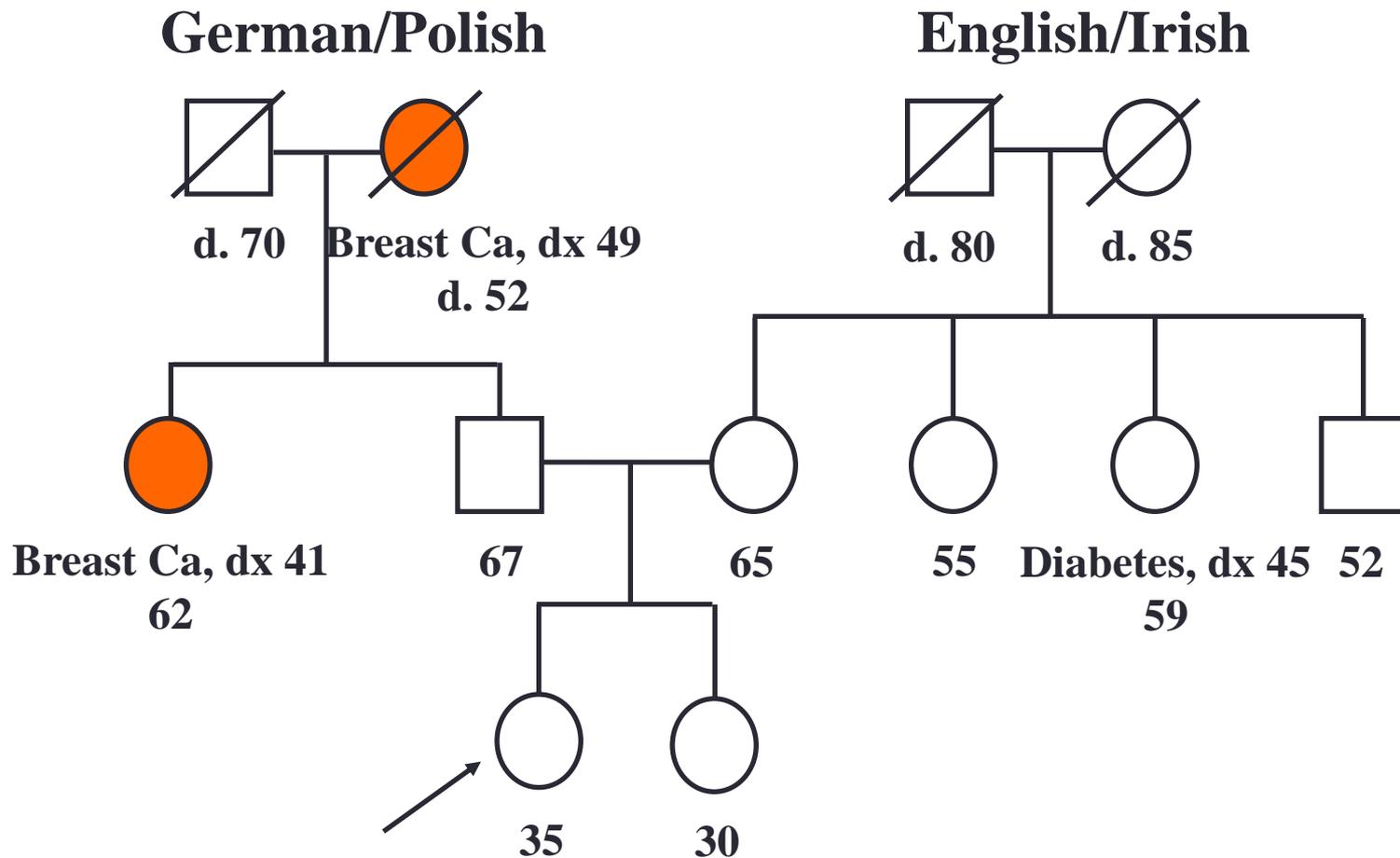


- Occur in nongermline tissues
- Are nonheritable



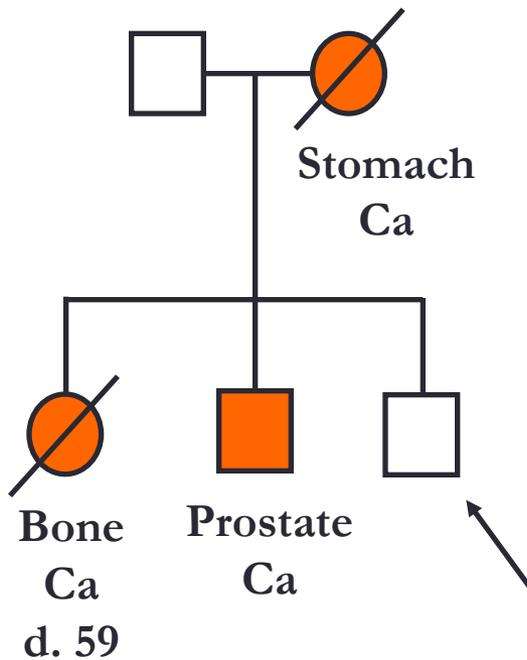
**"Your 2 p.m. arrived late, your 2:30 arrived early,
and your 2:15 is right on time."**

Three generation pedigree

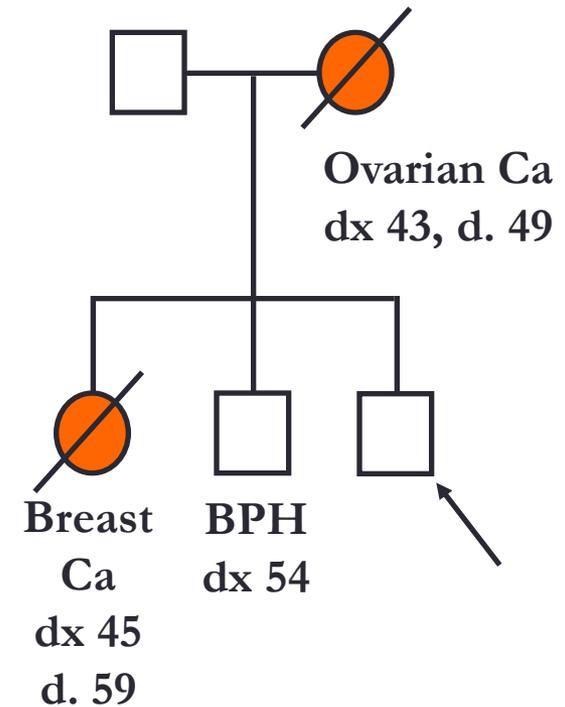


Verify family history

Verbally reported pedigree

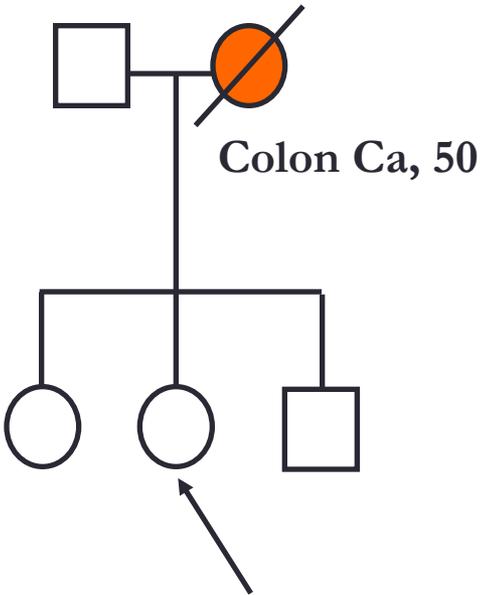


Revised pedigree based on pathology reports

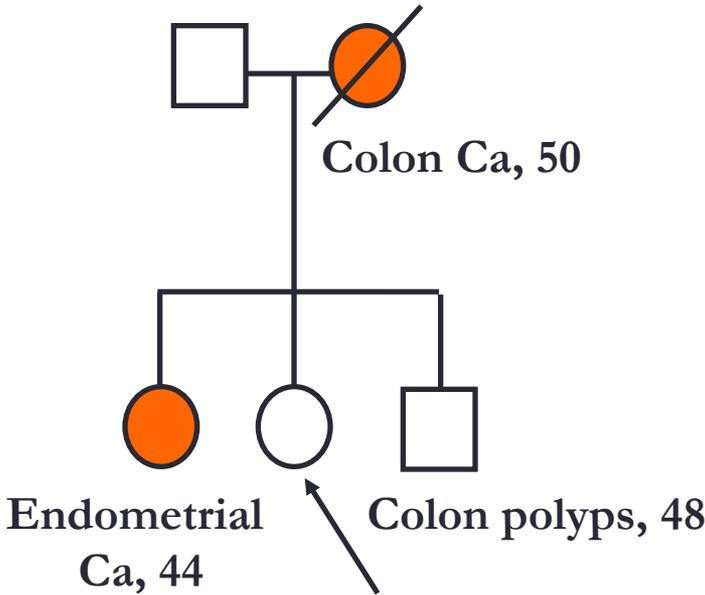


Family cancer histories are dynamic

Initial History



2 years later

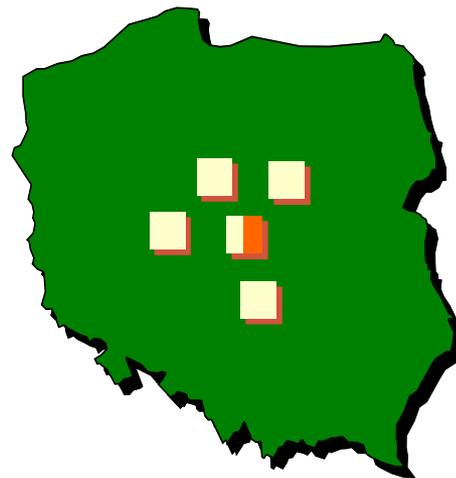


Founder effect

A high frequency of a specific gene mutation in a population founded by a small ancestral group



