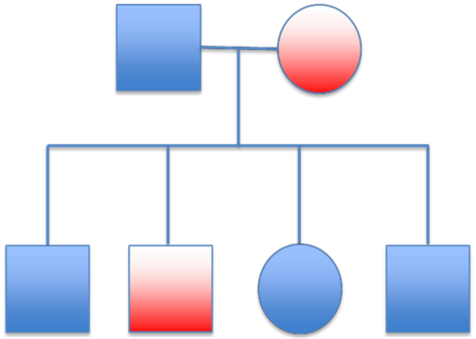
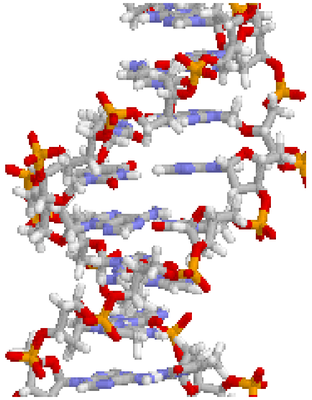
Breast Cancer Genetics:
Role of Genetic screening & assessment of Genetic Profile - Current Evidence.





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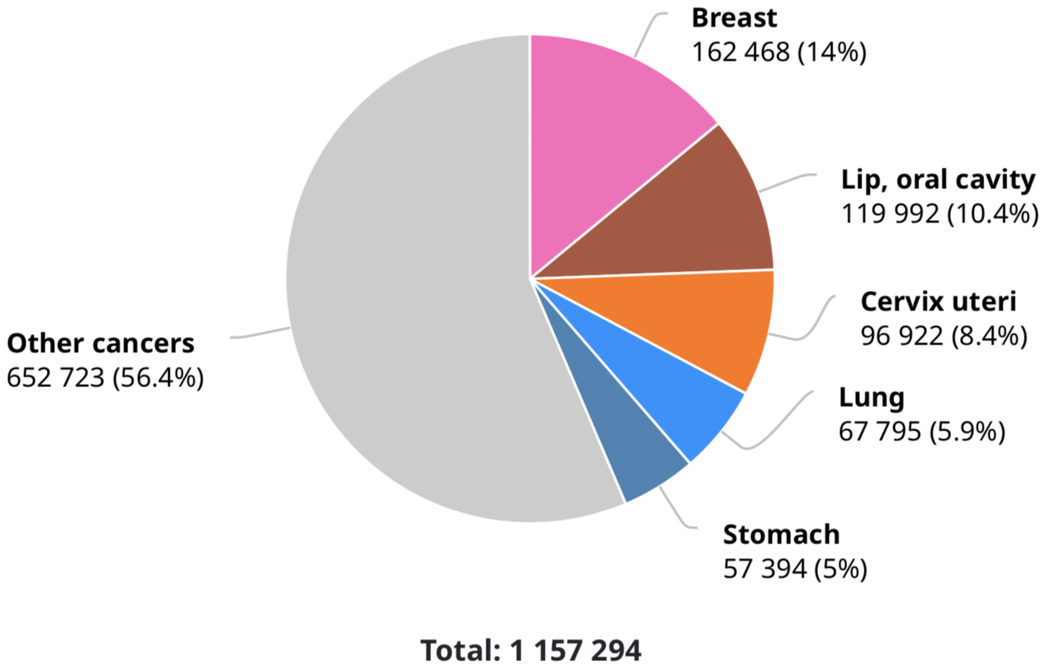
ASSOCIATE PROFESSOR,
RADIATION ONCOLOGY
AIIMS PATNA.

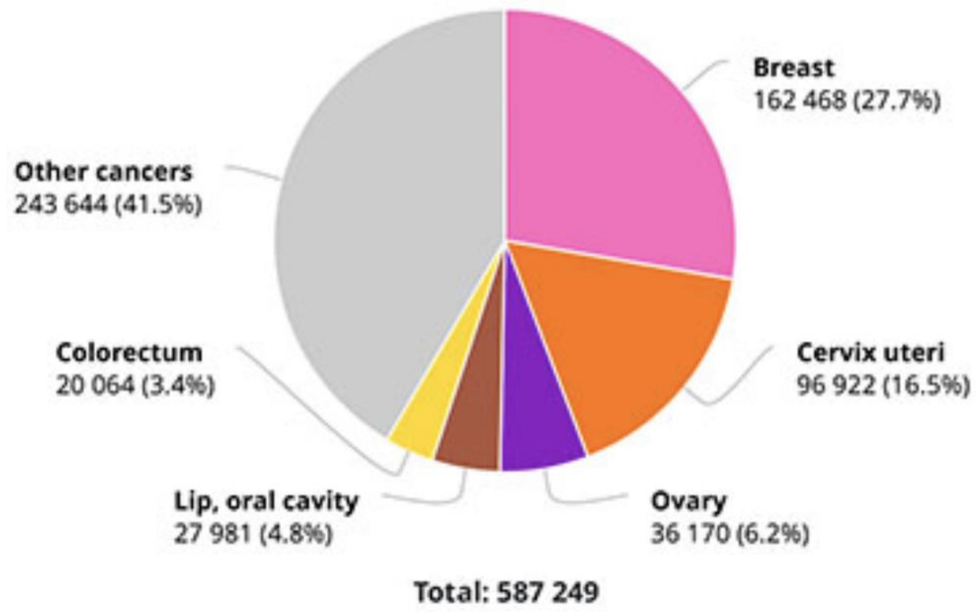
Breast cancer epidemiology Indian perspective

87,090 (12.11%) **deaths due to breast cancer**

Number of new cases in 2018, both sexes, all ages



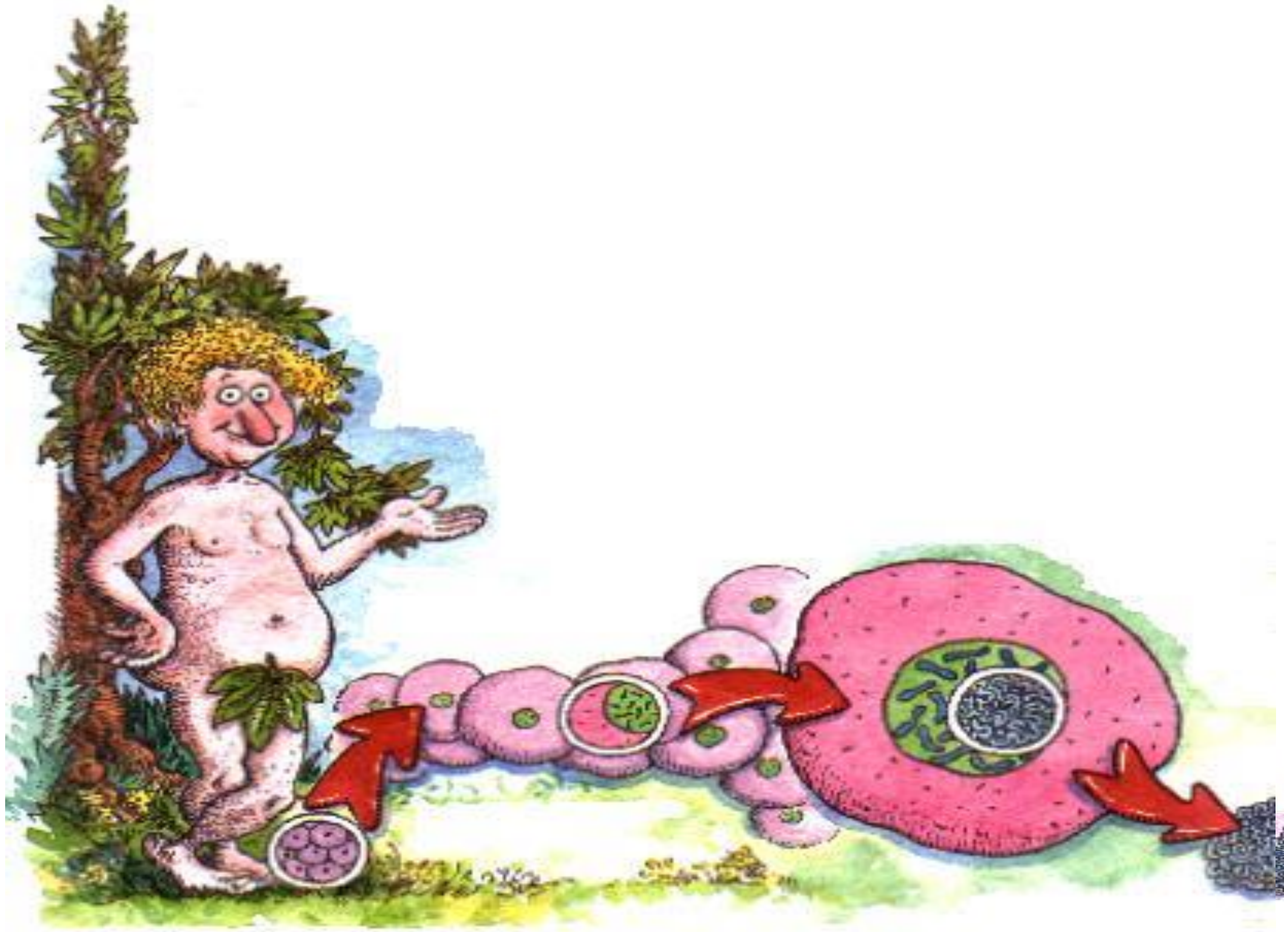
Number of new cases in 2018, females, all ages

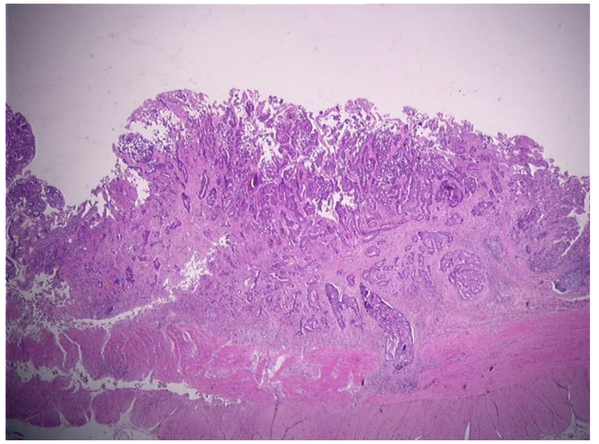


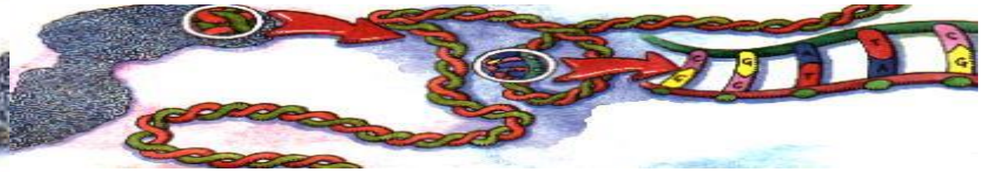
No:1 **cancer in terms of incidence, prevalence and mortality**

http://cancerindia.org.in/globocan-2018-india-factsheet/

Cancer is a genetic disease although mostly not heritable.



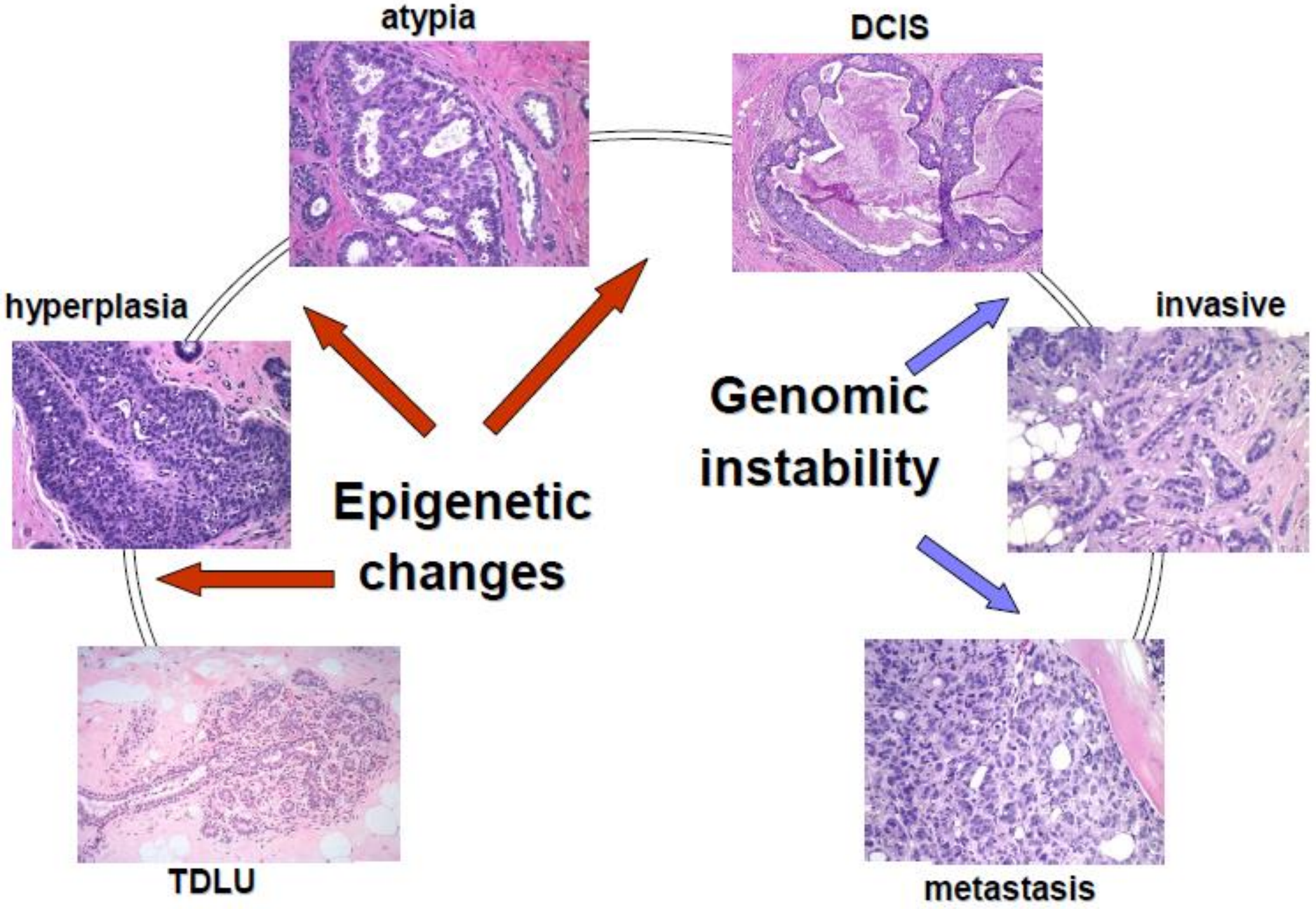




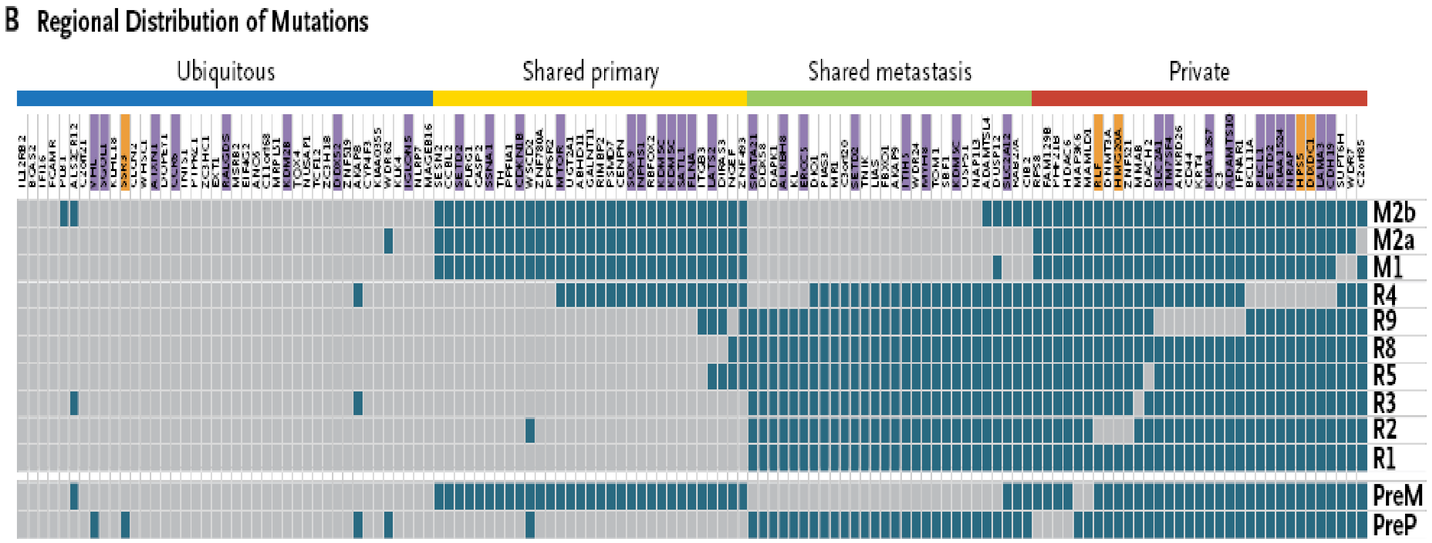
Organismal damage (cancer)