Original
population



Marked population
decrease, migration, or
isolation

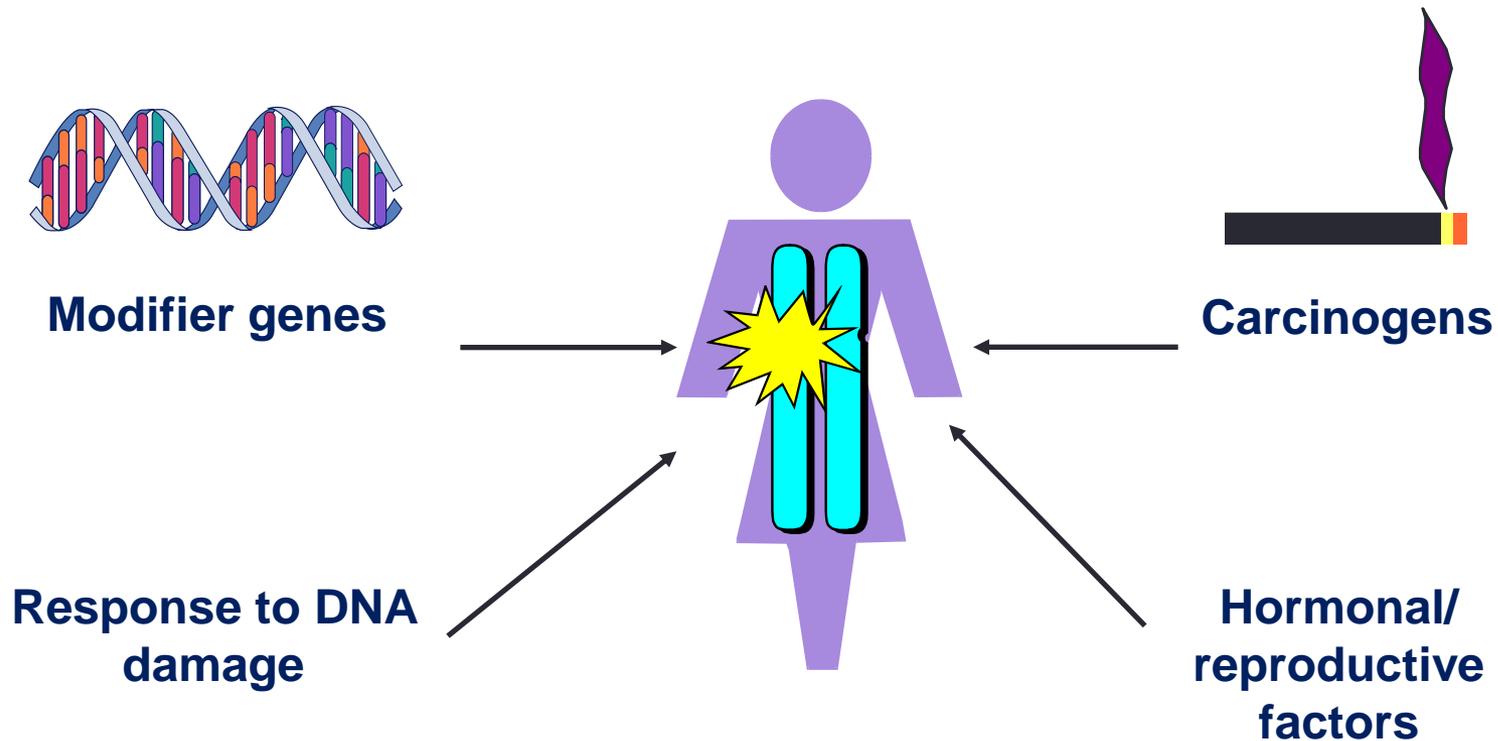


Generations
later

When to suspect hereditary cancer syndrome

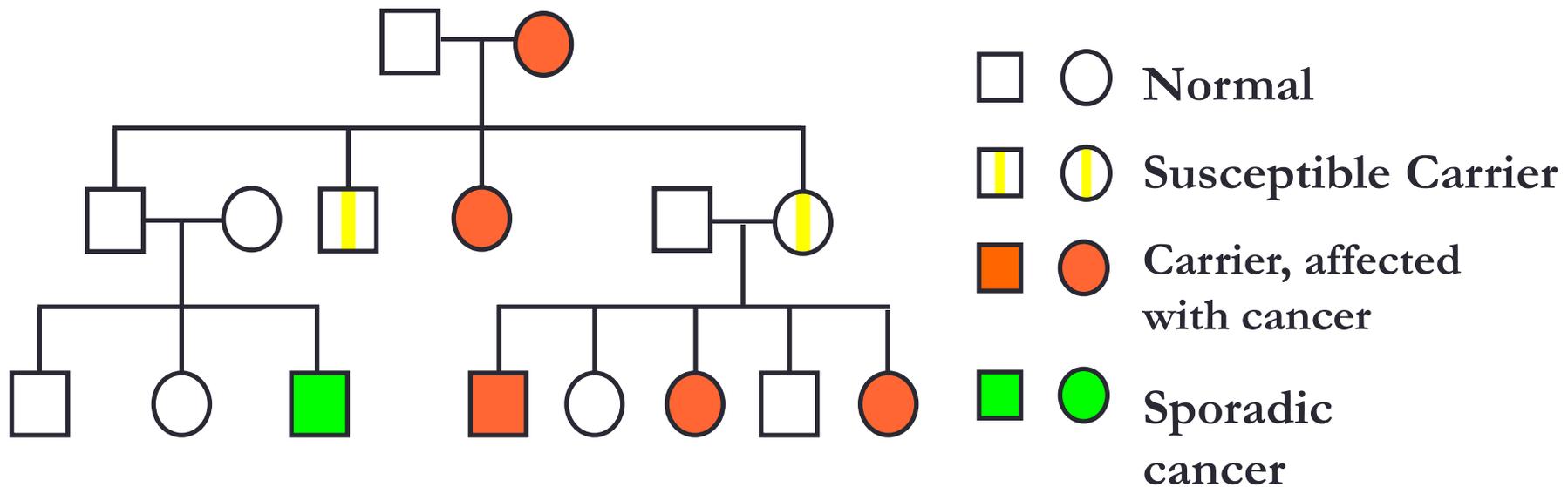
- Cancer in 2 or more close relatives (on same side of family)
- Early age at diagnosis
- Multiple primary tumors
- Bilateral or multiple rare cancers
- Constellation of tumors consistent with specific cancer syndrome (eg, breast and ovary)
- Evidence of autosomal dominant transmission
- Rare tumors

Factors affecting penetrance



Not everyone with an altered gene develops cancer

Most cancer susceptibility genes are dominant with incomplete penetrance



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



© 1993, 1994 SIDNEY HARRIS

*“How do you want it—the crystal mumbo-jumbo
or statistical probability?”*

Risk of Developing Breast Cancer

- Claus table
- Modified Gail
- BRCAPro
- Hughes
- Tyrer Cruzick
- Different models consider different factors
- Variability in risk figures
- Clinician needs to use clinical judgment in interpretation



Gail Model

Incorporates

- Age
- Reproductive history
- Benign breast disease history
- Breast cancer in mother or sisters

Does *not* incorporate

- Other cancers
- Second-degree relatives
- Paternal history
- Age at diagnosis in relatives

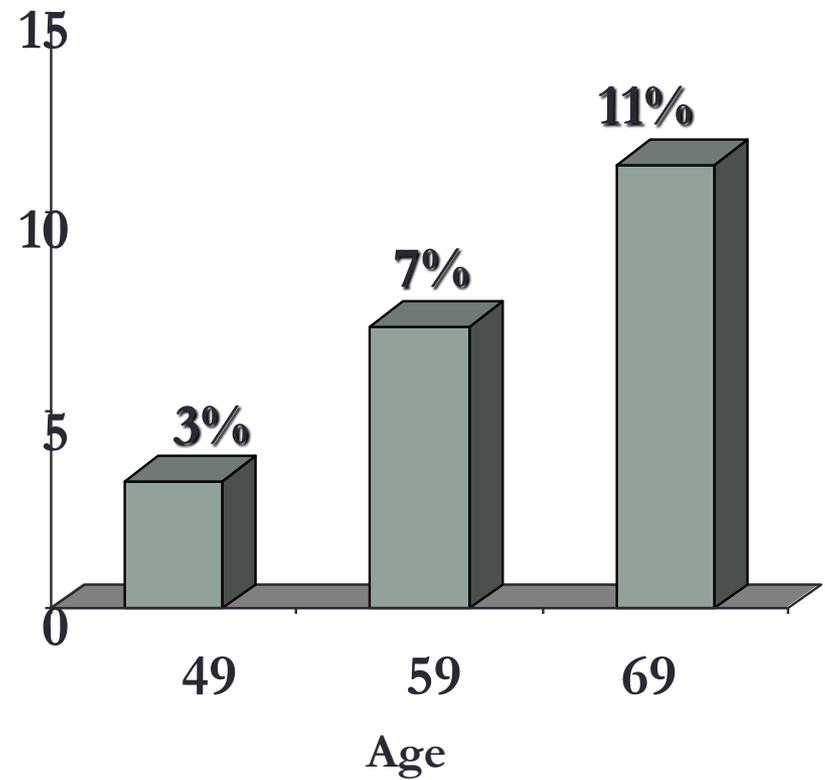
Risk Analysis Using Gail Model



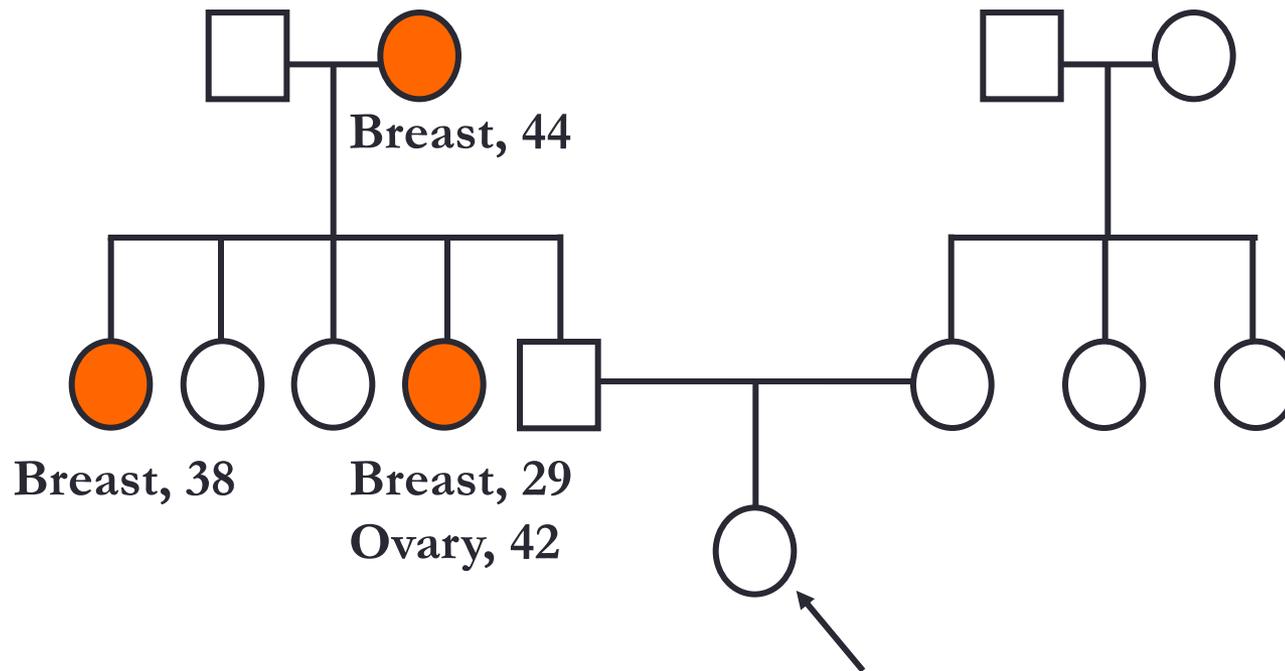
Age: 39

Age at menarche: 15
Previous breast biopsies: 0
Atypical hyperplasia: none
Age at birth of 1st child: none
Mother/sisters with breast cancer: 0