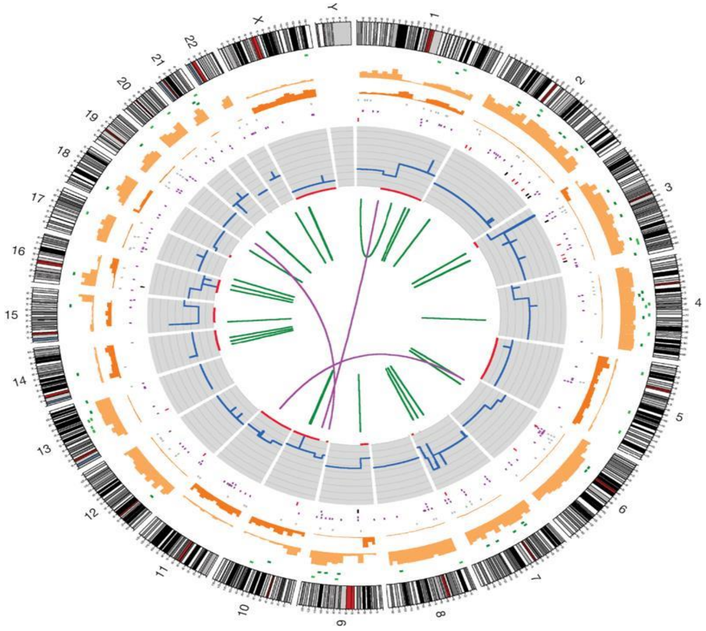
Cellular damage

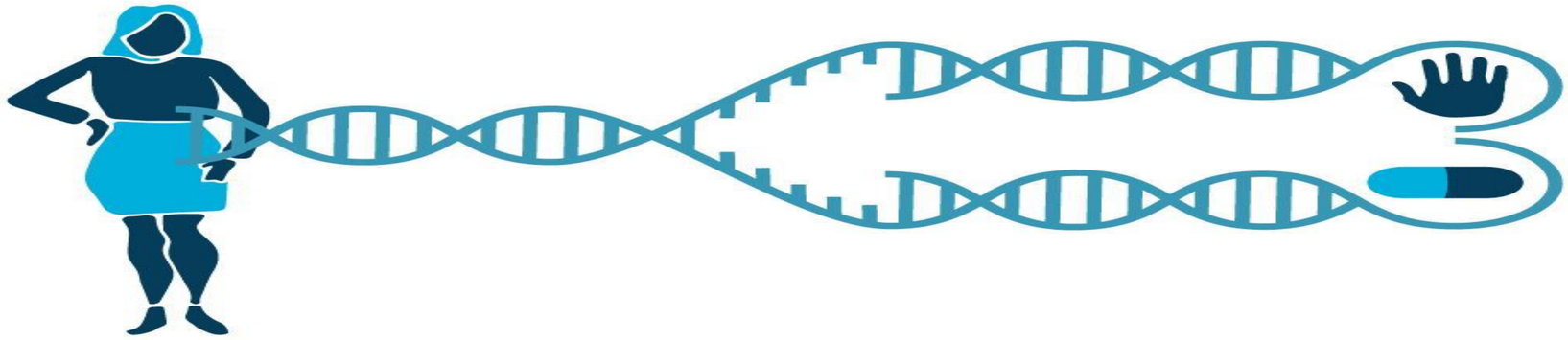
DNA damage (mutations)


atypia
DCIS
hyperplasia
invasive
Genomic
instability
Epigenetic
changes
TDLU
metastasis

WHOLE GENOMIC SEQUENCE







PREVENTION

THERAPEUTICS

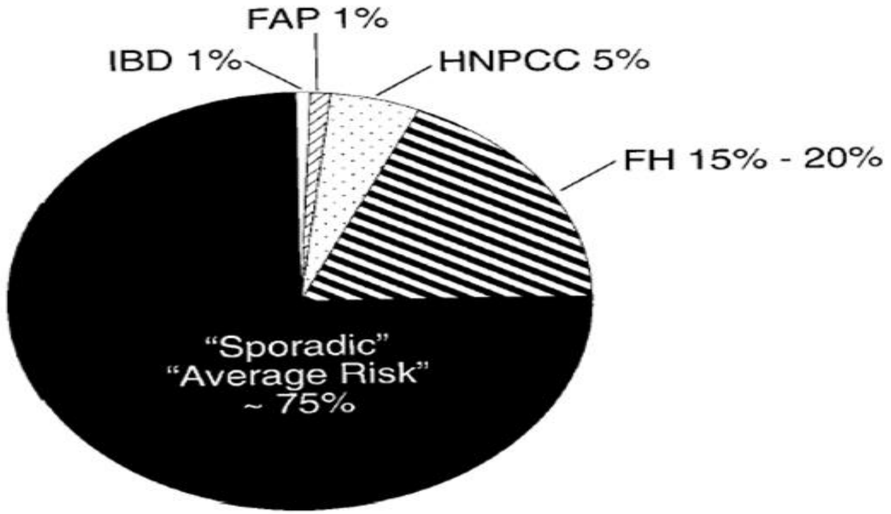
Germline vs Somatic Genetics

- **Germline – the genes you are born with(Inherited)**
  - **Can be passed on to relatives.**
  - **Does not mean that disease will happen.**
  - **Increased risk of disease.**
  - **There is no one “breast cancer gene”**

- **Somatic – changes in tumors that are acquired over time.**
- **(Combination of Envoirnmental & Genetic Factors)**
  - **Can not pass on to relatives**
  - **Can be tested as part of decision making for therapy for cancer**

GERMLINE SUSCEPTIBILITY

Inheritance	Susceptibility	Germline alleles
Hereditary	Strong	High/moderate penetrance, one gene
Familial	Modest	Low penetrance, many genes
Sporadic	None	None



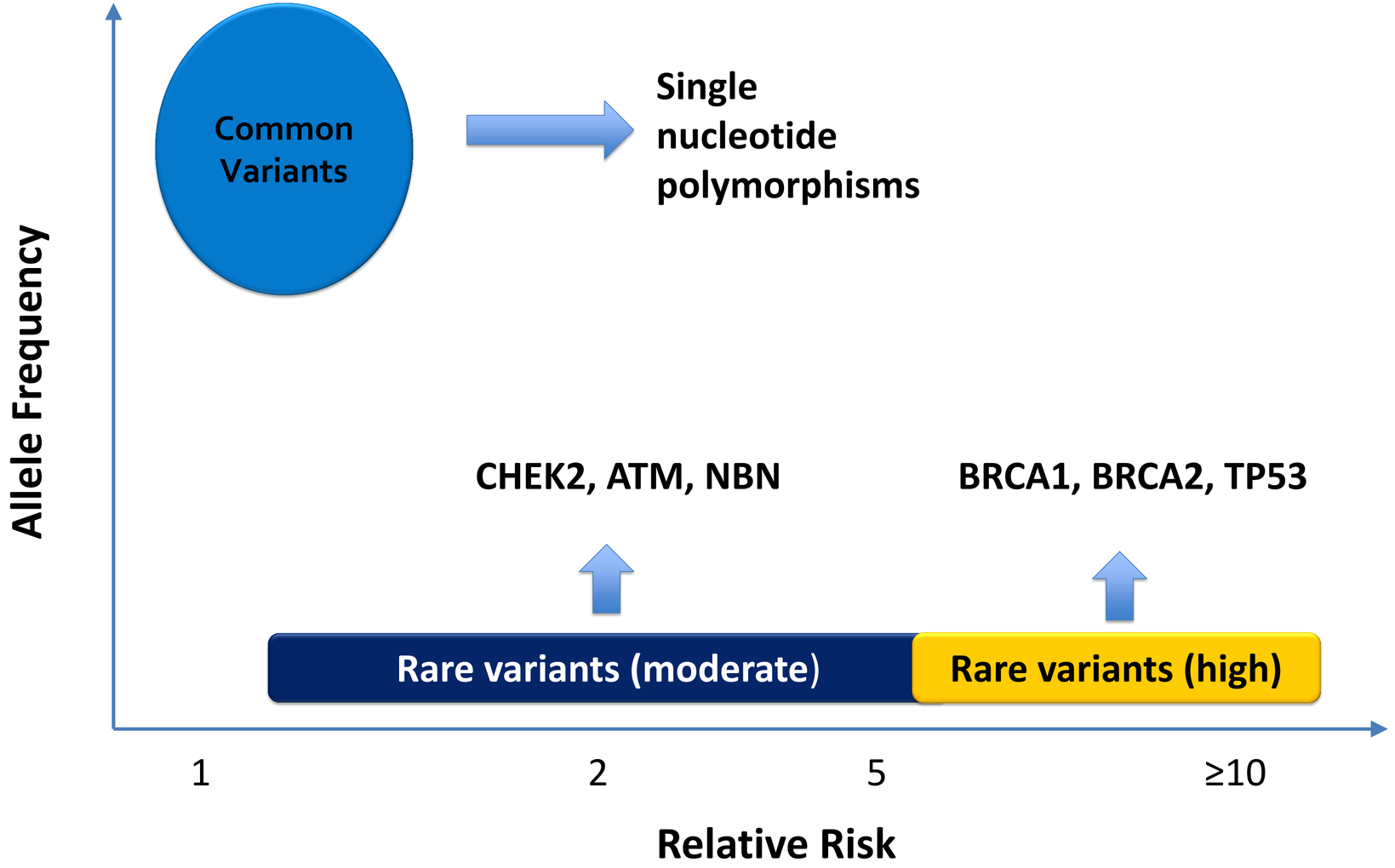
HEREDITARY VS SPORADIC CANCER

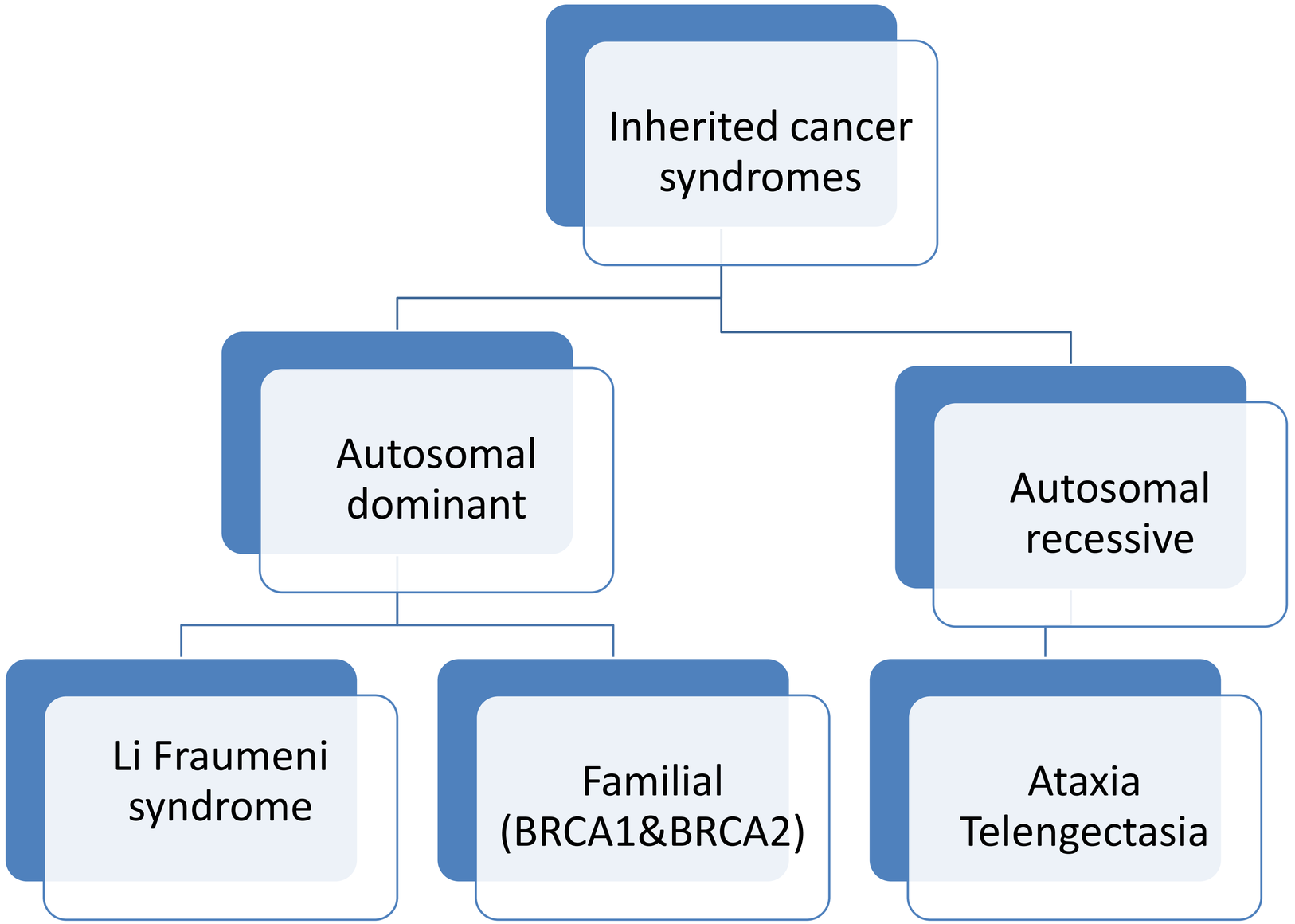
- Hereditary cancers, as compared to corresponding sporadic cancers, tend to be characterised by
- Earlier onset
- Multiple primary tumours
- Family history of same cancers in relatives

- Consistent with a first, germline mutation
- Already present at birth (hence earlier onset)
- In all cells of the body (hence multiple primaries in susceptible tissues)
- Including germ line of the patient (hence heritable in relatives)

- Cf Knudson model of retinoblastoma*

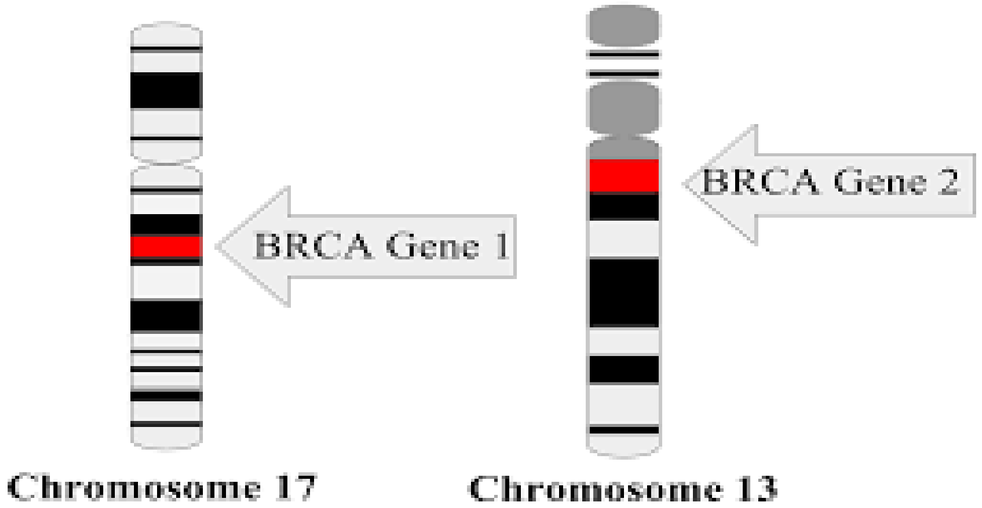
Genetics : Cancer Risk Variants




Inherited cancer syndromes
Autosomal dominant
Autosomal recessive
Li Fraumeni syndrome
Familial (BRCA1&BRCA2)
Ataxia Telengectasia

Associated Gene Mutations in Breast Cancer.

BRCA mutations



Association:

- Early-onset breast cancer
- Triple-negative breast cancer
- Bilateral breast cancer
- Family history of breast cancer

Less common

Non BRCA mutations

Most documented genes:

- TP53
- PTEN
- SKT-11

Association:

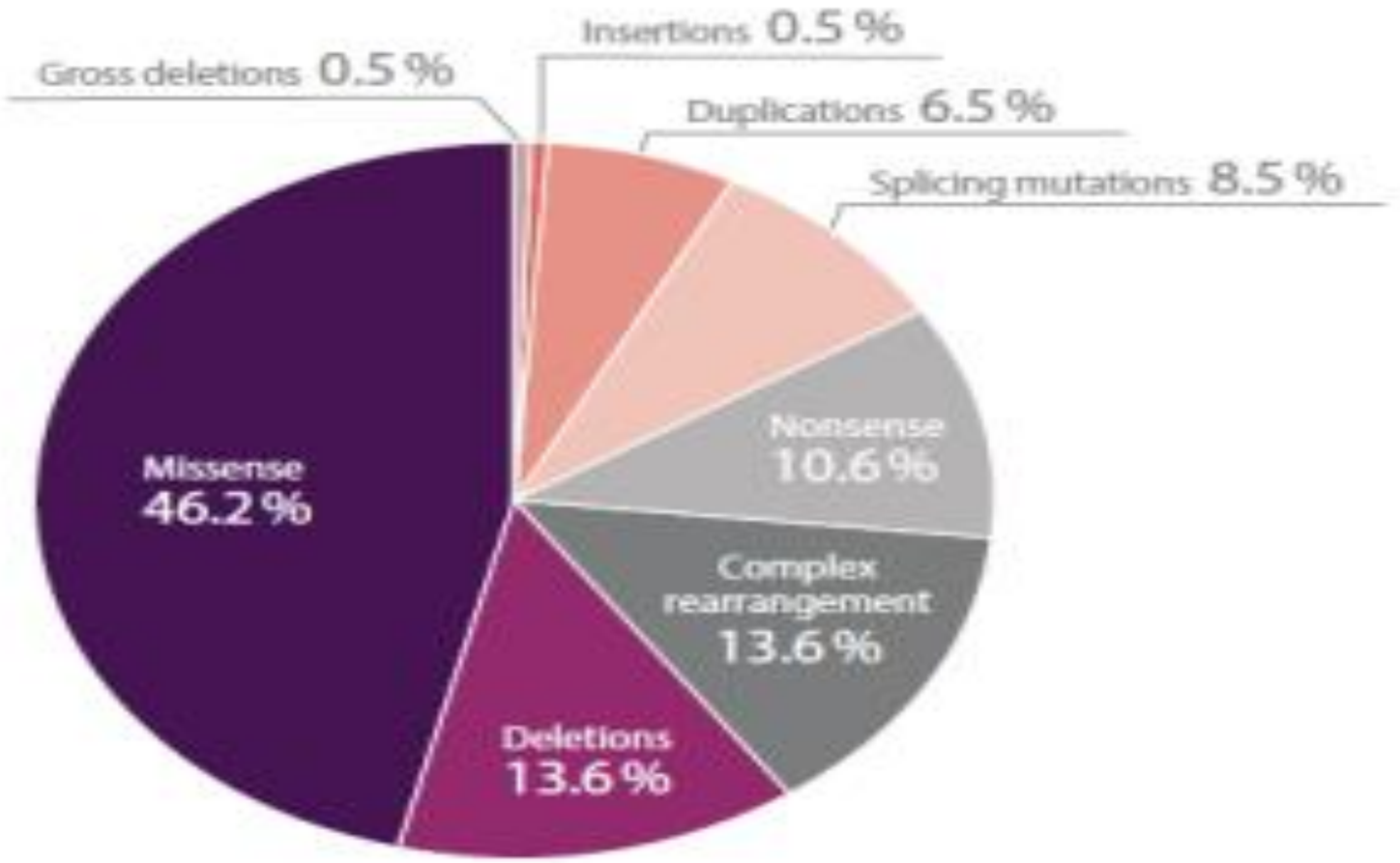
- Li-Fraumeni syndrome
- Cowden disease
- Peutz-Jeghers syndrome

Economopoulou et al. Cancer Treat Rev. 2015;41(1):1-8.
Sharma et al. Breast Cancer Res Treat. 2014; 145(3):707-714.

Christinat et al. Breast. 2013;22(4):375-382.
Grignol etal.. J Am Coll Surg. 2016;222(5):906-914.