Breast
Cancer
Risk (%)



The Gail Model can underestimate hereditary risk of breast cancer

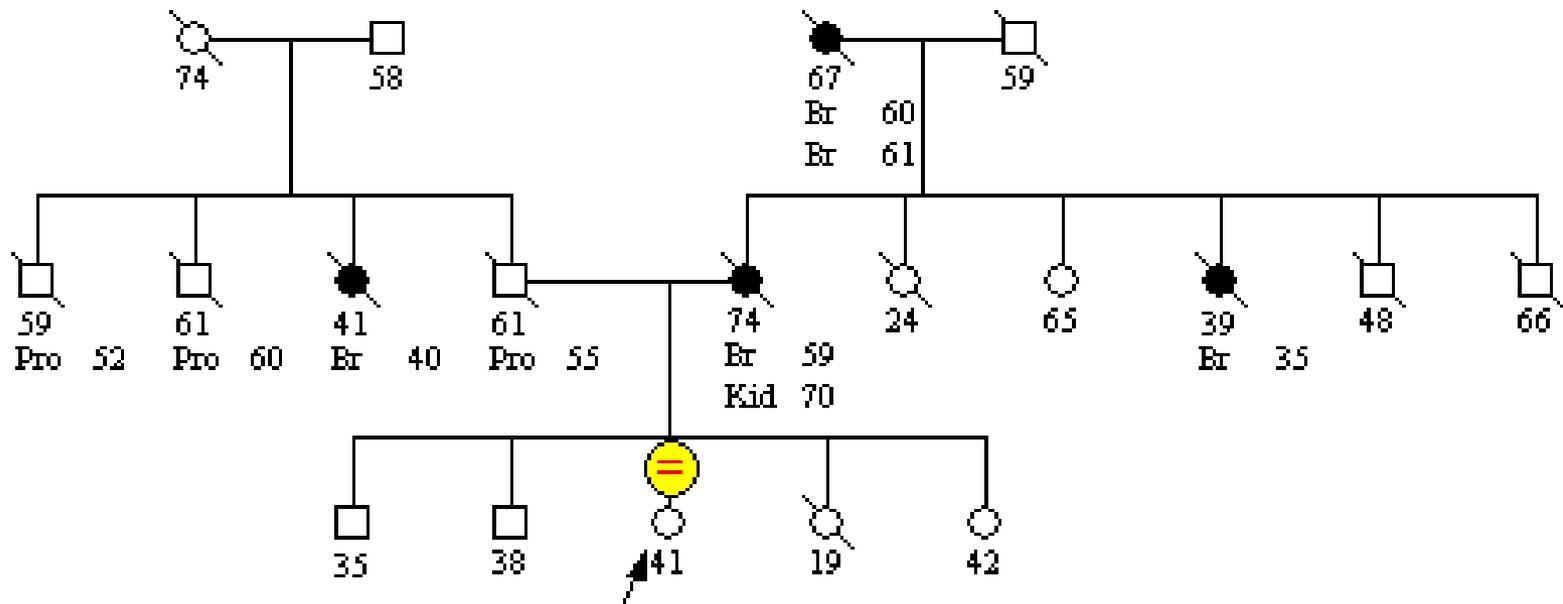


This woman's breast cancer risk would be greatly underestimated

Claus Tables

- Statistical model to calculate cumulative breast cancer risk based on family history
- Risk estimates derived from the family history of 5,000 breast cancer cases (age 20-54) and age-matched controls in US
- Family history of breast cancer is the *only* risk factor considered

Case



Case

Mutation Probabilities			
BRCA1			
Couch	0.035	MLH1	
Shattuck-Eidens	0.060	MMRpro	0.000
BRCAPRO	0.037	MSH2	
BRCA2		MMRpro	0.000
BRCAPRO	0.077	MSH6	
Any BRCA		MMRpro	0.000
Myriad	0.056	MLH1 or MSH2	
NCI CART	No Calc	MMRpro (+MSH6)	0.000
BRCAPRO	0.115	Weijnen	0.000
		Myriad	No Calc
p16	0.000	Pancreas Gene:	0.004

Cancer Risks	<u>5-Year</u>	<u>Lifetime</u>
Breast		
Gail		
Claus	0.033	0.289
BRCAPRO	0.016	0.143
Ovarian	0.002	0.048
Colorectal	0.001	0.029
Endometrial	0.001	0.018
Pancreas	0.000	0.010
Melanoma	0.002	0.017

Case

MODIFIED GAIL

Race/Ethnicity:

The tool may underestimate risk for African American women with one or more biopsies.

5 Year Risk

This woman (age 41) 2.2%

Average woman (age 41): 0.7%

Lifetime Risk

This woman (to age 90): 27%

Average woman (to age 90): 9.9%



Does the woman have a medical history of any breast cancer or of <u>ductal carcinoma in situ (DCIS)</u> or <u>lobular carcinoma in situ (LCIS)</u> ?	No
.....
What is the woman's age?	41
.....
What was the woman's age at the time of her first <u>menstrual period</u> ?	7 to 11
.....
What was the woman's age at the time of her first live birth of a child?	No births
.....
How many of the woman's first-degree relatives - mother, sisters, and/or daughters - have had breast cancer?	1
.....
Has the woman ever had a breast <u>biopsy</u> ?	Yes
a How many breast biopsies (positive or negative) has the woman had?	1
b Has the woman had at least one breast biopsy with <u>atypical hyperplasia</u> ?	Yes
.....
What is the woman's race/ethnicity?	African American
.....

Case

Tyrer Cruzik Model

Woman's age is 41 years.

Age at menarche was 11 years.

Person is nulliparous.

Person is premenopausal.

Height is 5 ft 6 ins.

Weight is 0 st 186 lb.

Woman has never used HRT.

Woman has had atypical hyperplasia.

Risk after 10 years is 25.9%.

10 year population risk is 1.74%.

Lifetime risk is 80.96%.

Lifetime population risk is 9.633%.

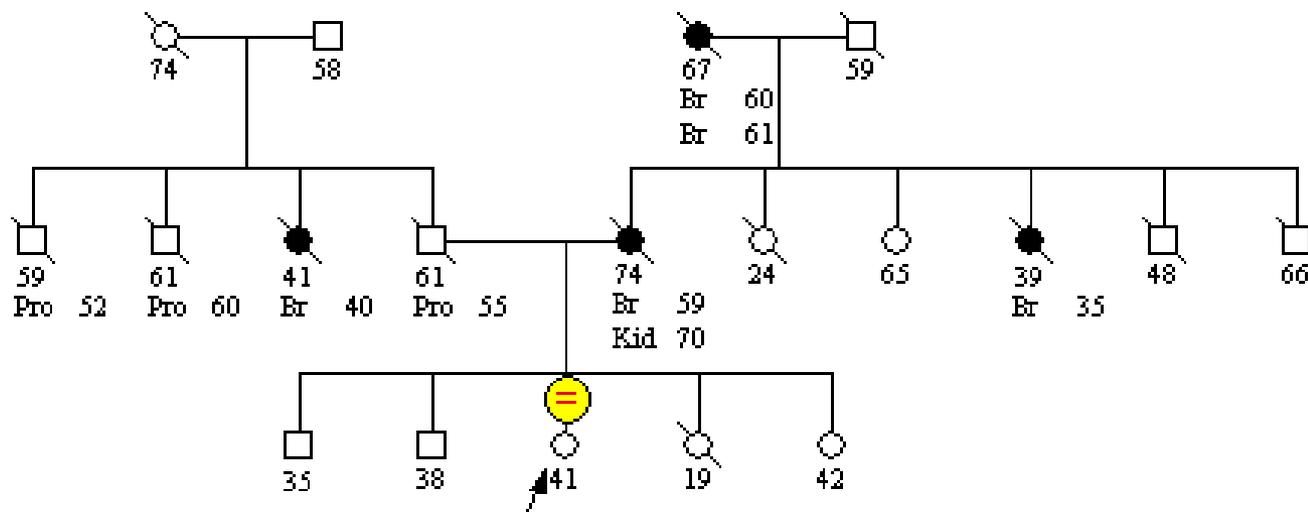
Probability of a BRCA1 gene is 0.684%.

Probability of a BRCA2 gene is 3.928%.



Risk of Developing Breast Cancer

- Claus table 29%
- Modified Gail 27%
- BRCAPro 14%
- Tyrer Cruzick 81%

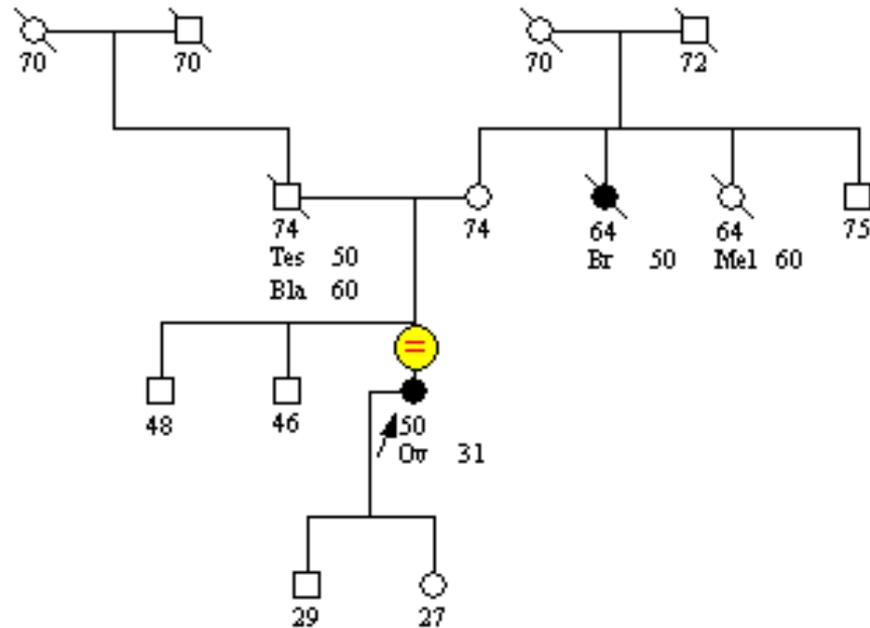


Why Assess the Risk?