BRCA mutations

Types of BRCA mutations in Hereditary Breast and Ovarian Cancer (HBOC)



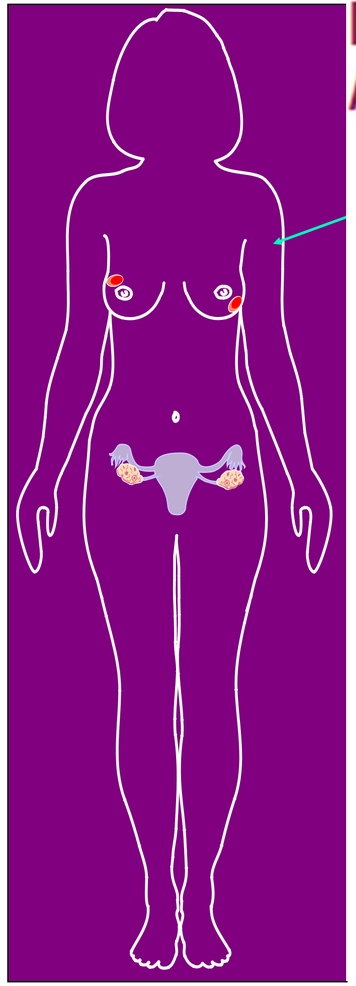
BRCA1 Gene (17q21)

- Responsible for up to 1/2 of “inherited” breast cancers (5% of cancers)
- Increased risk of ovarian and colon cancers (“Breast-Ovarian” cancer gene)
- Breast cancer develops in >50% of these women by age 50 (“Early onset” breast cancer gene). Lifetime risk of breast cancer is 85%.
- Majority are Triple negative.
- 20% are ER/PR positive while approx 03% are Her-2 positive/amplified.

BRCA2 Gene (13q)

- Responsible for up to 70% of inherited breast cancer NOT due to BRCA1 (3.5% of cancers)
- Characterized by increased risk of breast cancer in women and MALE breast cancer (“Male Breast Cancer” gene)
- 30-40% lifetime risk of breast cancer.
- Unlike BRCA1; ER/PR positivity is similar to sporadic cancer, while Her-2 positvity is similar to that of BRCA1(3%)

BRCA1/2-associated cancers: lifetime risk



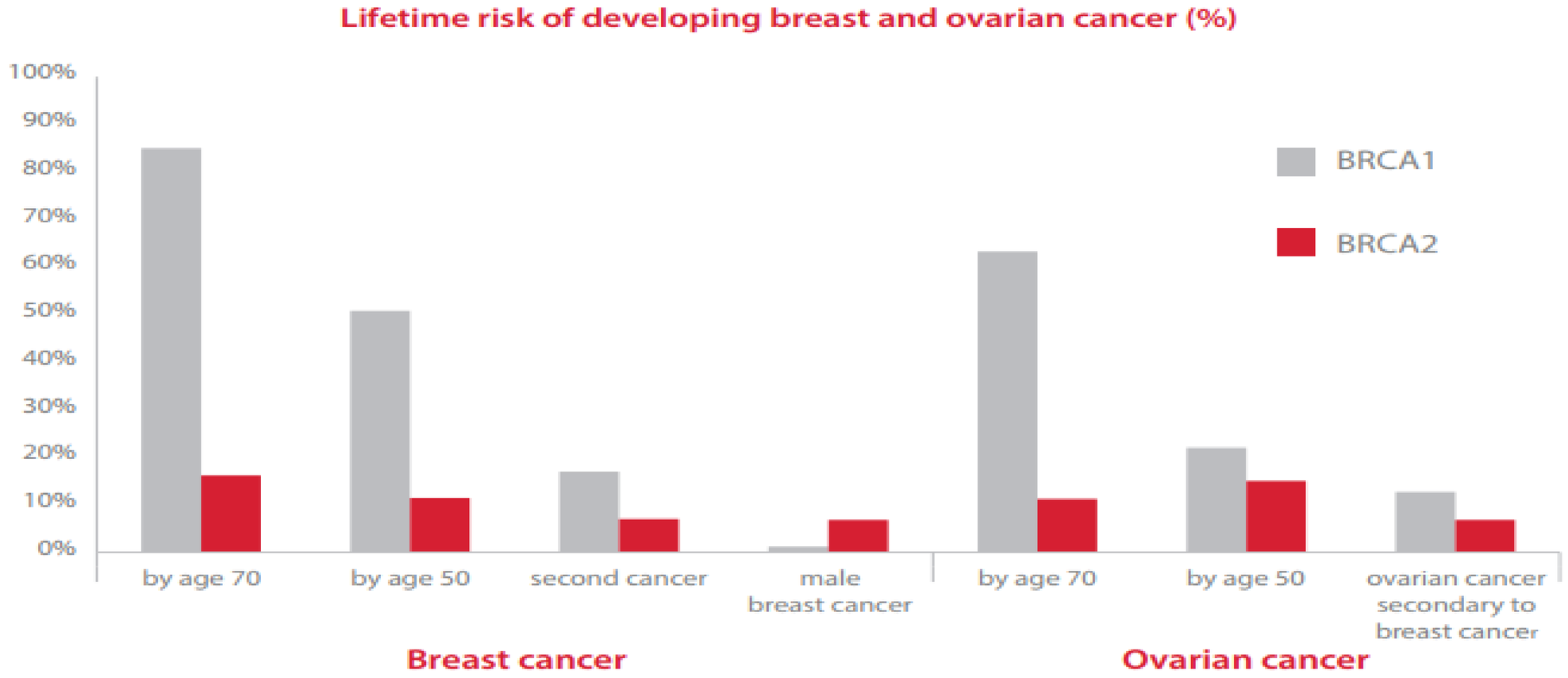
LIFETIME CANCER RISKS

KUCHENBAECKER, 2017

Cancer	General population	BRCA1	BRCA2
BC	11%	50-85% 65-79%	50-85% 61-77%
OC	1.4%	20-50% 36-53%	10-30% 11-25%
2nd BC (20y risk)	n/a	35-45%	20-33%
Pancreatic	3%	3%	6%
Prostate	13%	13%	26%

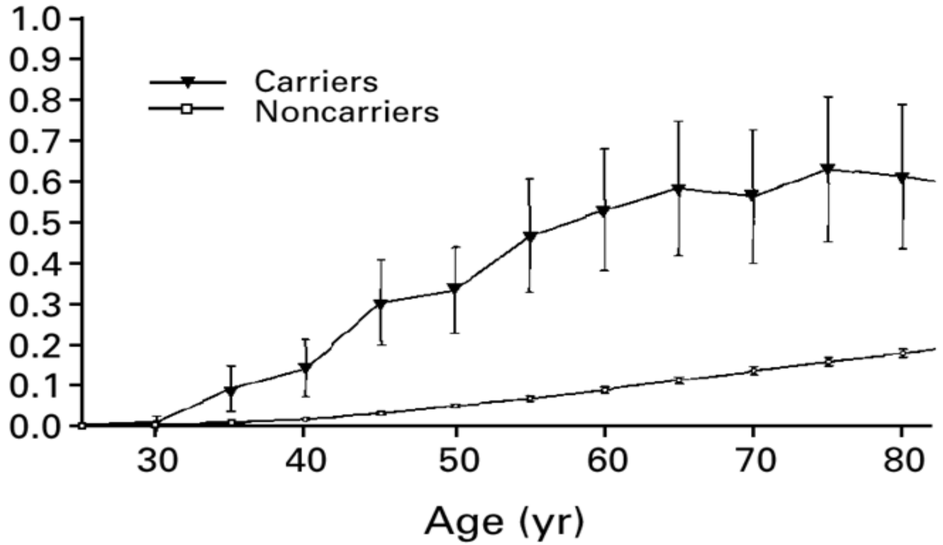
BRCA mutations increase the risk of developing cancer

In the general population, approximately 12% of women will develop breast cancer in their lifetime. In comparison, 55-65% of women carrying a BRCA1 mutation and ~45% of women carrying a BRCA2 mutation will develop breast cancer by age 70.



PENETRANCE OF THE BRCA GENE DEFECT

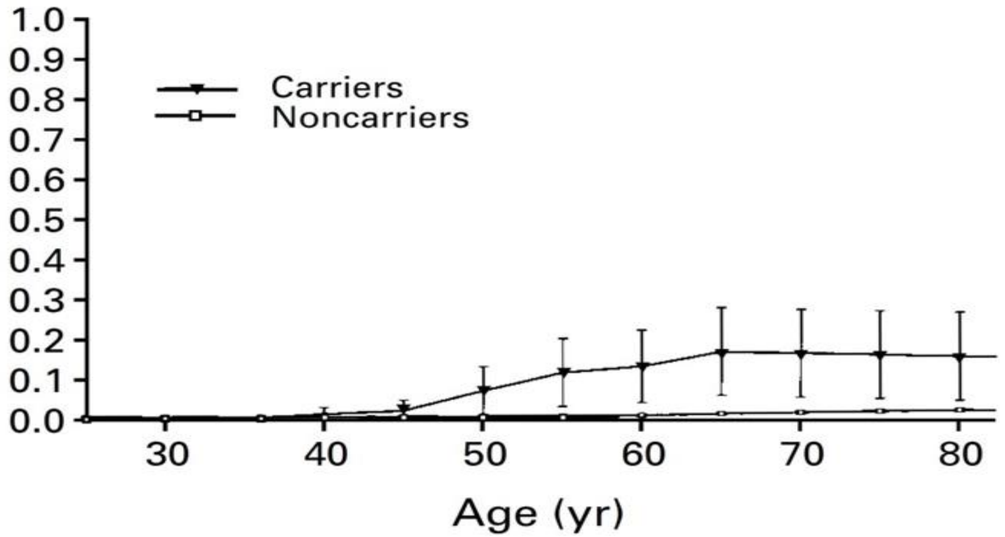
Estimated Risk of Breast Cancer1



Breast cancer in BRCA1 carrier:

- ✓Typically triple negative (TNBC)[2]
- ✓2-3 recurrence /100 women/year
- ✓Shorter interval if earlier onset[3]

Estimated Risk of Ovarian Cancer1
BRCA2



Ovarian cancer in BRCA1/2 carrier:

- ✓Serous, papillary epithelioma[4]
- ✓most tumours start in tubes[5]
- ✓No efficient surveillance tools

1. From N Engl J Med, Struewing JP, *et al.* The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews, 336, 1401–8. Copyright © 1997 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society;
2. Lakhani SR, *et al.* Clin Canc Res 2005; 3. Graeser MK, *et al.* J Clin Oncol 2009; 4. Zhang et al 2011; 5. Mehrad M, *et al.* Adv Anat Pathol 2010.

BRCA mutations

Subtypes: BRCA1 and BRCA2.

Other associated cancers: Ovaries, uterine tubes, male breast cancers, pancreatic & melanoma

Increase risk: Ashkenazi Jewish, hispanic individuals.

Indications for genetic testing in women with and without cancer

Guidelines by:

American Society of Breast Surgeons (ASBrS)

The National Comprehensive Cancer Network (NCCN)

US Preventive Services Task Force (USPSTF)

Basis of recommendation:

- Family history of BRCA1 and BRCA2
- Early onset breast cancer
- 2 or more primary cancers
- Ashkenazi Jewish heritage

https://www.breastsurgeons.org/new_layout/about /statements/PDF_Statements/BRCA_Testing.pdf.

https://www.nccn.org /professionals/physician_gls/pdf/genetics_screening .pdf.

Moyer VA Ann Intern Med. 2014;160(4):271-281.

NON- BRCA mutations

Non BRCA mutations

Gene	Gene Location	Gene Function	Hereditary Syndrome; Associated Cancers	Associated Lifetime Risk for BC, %
TP53	17p13.1	Tumor suppressor gene (cell growth regulator)	Li-Fraumeni syndrome; BC, adrenocortical carcinomas, brain cancer, leukemias, sarcomas	90
PTEN	10a23.3	Phosphatase tension homologue; specific function unclear; mutation associated with improper cell cycle arrest	Cowden disease; BC, disseminated benign and malignant hamartomas, endometrial and thyroid cancers	~ 50
SKT-11	19p13.3	Tumor suppressor gene; associated with apoptosis; also negative regulator of mTOR pathway	Peutz-Jeghers syndrome; BC, ovarian, pancreatic, gastric, small intestine, and colorectal cancers	~ 50
CDH1 (E-cadherin gene)	16q22.1	Epithelial cell-cell adhesion molecule	Hereditary diffuse gastric cancer; BC	39
MLH1, *MSH2*, *MSH6*, *PMS2* (MMR genes)	3p22.2, 2p21-p16, 2p16.3, 7p22.1	DNA mismatch repair	Lynch syndrome; BC,[b] ovarian, endometrial, stomach, and colorectal cancers	NA

Valencia et al. JAMA Surg. 2017 Jun 1;152(6):589-594.

Non BRCA mutations

Gene	Gene Location	Gene Function	Hereditary Syndrome; Associated Cancers	Associated Lifetime Risk for BC
CHEK2 (checkpoint kinase 2)	22q12	Serine threonine kinase associated with DNA double-strand break repair; also phosphorylates *BRCA1*	BC	37%
ATM	11q22	Associated with DNA double-strand break repair and cell cycle progression	Ataxia telangiectasia; BC	3- to 5-Fold increased risk
PALB2, *BR1P1*	16p12.2,17q23.2	*PALB2*: binding partner and localizer of *BRCA2* associated with DNA homologous recombination repair; *BR1P1*: encodes protein serving as binding partner of *BRCA1*	Fanconi anemia; BC, solid tumors, leukemias; *PALB2*: various additional cancers	2-Fold increased risk
RAD51C	17q22	Associated with DNA double-strand break repair via homologous recombination and Fanconi anemia, *BRCA* pathway	BC	NA
RAD51D	17q12	Associated with DNA double-strand break repair via homologous recombination	BC	No statistically significant increased risk
BARD1	2q35	Associated with DNA double-strand break repair via homologous recombination; also interacts with *BRCA1*	BC	Conflicting data
MRE11, *RAD50*, *NBS1* (MRN complex)	11q21,5q.31.1, 8q21.3	Associated with DNA double-strand break repair	*MRE11*: ataxia telangiectasia-like disorder; weak association with BC; *RAD50*: Nijmegen breakage syndrome-like disorder, weak association with BC; *NBS1*: Nijmegen breakage syndrome, association with BC	2- to 3-Fold increased risk (limited evidence)
FANCM	14q21	Associated with DNA repair	Fanconi anemia; BC, solid tumors, leukemias	Increased risk (not quantified)

NCCN: Individuals who test negative for BRCA1 and BRCA2 and are suspected of having 1 or more inherited syndromes may be considered for multi-gene assessment for efficiency and cost-effectiveness

https://www.nccn.org /professionals/physician_gls/pdf/genetics_screening .pdf.

Cowden Disease

- mutation in PTEN (601728 OMIM), a phosphate tensin homologue located at 10q23.3
- > 1% of breast cancer diagnoses.
- Lifetime risk of breast cancer is approximately 50%
- Other associated cancers: disseminated benign and malignant hamartomas, endometrial and thyroid cancer, and mucous membrane lesions.

Screening criteria

- Family history of PTEN mutations
- Various combinations of
  - major criteria (eg: breast cancer, macrocephaly, or follicular thyroid carcinoma)
  - minor criteria (eg: nonmalignant thyroid lesions, colon cancer, or autism spectrum disorder)

Economopoulou et al. Cancer Treat Rev. 2015;41(1):1-8.

Germline genetic screening as a paradigm for individualized care

- **Risk Assessment.**
- **Disease Prevention.**
- **Therapeutics.**

***BRCA1/2* as the prototype**

CANCER PATIENT TRAJECTORY WITH GENETIC COUNSELLING (GC)

Suspected hered c. → **Pre-test GC** → **Genetic Test** → **Post-test GC**

Personal history

Family history

Family tree
Inform patient about outcomes of genetic test
Consent signed.

Blood sample
DNA analysis

Give results
+ interpretation
Family issues Psychological support

PRE TEST COUNSELLING

- Pre-test counseling includes:
  - Collection of a comprehensive family history
    - Note that when assessing family history, close blood relatives include first-, second-, and third-degree relatives on each side of the family (See BR/OV-B)
  - Evaluation of a patient's cancer risk
  - Generating a differential diagnosis and educating the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity
  - Preparing the patient for possible outcomes of testing including positive (pathogenic, likely pathogenic), negative, and uncertain findings and obtaining informed consent

RISK ASSESSMENT MODELS

- Computerised algorithms
- Breast Cancer Risk Assessment Tool (BCRAT)
- (Gail model) BRCAPRO
- IBIS
- BOADICEA
- Ontario Family History Assessment Tool

Manchester Scoring System
Referral Screening Tool
Pedigree Assessment Tool
FHS-7

USPSTF recognizes that each risk assessment tool has limitations and found insufficient evidence to recommend one tool over another.

- Help in deciding
- whether to test or not to test for gene mutation
- What surveillance and prevention, e.g. breast MRI, especially if no mutation found

- Case-by-case pedigree-based analysis remains mandatory

Gail Model

RISK FACTORS USED IN THE MODIFIED GAIL MODEL, AGE ≥35 YEARS[1]

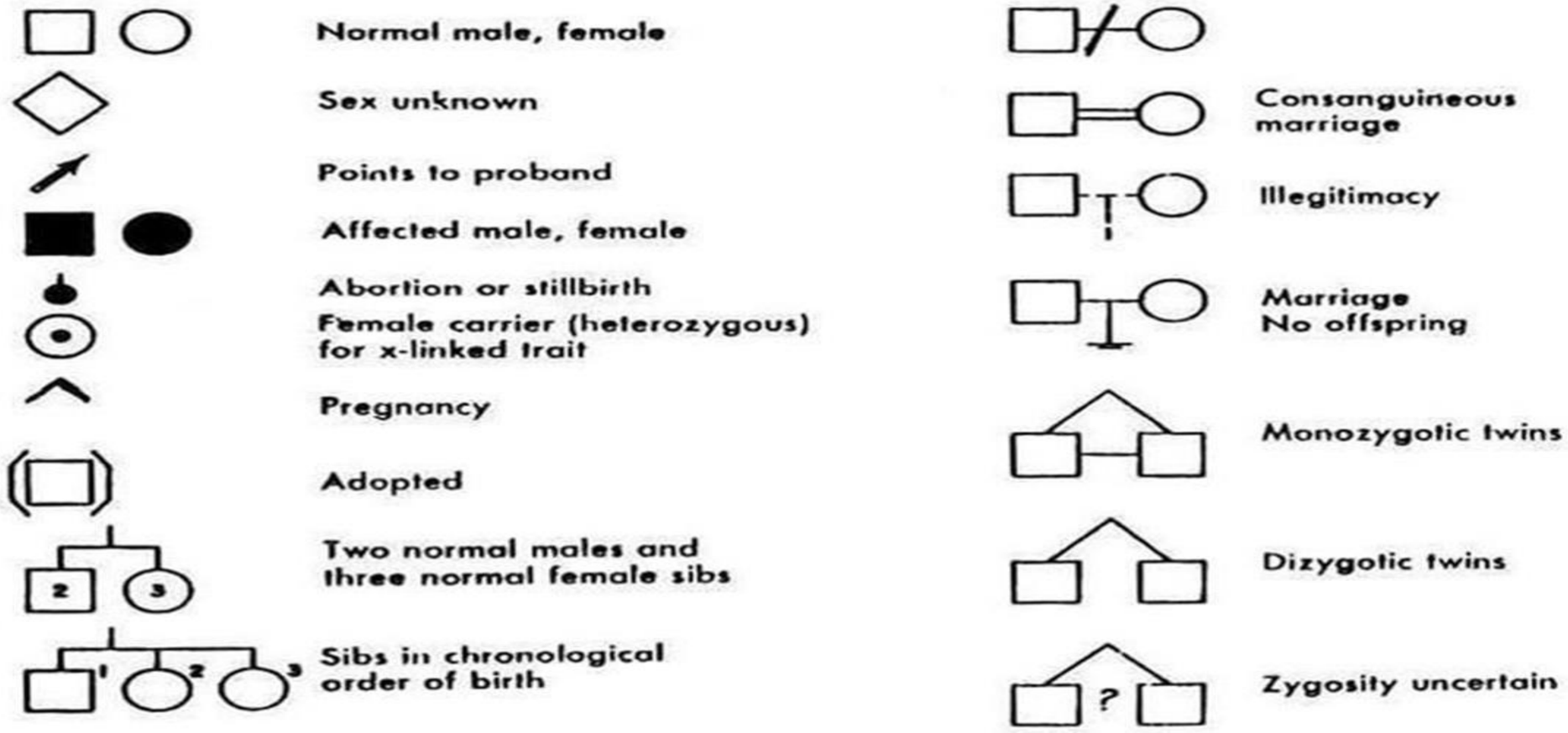
- **Current age**
- **Age at menarche**
- **Age at first live birth or nulliparity**
- **Number of female first-degree relatives with breast cancer**
- **Number of previous benign breast biopsies[2]**
- **Atypical hyperplasia in a previous breast biopsy**
- **Race[3]**