- NCCN and ACS recommend more aggressive screening when risk of breast cancer is greater than 20%
 - Mammography at a younger age
 - Biannual professional examination
 - Discuss breast awareness
 - Consider breast MRI

Risk of a Mutation

- Some syndromes have clinical criteria for offering testing
- Some syndromes can calculate risk of mutation



Risk of a Mutation

Mutation Probabilities			
BRCA1			
Couch	0.162	MLH1	
Shattuck-Eidens	0.380	MMRpro	0.000
BRCAPRO	0.016	MSH2	
BRCA2		MMRpro	0.000
BRCAPRO	0.005	MSH6	
Any BRCA		MMRpro	0.000
Myriad	0.077	MLH1 or MSH2	
NCI CART	No Calc	MMRpro (+MSH6)	0.000
BRCAPRO	0.021	Weijnen	0.000
p16	0.000	Myriad	0.143
		Pancreas Gene:	0.004
Cancer Risks			
	<u>5-Year</u>	<u>Lifetime</u>	
Breast			
Gail	0.009	0.088	
Claus	0.011	0.076	
BRCAPRO	0.013	0.114	
Ovarian	0.000	0.000	
Colorectal	0.002	0.033	
Endometrial	0.002	0.018	
Pancreas	0.000	0.015	
Melanoma	0.002	0.016	

Clinical criteria for testing

Hereditary Breast Cancer

- Diagnosed age ≤ 45 years
- Two breast primaries when first breast cancer diagnosis occurred prior to age 50
- Diagnosed age < 60 y with a triple negative breast cancer (ER-, PR-, HER2-)
- Diagnosed at any age, with ≥ 2 close blood relatives with breast and/or ovarian cancer
- Male breast cancer
- Ovarian cancer
- Ethnicity associated with higher mutation frequency
- A close relative with a known BRCA1 or BRCA2 gene mutation

Colon Polyposis

- A beneficiary with ≥ 20 cumulative colorectal adenomas over a lifetime.
 - Testing for APC gene mutations should precede testing for the less common MYH mutation.





Mission not so impossible

A multi-step process: Pretest genetic counseling

Assess

- Personal and family medical history
- Risk perception and motivation for testing

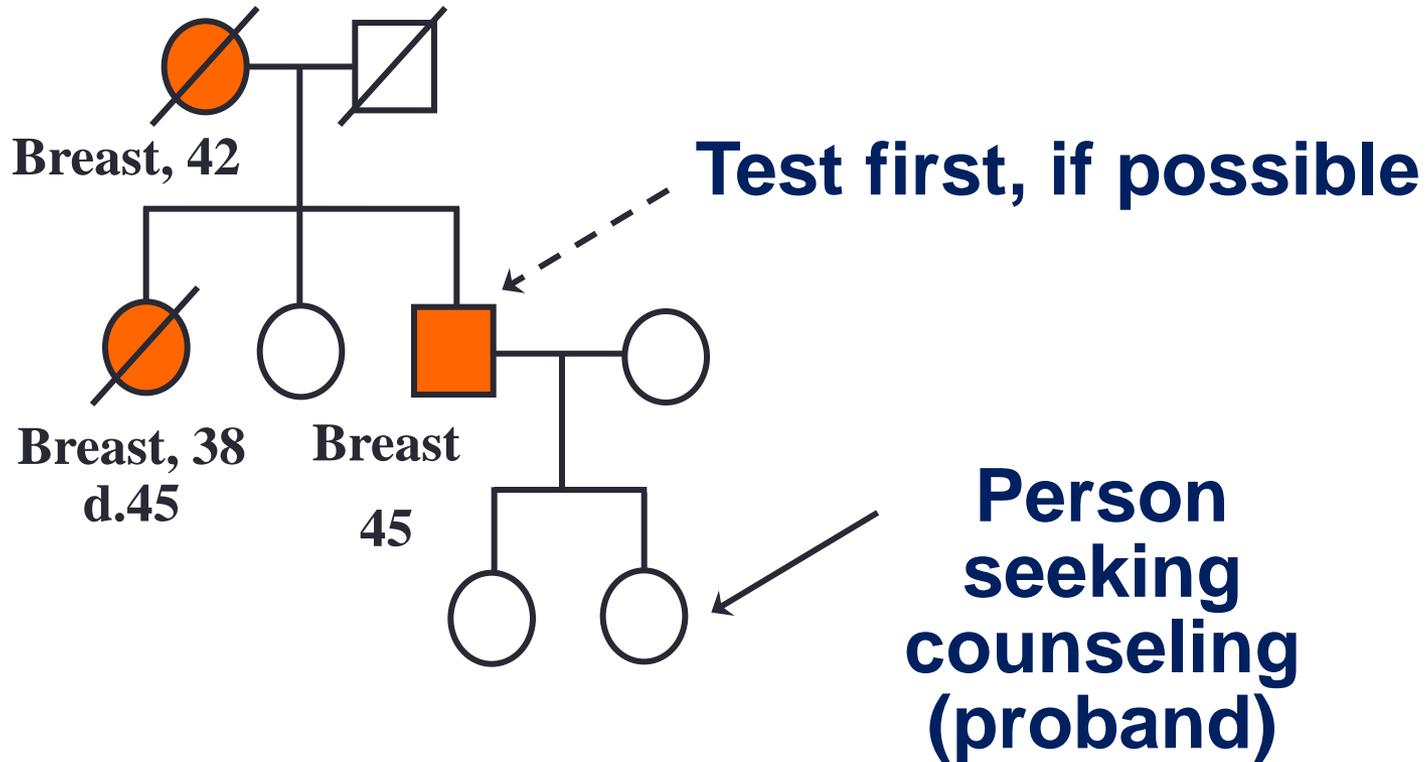
Educate

- Basic genetics and inheritance
- Cancer genetics and risk

Discuss

- Risks, benefits, and limitations of testing
- Test procedure - blood work
- Alternatives to testing
- Management options – depending on test results

Ideally, begin testing with an affected person





Why get counseling?

- Accurate assessment of risk
- Motivation for testing
- Anticipatory guidance
- Patient and family education
- Issues in test selection
- Care for the entire family
- Options for research studies

Genetic Testing Has Implications for the Entire Family

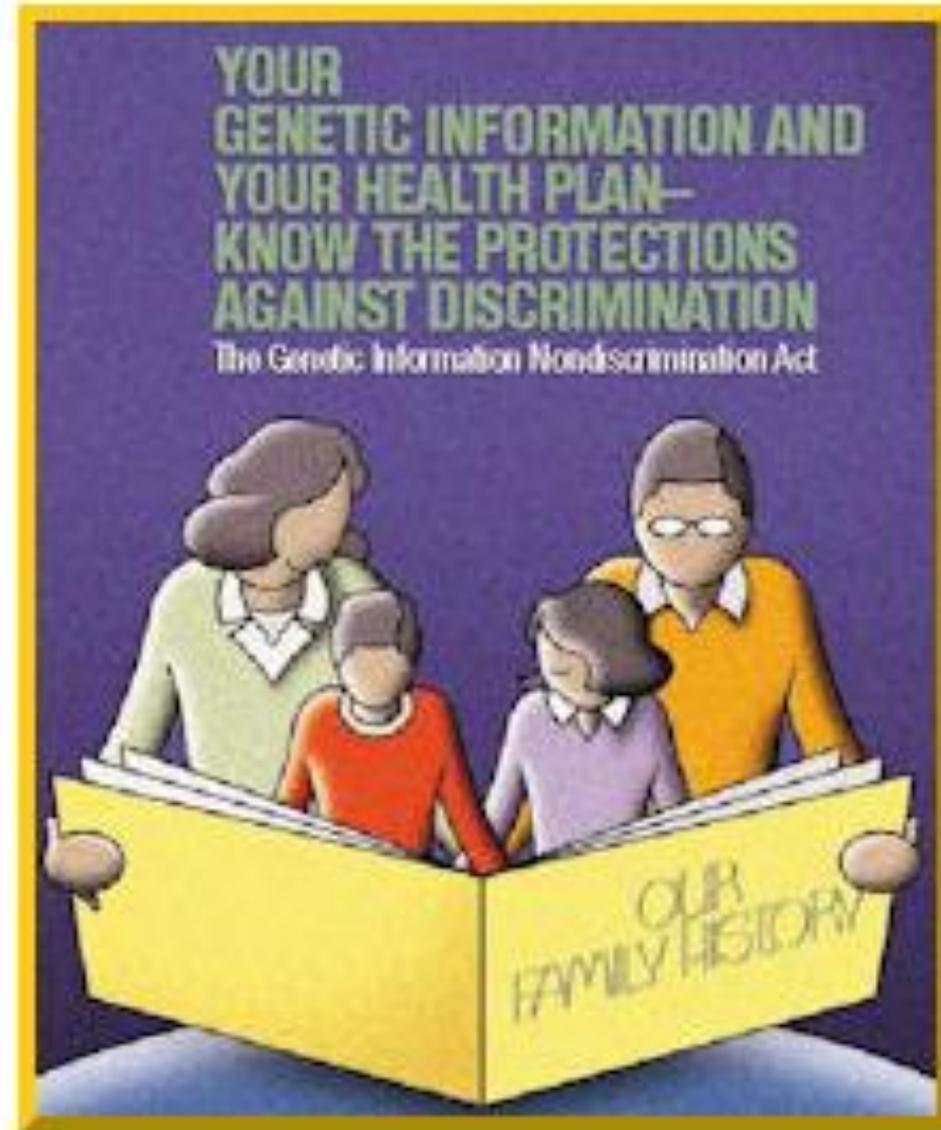


- Consider the impact of testing on all family members
- Ultimately, testing is the individual's choice

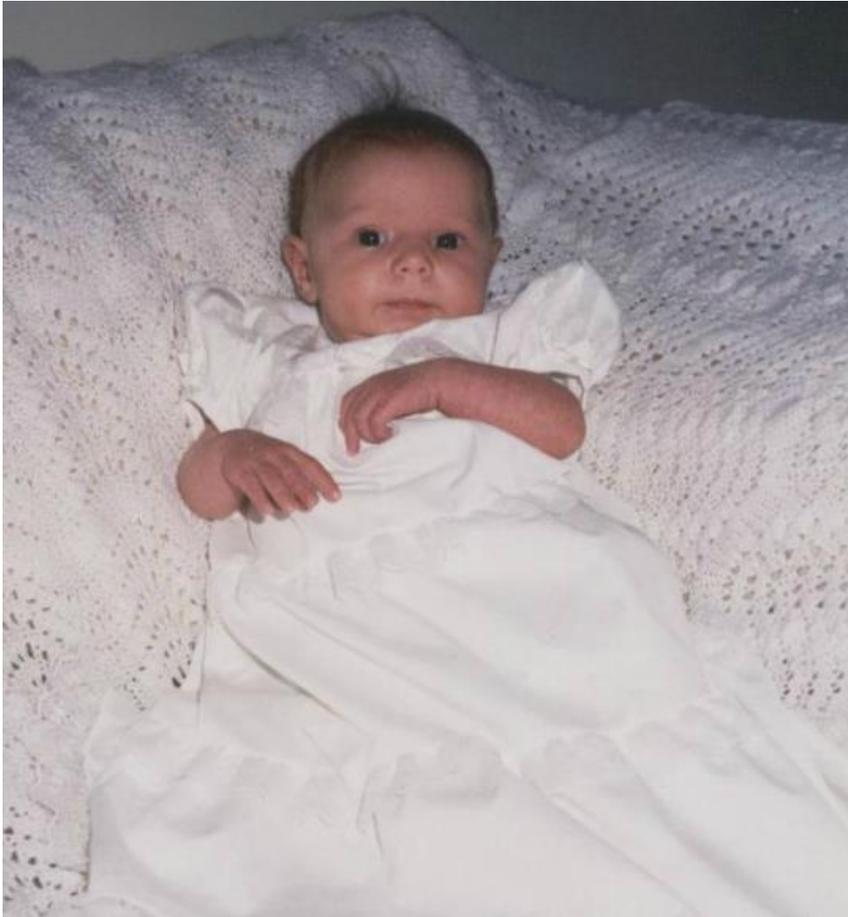


Informed consent: Potential risks of genetic testing

- Psychological distress
- Loss of privacy
- Discrimination by employers and insurers
- Change in family dynamics
- False sense of security



Informed consent: Potential benefits of genetic testing



- Improved cancer risk management
- Relief from uncertainty and anxiety about cancer risk
- Information for individual and family members
- Lifestyle decision making

Informed consent: Limitations of genetic testing



- **Not all mutations are detectable**
- Uncertain significance of some mutations
- Negative result is fully informative only if mutation has been identified in family
- Results indicate probability, not certainty, of developing cancer

Process of clinical DNA testing

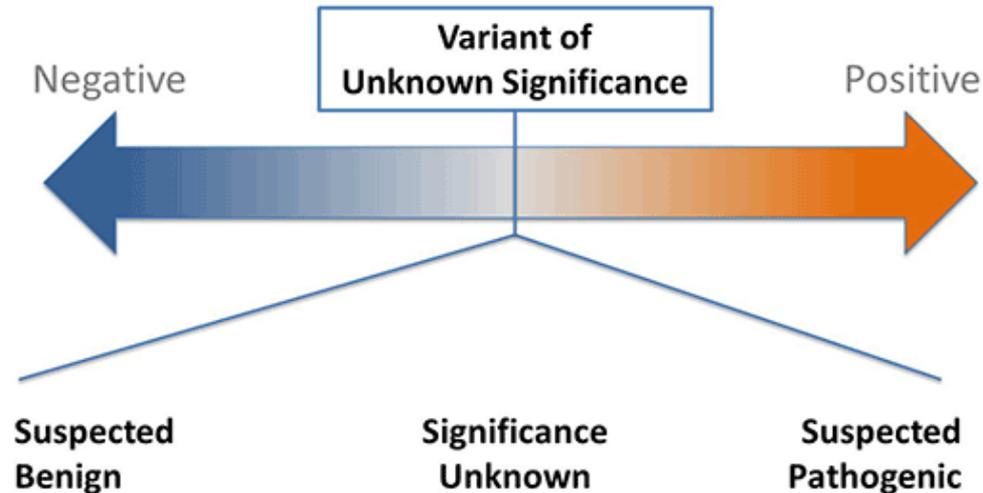
- Blood or saliva
- Costs \$440 - \$4,000
- Results available in 2-16 weeks