For calculation of risk, based on the modified Gail Model, see http://www.cancer.gov/bcrisktool/Default.aspx

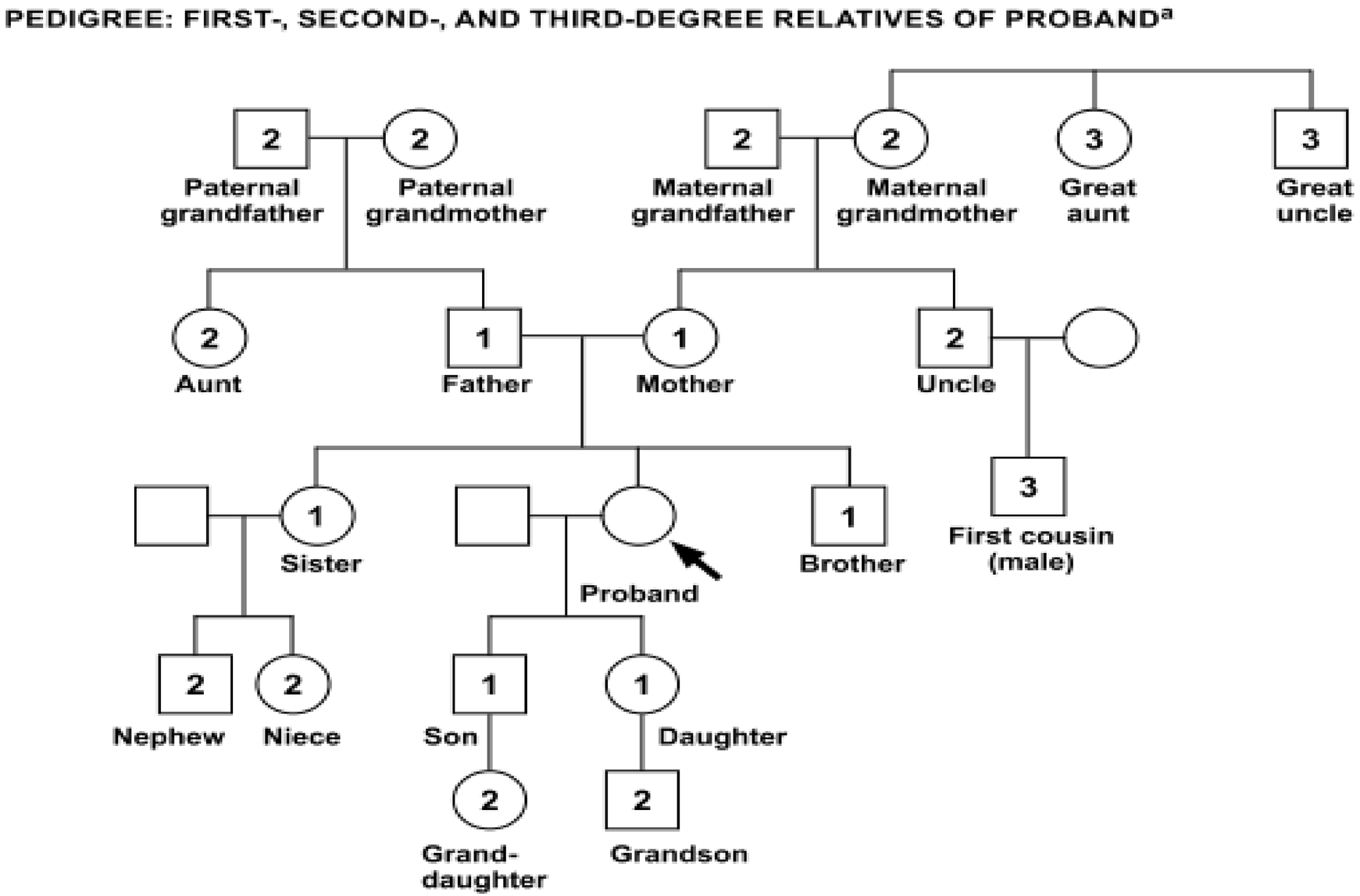
Pedigree Assessment Tool

Risk Factor	Score
Breast cancer at age ≥50 y	3
Breast cancer at age <50 y	4
Ovarian cancer at any age	5
Male breast cancer at any age	8
Ashkenazi Jewish heritage	4

PEDIGREE: SYMBOLS USED



PEDIGREE FIRST , SECOND AND THIRD RELATIVES OF PROBAND



Results

Classification

(1)Positive for a deleterious mutation

(2)Genetic variant

(3)No deleterious mutation

Result	Interpretation
Positive for a deleterious mutation	Mutation deemed to be clinically relevant; should prompt discussion regarding risk-reducing strategies and/or therapy
Genetic variant	Varied clinical significance
Suspected deleterious	Mutation likely, but not proven to be, deleterious
Favor polymorphism	Mutation will likely not augment breast cancer risk to great extent
Uncertain significance	Mutation lacks documented clinical significance
Specific variant/mutation not identified	Mutation or variant not detected in individual
No deleterious mutation	Negative test; does not predispose the individual to developing *BRCA*-associated breast cancer but does not guarantee an absent risk of breast cancer due to other genes

Assuming a 10% probability of a positive test result, the likelihood of an incorrect result is reported as <1%

MyriadGeneticLaboratories.TestingOptions. My support 360. https://mysupport360.com /genetic-testing/genetic-testing-process/

GENETIC VARIANTS

VUS = Variant of Uncertain clinical Significance

.2-10% people in normal population carry a VUS, depending on gene and ethnicity (Yurgelun MB, *et al.* J Clin Oncol 2015, Vol 33 (28) 2015: 3092-3095)

.Most are expected to be harmless, statistically

VUS classification will require epidemiology of variant and/or functional data (bioinformatics, machine learning approach)

VARIANT type	Frequency	Penetrance (fonctional effect)
Mutation	Rare	High
VUS	Rare	? ?
Polymorphism	Frequent	Low or null
« Rare polymorphism »	Rare	Low or null

HOW TO HANDLE VUS?

- Do not report variant if no clear evidence that it is disease-causing
- Protein-truncating mutation, and/or
- Already reported in other patients
- In-house data
- Publically available databases, e.g. ClinVar-NCBI
- (https://www.ncbi.nlm.nih.gov/clinvar/)

- Periodically re-assess VUS for reclassification as benign (most) or disease-causing (few) in large databases
- And recall patients to the clinic for update if disease-causing

POST TEST GC

- Post-test counseling includes discussions of:
  - Results along with their significance and impact and recommended medical management options
  - Interpretation of results in context of personal and family history of cancer
  - Informing and testing at-risk family members
  - Available resources such as disease-specific support groups and research studies

Genetic Tests for Breast cancers

Clinical Review & Education

JAMA Surgery | Review

The Role of Genetic Testing in Patients With Breast Cancer
A Review

Olivia M. Valencia, BA; Selyne E. Samuel, MD; Rebecca K. Viscusi, MD; Taylor S. Riall, MD, PhD; Leigh A. Neumayer, MD; Hassan Aziz, MD

IMPORTANCE In the United States from 2009 to 2013, the incidence of breast cancer was the highest of any cancer and the death rate was second to that of lung cancer. Approximately 5% to 10% of breast cancers are inheritable.

OBSERVATIONS *BRCA1* and *BRCA2* germline mutations account for up to 30% of inheritable breast cancers and are the most commonly assessed mutations in patients presenting with early-onset breast cancer, triple-negative breast cancer, bilateral breast cancer, and a family history of breast cancer. Less common non-*BRCA* mutations have also been identified and contribute to hereditary breast cancer syndromes. Although established in *BRCA* mutations, indications and interpretations of genetic testing in non-*BRCA* mutations are not well defined. Furthermore, costs associated with genetic testing are highly variable and dependent on laboratory pricing, insurance coverage, and individual risk factors.

CONCLUSIONS AND RELEVANCE Genetic testing is a powerful tool that allows for the detection of *BRCA* and non-*BRCA* germline mutations in individuals with high risks of breast cancer, which in turn aids in the individualization of treatment. Given the magnitude of this disease, it is of great benefit for physicians, including general surgeons, to understand the indications, interpretations, and costs associated with genetic testing in patients with breast cancer. Cost is an especially important part of the genetic testing process and point of discussion with patients.