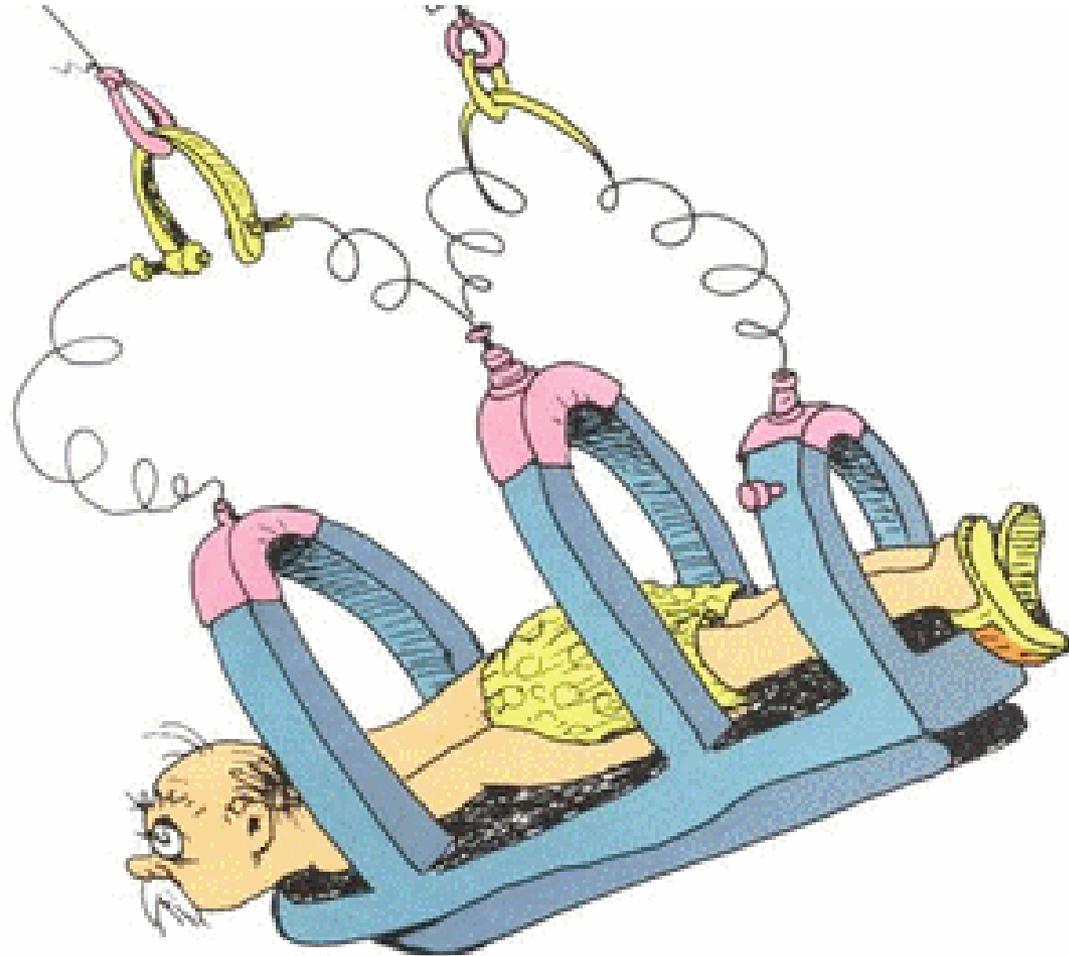
Interpreting Test Results

- Positive
- Negative
- Undetermined Significance

Range of **VUS** results



Follow-up is critical



Primary cancer prevention



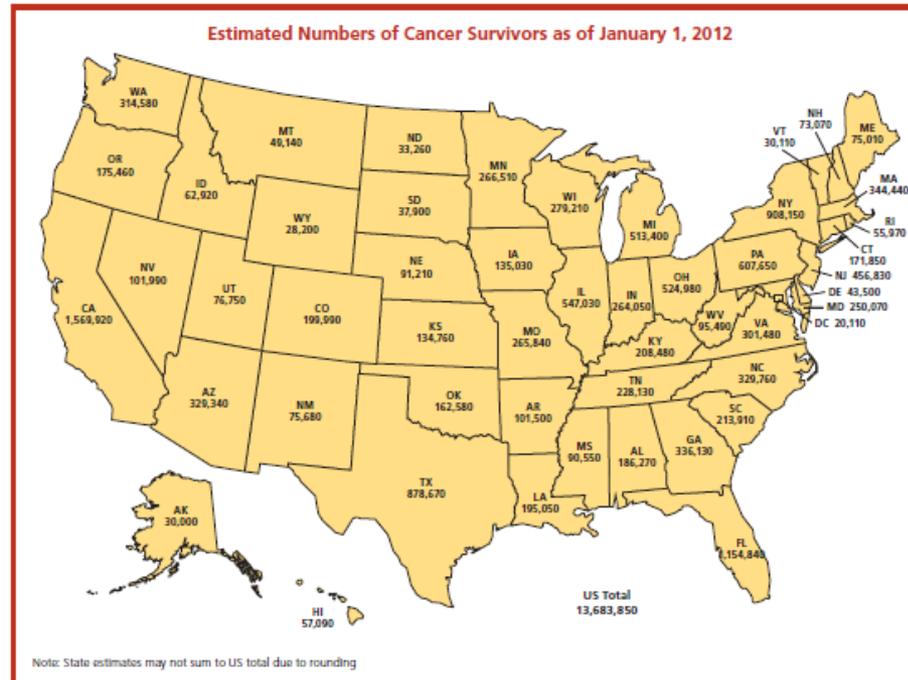
Secondary cancer prevention



Tertiary cancer prevention

Cancer Treatment & Survivorship Facts & Figures

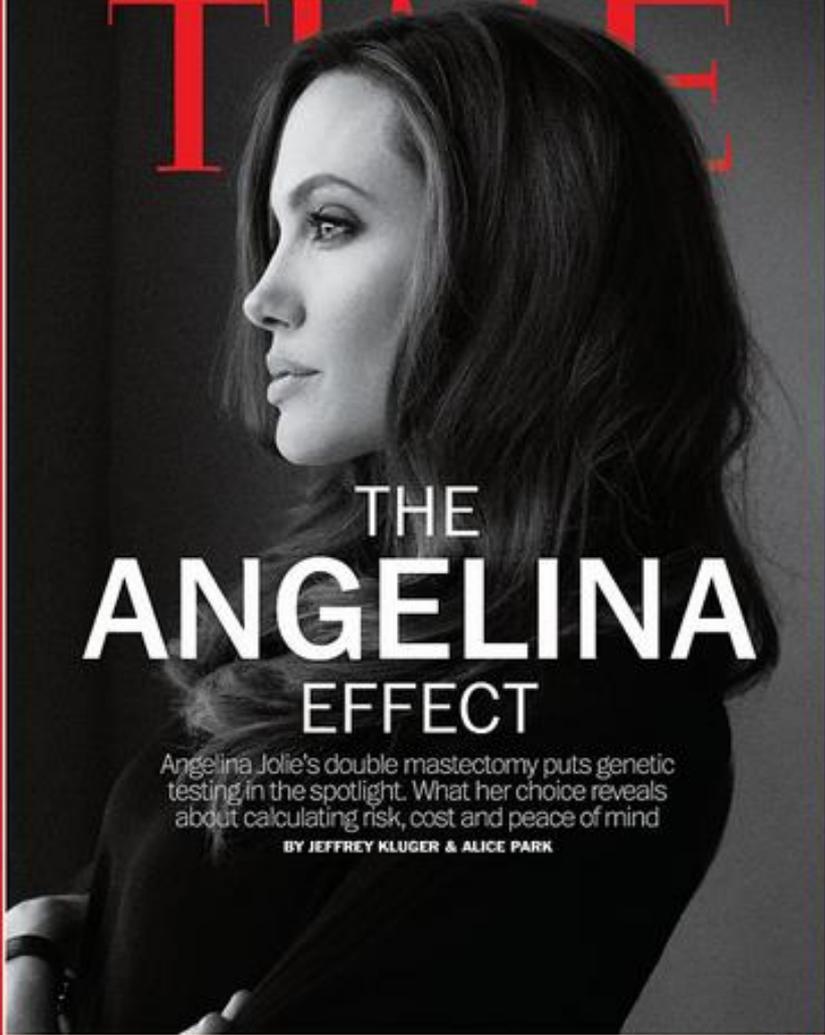
2012-2013



MAY 27, 2013

The IRS Mess / Syria's YouTube War / The End of Alimony

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

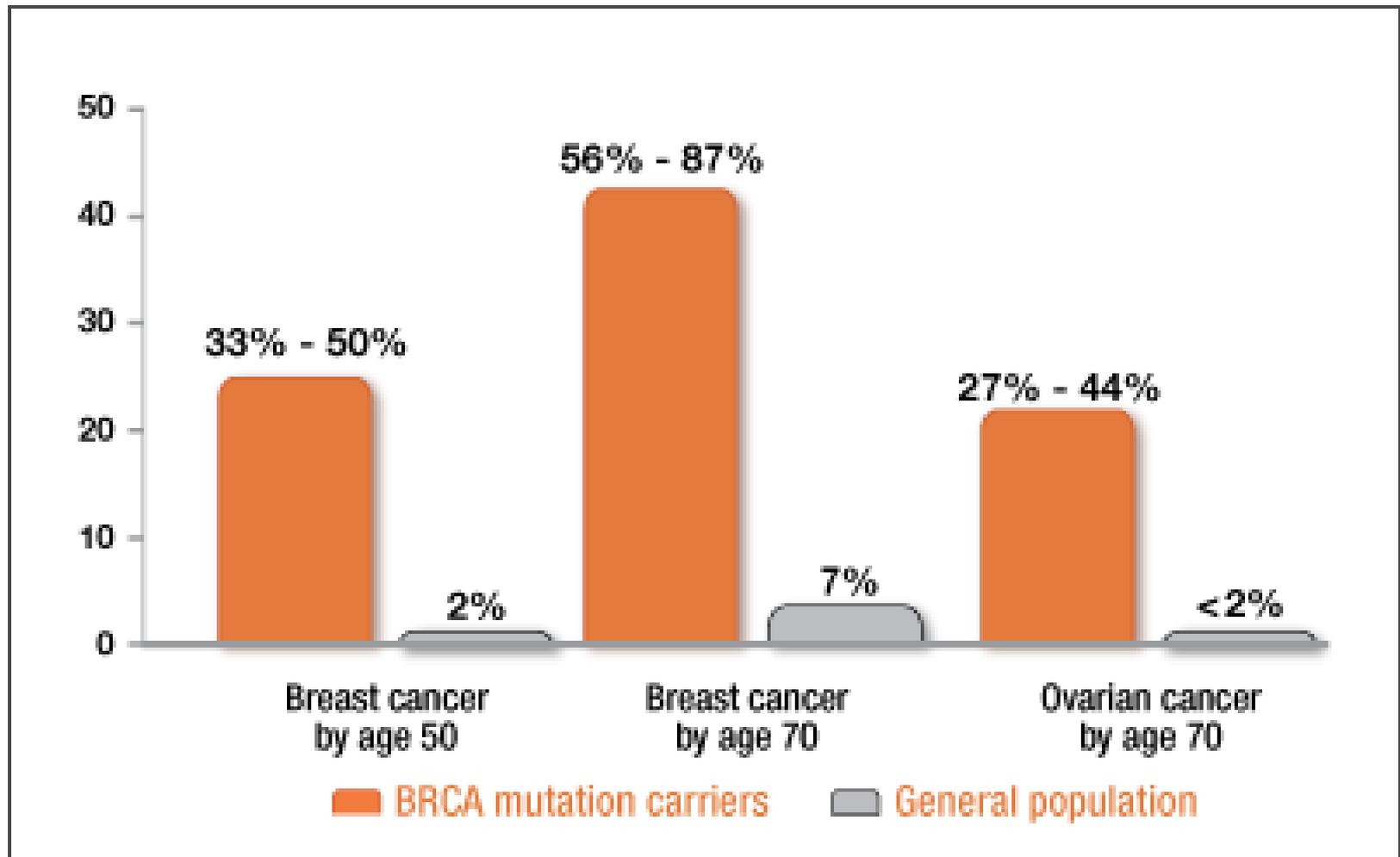
BY JEFFREY KLUGER & ALICE PARK

TIME.COM

What are the characteristics of hereditary breast cancer?

- Early age of onset (< age 50)
- Strong family history
 - >2-3 relatives –
 - Multiple generations
- Bilateral cancer
- Ovarian cancer in the patient or family
- Ashkenazi ancestry
- Male breast cancer in the family

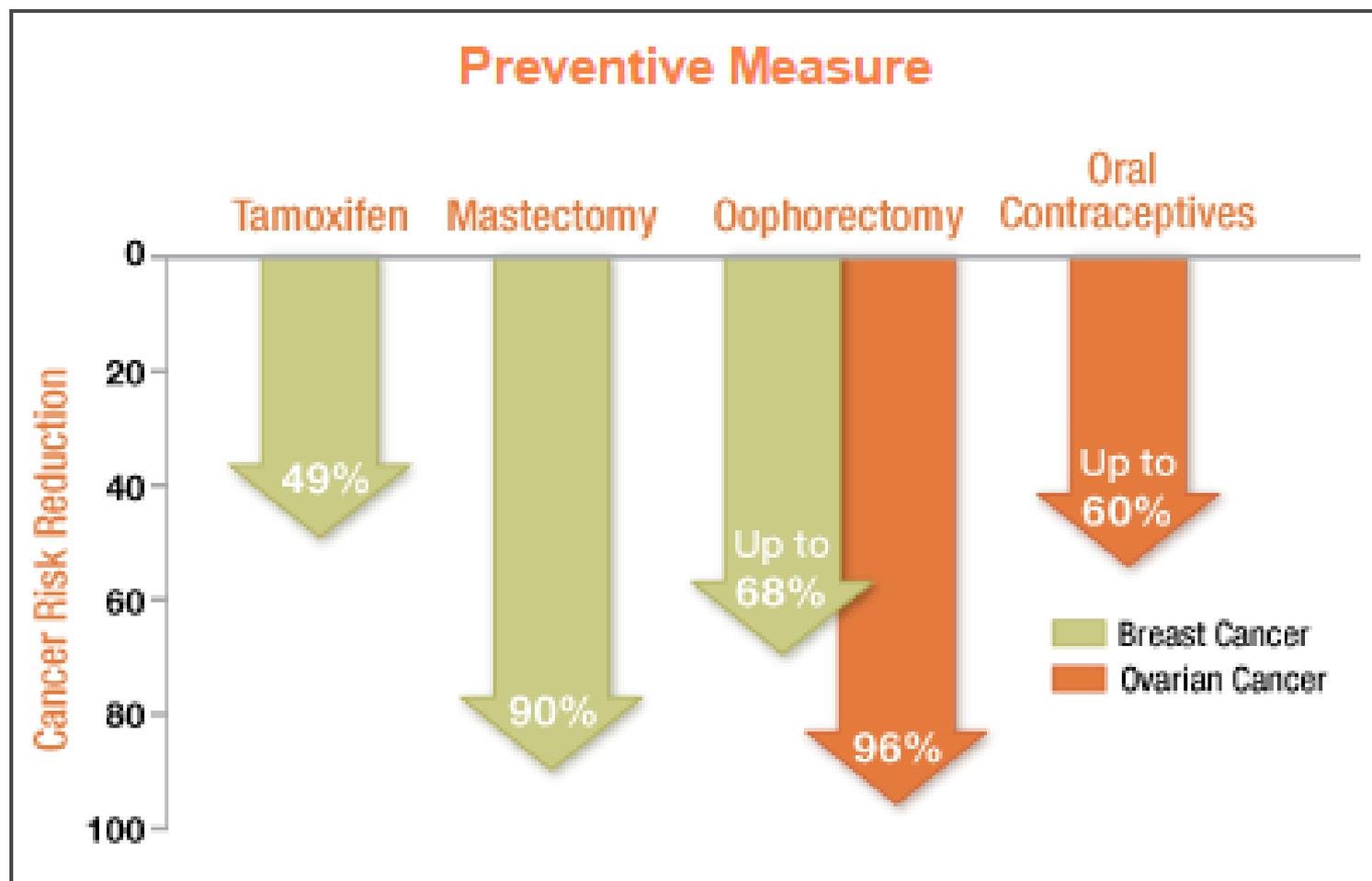
BRCA1-2 mutations increase risk of multiple cancers



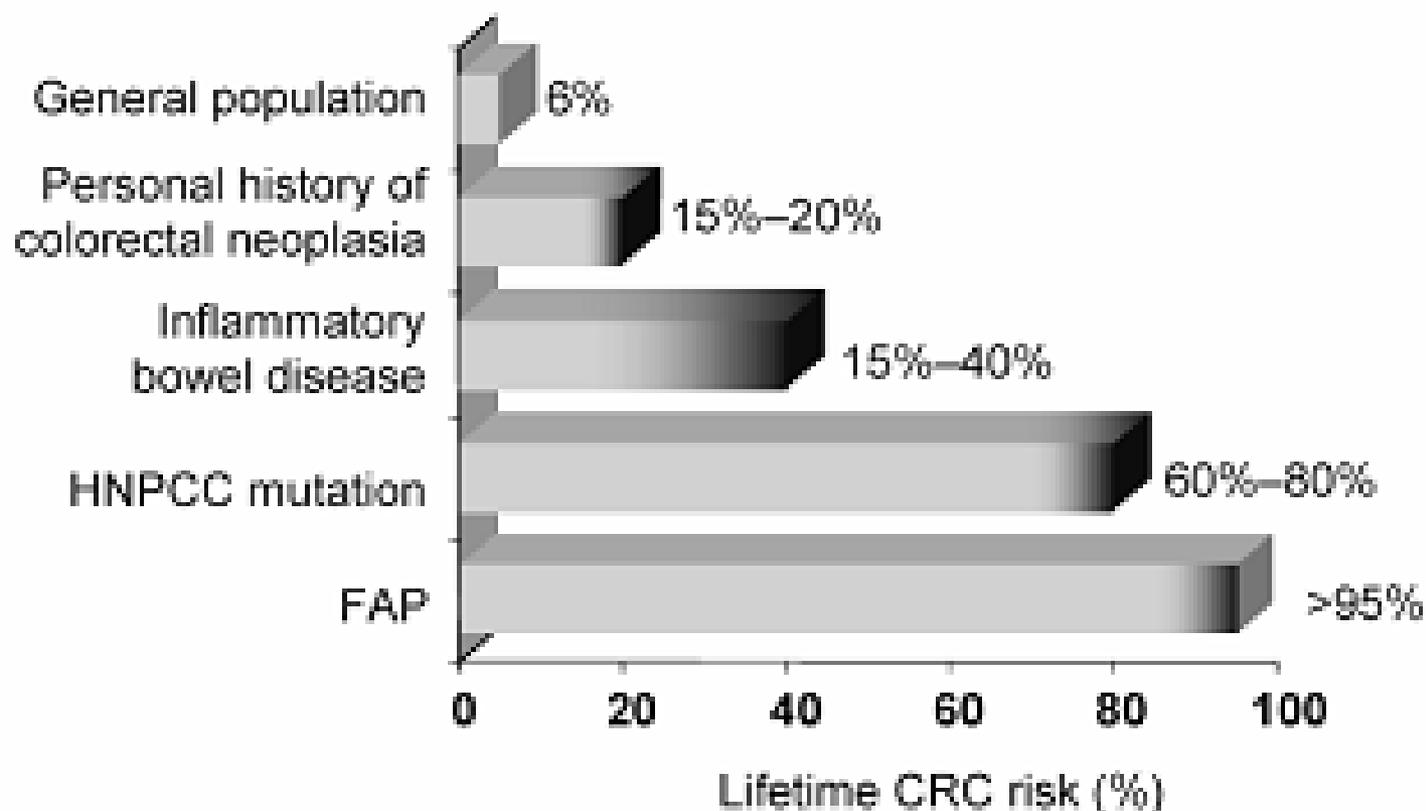
Management of high risk families

- **Increased surveillance**
 - Mammography at an earlier age
 - More frequent breast exams
 - Consider breast MRI
- **Chemoprevention**
 - Tamoxifen
- **Prophylactic surgery**
 - Mastectomy
 - Oophorectomy
- **Pancreatic screening**
- **Melanoma screening**
- **Prostate cancer screening**
- **Clinical trials**

Benefits of preventive measures



Risk of Colorectal Cancer



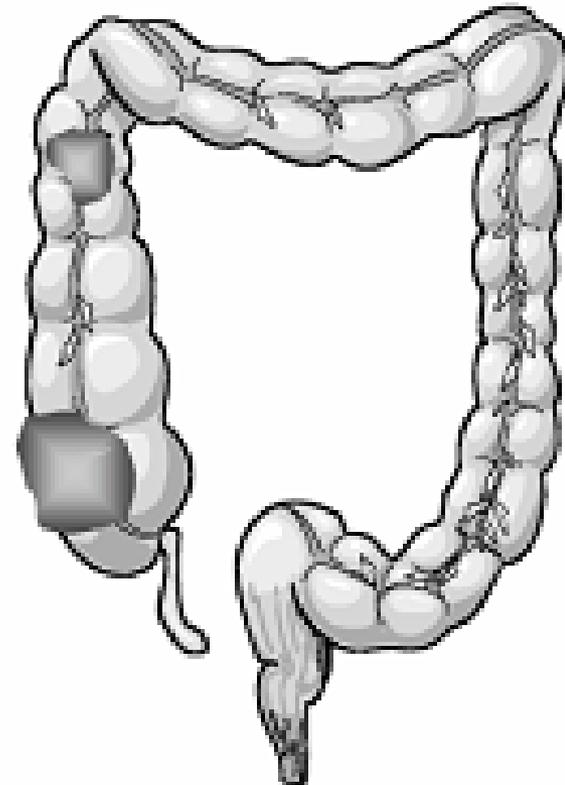
Management of high risk families with FAP

- Annual colonoscopy starting at age 10 to 15 years
- Surgical removal of the colon when the polyp burden becomes too high
- Chemoprevention with aspirin/NSAIDs/Cox2



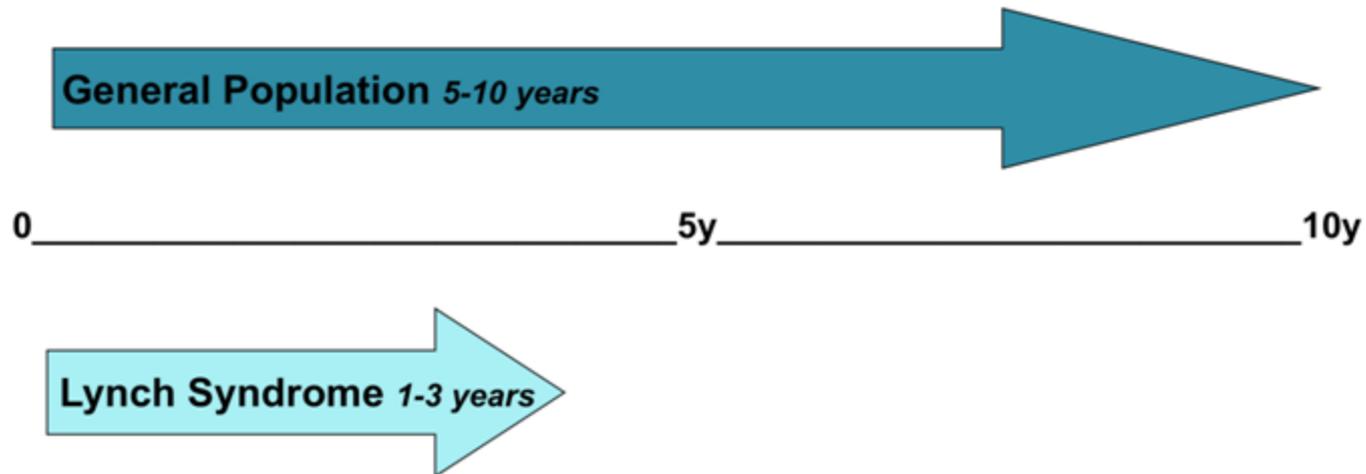
Clinical Features of Hereditary Nonpolyposis Colorectal Cancer

- Early but variable age at CRC diagnosis (~ 45 years)
- Tumor site in proximal colon predominates
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors, brain



Rationale for Frequent Colonoscopy

Accelerated progression from adenoma to cancer



Cancer Risks in Lynch Syndrome up to age 70 compared to general population

Cancer	General Population Risk	HNPCC	
		Risks	Mean Age of Onset
Colon	5.5%	80%	44 years
Endometrium	2.7%	20%-60%	46 years
Stomach	<1%	11%-19%	56 years
Ovary	1.6%	9%-12%	42.5 years
Hepatobiliary tract	<1%	2%-7%	Not reported
Urinary tract	<1%	4%-5%	~55 years
Small bowel	<1%	1%-4%	49 years
Brain/central nervous system	<1%	1%-3%	~50 years

Management of high risk families

- Annual colonoscopy with upper endoscopy starting at age 25
- Careful gynecologic exam ages 25 until total hysterectomy
- Total hysterectomy age 35 to 45
- Consider annual urinalysis and pelvic ultrasound

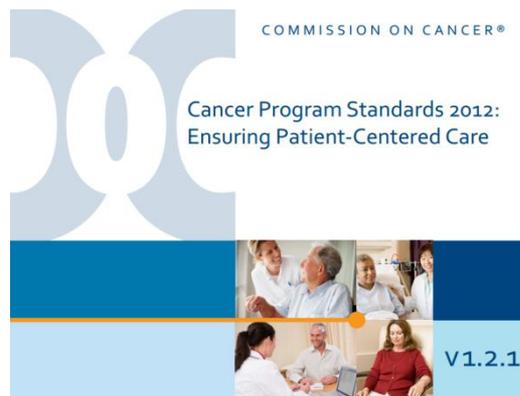
Previvor care

- Prevention decisions
- Support
- Care for other at-risk relatives
- Screening for other cancers



Limitations of providing genetics care outside of formal genetics counseling

- Direct to consumer testing
- **Wrong genetic test is ordered**
- Genetic test results are misinterpreted
- Inappropriate or inadequate genetic counseling results in psychosocial distress or other negative outcomes
- **Poorly coordinated care for the rest of the family**



STANDARD 2.3 Risk Assessment and Genetic Counseling

Cancer risk assessment, genetic counseling, and testing services are provided to patients either on-site or by referral, by a qualified genetics professional.

Direct to consumer testing



DECEMBER 24, 2012

Egypt Divided / Pot's Big Moment / Best of 2012 Movies, Music, Books & More

TIME

Want to Know My Future?



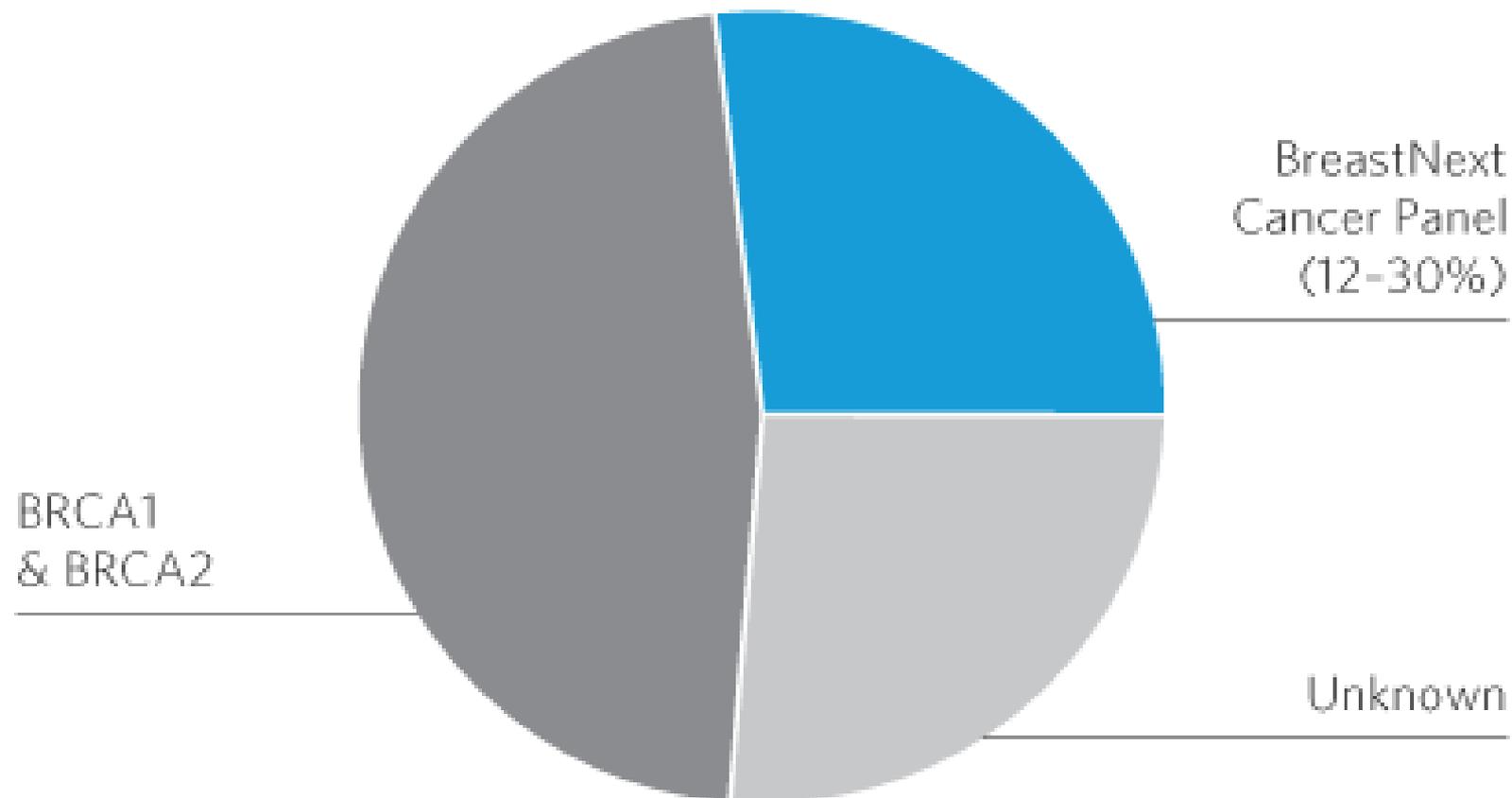
New genetic tests can point to risks —
but not always a cure

BY BONNIE ROCHMAN

www.time.com

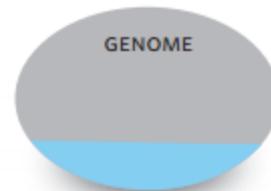
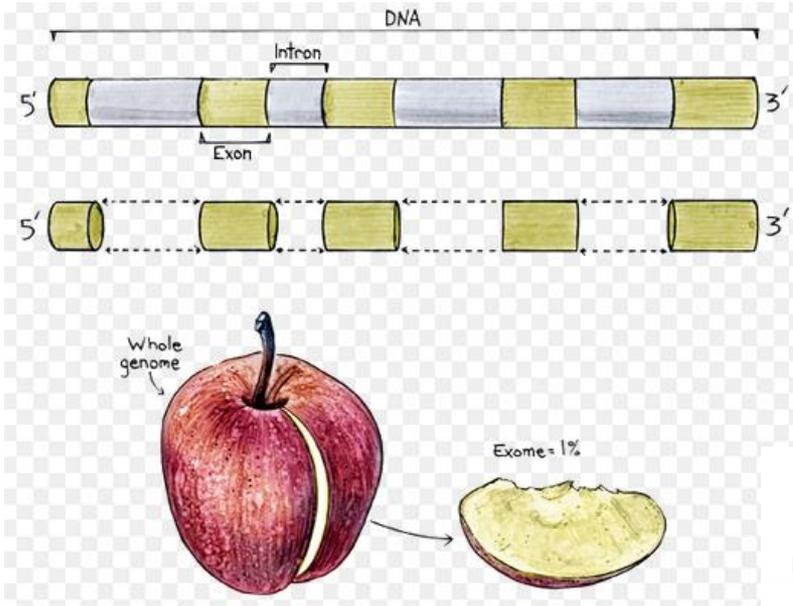
Next Generation Genetic Testing Panels

Hereditary breast cancer



	Gene	Associated Cancers and Risks
High-Risk Genes	BRCA1	Female Breast (57-84%), Ovarian (24-54%), Prostate (16-20%), Male Breast (4%), Pancreatic (3%), Fallopian tube, Primary peritoneal, Endometrial (serous) ^{9,10,11,12,13}
	BRCA2	Female Breast (41-84%), Ovarian (11-27%), Prostate (20-34%), Pancreatic (5-7%), Male Breast (4-7%), Melanoma, Fallopian tube, Primary peritoneal, Endometrial (serous) ^{9,10,11,12,13}
	CDH1	Female Breast (39-52%), Diffuse gastric cancer (40-83%), Colon ^{14,15,16}
	EPCAM* MLH1 MSH2 MSH6* PMS2*	Ovarian (1-24%), Colorectal (15-80%), Endometrial (12-61%), Gastric, Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms ^{5,17,18,19,20,21,22,23,24}
	PTEN	Female Breast (25-50%), Thyroid (10%), Endometrial (5-10%), Colon, Renal, Melanoma ^{25,26,27}
	STK11	Female Breast (32-54%), Ovarian tumors (21%), Colorectal (39%), Pancreatic (11-36%), Gastric (29%), Lung (15%), Small intestine (13%), Cervical (10%), Endometrial (9%), Testicular tumors (9%) ^{6,28,29}
	TP53	Female Breast, Soft tissue sarcoma, Osteosarcoma, Brain, Hematologic malignancies, Adrenocortical carcinoma Overall risk for cancer: nearly 100% in females, 73% in males ^{4,30,31,32,33,34}
	Moderate-Risk Genes	ATM
CHEK2		Female Breast, Male Breast, Colon, Prostate, Thyroid, Endometrial (serous), Ovarian ^{27,38,39}
PALB2		Female Breast, Male Breast, Pancreatic, Ovarian ^{2,40,41,42,43}
Newer Genes	BARD1	Female Breast, Ovarian ^{2,44}
	BRIP1	Female Breast, Ovarian ^{45,46}
	FANCC	Female Breast ⁴⁷
	NBN	Female Breast, Melanoma, Non-Hodgkin lymphoma ^{48,49}
	RAD51C	Female Breast, Ovarian ⁵⁰
	RAD51D	Female Breast, Ovarian ⁵¹
	XRCC2	Female Breast, Pancreatic ^{52,53}

Exome Sequencing

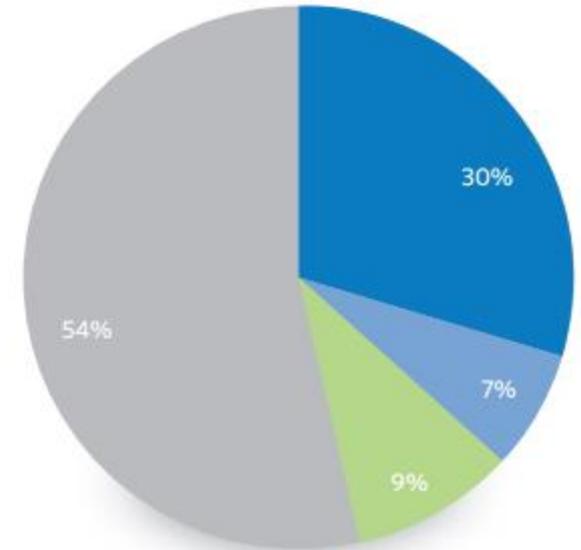


EXOME



← Characterized Genes

← Novel Genes



POSITIVE/LIKELY POSITIVE, CHARACTERIZED GENE

UNCERTAIN VARIANT, CHARACTERIZED GENE

POSITIVE/LIKELY POSITIVE, NOVEL GENE

NEGATIVE

Uncertainties still exist

- Gene penetrance
- **Variants of unknown significance**
- Marked variability in expression of phenotype
- Cancer risks
 - cancer site
 - age specific
- Medical management
 - prevention
 - surveillance
 - treatment
- Psychological and social issues



ZIGGY / By Tom Wilson

THE SUPER GIANT-SIZE SOFT
DRINK IS THE BEST BUY...
...BUT YOU'LL MISS MOST OF THE
MOVIE WITH SO MANY TRIPS TO
THE RESTROOM!

CINEMA 1