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CME Quiz at jamanetwork.com/learning and CME Questions page 612

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Breast cancer is a common disease with significant morbidity and mortality.[1,2] In the United States from 2009 to 2013, the incidence of breast cancer was 123.3 per 100 000 women—the highest of any cancer. The death rate was second to lung cancer (21.2 vs 44.7 per 100 000 women, respectively).[3] In 2017, approximately 255 180 new cases will be diagnosed and 41 070 deaths will result from breast cancer.[3] In addition, 5% to 10% of breast cancers may be inheritable.[2]

The role of genetic testing in breast cancer is rapidly changing and is an area of active research. Identification of germline mutations in high-risk individuals allows for increased surveillance and earlier implementation of risk-reduction strategies.[2,4] The aim of this review is to assess the role of genetic testing in breast cancer, specifically, to guide the general surgeon regarding the indications, interpretations, and costs of such testing.

Associated Gene Mutations and Available Genetic Tests

BRCA1 and *BRCA2* Gene Mutations

Genetics

BRCA1 (113705 OMIM) and *BRCA2* (600185 OMIM) germline mutations have been strongly associated with breast cancer development and are the most commonly assessed mutations in individuals presenting with early-onset breast cancer, triple-negative (estrogen receptor–negative, progesterone receptor–negative, and human epidermal growth factor receptor 2–negative) breast cancer, bilateral breast cancer, or a family history of breast cancer. Together, these mutations account for up to 30% of inheritable breast cancers.[2,5,6] *BRCA1* and *BRCA2* mutations also increase the risk of cancers of the ovaries, uterine tubes, peritoneum, and, specific to *BRCA2* mutations, breast cancer in males, pancreatic cancer, and melanoma, all of which collectively compose hereditary breast and ovarian cancer syndrome.[7]

Both genes are inherited in an autosomal dominant fashion and function as tumor suppressor genes.[8] *BRCA1*, located at 17q21, encodes for an E3 ubiquitin ligase with roles in homologous recombination repair of double-stranded DNA damage and chromatin remodeling, among other functions.[9] *BRCA2* is located at 13q12.3 and encodes for a protein that also contributes to homologous recombination repair, albeit via a mechanism different from that of *BRCA1*.[8] Ashkenazi Jewish and Hispanic individuals, among other races and ethnicities, have increased incidences of pathogenic *BRCA* mutations.[10,11]

Indications for Genetic Testing in Women With and Without a Breast Cancer Diagnosis

Indications for genetic testing for *BRCA* mutations may be found in clinical practice guidelines provided by various organizations,

INDICATIONS

Genetic testing is a powerful tool that allows for BRCA and non-BRCA germline mutations in high risk individuals

Indications for patients with a personal h/o breast cancer

ASBrS Guidelines (September 2016)[12]

1. Age 50 years or younger at time of BC onset
2. Triple-negative BC and age 60 years or younger
3. Two or more primary BCs (including asynchronous, synchronous, bilateral, or multicentric)
4. First-degree relative with BC at 50 years or younger
5. Two relatives on same side of family with BC and/or pancreatic cancer
6. Family or personal history of ovarian cancer, fallopian cancer, or primary peritoneal cancer
7. Male BC
8. Ashkenazi Jewish heritage and family history of BC at any age
9. Family member with a known mutation

NCCN Guidelines (December 2016)[13]

1. BC diagnosis at 50 years or younger
2. Two or more primary BCs (including bilateral tumors or ≥2 clearly separate ipsilateral tumors, synchronous or asynchronous), with the first at 50 years or younger
3. BC diagnosis at 50 years or younger with 1 or more close relatives[e] with BC at any age, pancreatic cancer, or prostate cancer (Gleason score ≥7), or with a limited/unknown family history
4. Triple-negative BC at 60 years or younger
5. BC at any age with 1 or more close relatives with BC at 50 years or younger
6. BC at any age with 2 or more close relatives with BC at any age
7. BC at any age with 1 or more close relatives with ovarian carcinoma (including fallopian tube and primary peritoneal cancer) at any age
8. BC at any age with 2 or more close relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age
9. Close relative with male BC
10. Personal history of BC and Ashkenazi Jewish heritage (no other family history required)
11. Personal history of ovarian carcinoma
12. Personal history of male BC

USPSTF Guidelines (February 2014)

Excludes

- **Patients post diagnosis of breast cancer.**
- **Men with breast cancer.**

https://www.breastsurgeons.org/new_layout/about /statements/PDF_Statements/BRCA_Testing.pdf.

https://www.nccn.org /professionals/physician_gls/pdf/genetics_screening .pdf.

Moyer VA Ann Intern Med. 2014;160(4):271-281.

Indications for patients without a personal h/o breast cancer

ASBrS Guidelines (September 2016)[12]

1. First- or second-degree relative with BC, onset at 45 years or younger (early-age onset)
2. Two or more primary BCs (includes asynchronous, synchronous, bilateral, or multicentric) in 1 relative
3. Two or more relatives on the same side of the family with BC and/or pancreatic cancer
4. Family or personal history of ovarian cancer, fallopian cancer, or primary peritoneal cancer
5. Male BC
6. Ashkenazi Jewish heritage and family history of BC at any age
7. Family member with a known mutation

NCCN Guidelines (December 2016)[13,a]

1. Presence of known deleterious *BRCA1* or *BRCA2* germline mutation in family
2. Presence of *BRCA1* or *BRCA2* mutation in tumor profiling without germline mutation
3. Personal history of ovarian carcinoma
4. Ashkenazi Jewish heritage and personal history of pancreatic cancer
5. Personal history of prostate cancer (Gleason score ≥7) at any age with 1 or more close relatives[b] with ovarian carcinoma at any age, or BC at 50 years or younger, or 2 close relatives with BC, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
6. Family history only[c]:
   a. First- or second-degree relative with any criteria listed above
   b. Third-degree relative who has BC and/or ovarian carcinoma and who has 2 or more family members with BC (at least 1 with BC at 50 years or younger) and/or ovarian carcinoma

USPSTF Guidelines (February 2014)[14]

1. Family history[d] of BC and ovarian cancer
2. Family history of bilateral BC
3. Family history of BC diagnosis at younger than 50 years
4. Multiple cases of BC in family
5. At least 1 family member with 2 primary cancers associated with a *BRCA* mutation
6. At least 1 male family member with BC
7. Ashkenazi Jewish heritage

https://www.breastsurgeons.org/new_layout/about /statements/PDF_Statements/BRCA_Testing.pdf.

https://www.nccn.org /professionals/physician_gls/pdf/genetics_screening .pdf.

Moyer VA Ann Intern Med. 2014;160(4):271-281.

SOME GENERAL INDICATIONS FOR TESTING

HBOC suspected any of the following:

- TNBC < 50 years
- Ovarian epithelial, serous, high grade cancer Breast and ovarian cancer, any age
- 2 (first-degree) relatives with breast cancer
- before 50 years
- Breast cancer <50 years and (first degree) relative with ovarian cancer

Lynch suspected any of the following
Amsterdam criteria

3 affected, over 2 generations, 1 < 50 yrs. (Giardiello FM, et al. 2001 Gastroenterology)

Bethesda criteria
If present, test tumour for MSI (DNA analysis; IHC)
If MSI+, test patient for germ-line MMR gene mutation

With room for clinical judgement in deciding to test or not to test

Underdiagnosis of Hereditary Breast Cancer : Are Genetic Testing Guidelines a Tool or an Obstacle?

NCCN Guidelines Version 3.2019
BRCA-Related Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
Table of Contents
Discussion

BRCA1/2 TESTING CRITERIA[a,b]

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.

Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known *BRCA1/2* pathogenic/likely pathogenic variant, including such variants found on research testing[b]
- Personal history of breast cancer[c] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed 46-50 y with:
    - An additional breast cancer primary at any age[d]
    - ≥1 close blood relative[e] with breast cancer at any age
    - ≥1 close blood relative[e] with high-grade (Gleason score ≥7) prostate cancer
    - An unknown or limited family history[a]
  - Diagnosed ≤60 y with:
    - Triple-negative breast cancer
  - Diagnosed at any age with:
    - ≥1 close blood relative[e] with:
      - breast cancer diagnosed ≤50 y; or
      - ovarian carcinoma;[f] or
      - male breast cancer; or
      - metastatic prostate cancer;[g] or
      - pancreatic cancer
    - ≥2 additional diagnoses[d] of breast cancer at any age in patient and/or in close blood relatives
  - Ashkenazi Jewish ancestry[h]
- Personal history of ovarian carcinoma[f]
- Personal history of male breast cancer
- Personal history of pancreatic cancer[i]
- Personal history of metastatic prostate cancer[g]
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with
  - ≥1 close blood relatives[e] with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer[g] at any age or breast cancer <50 y; or
  - ≥2 close blood relatives[e] with breast, or prostate cancer (any grade) at any age; or
  - Ashkenazi Jewish ancestry[h]
- *BRCA1/2* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis
- Regardless of family history, some individuals with an *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted treatment[j]
- An individual who does not meet the other criteria but with ≥1 first- or second-degree blood relative[k] meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.

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

If *BRCA* testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

[a]For further details regarding the nuances of genetic counseling and testing, see BR/

ASBrS Recent Recommendations

ASBrS RECOMMENDATIONS ON GENETIC TESTING

- 1. Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling, can make recommendations to their patients regarding genetic testing, and can arrange testing.
- 2. Genetic testing should be made available to all patients with a personal history of breast cancer.
- 3. Patients who have previously had genetic testing may benefit from updated testing.
- 4. Genetic testing should be made available to patients without a history of breast cancer who meet NCCN Guidelines.
- 5. Variants of uncertain significance are not clinically actionable.

Adapted from American Society of Breast Surgeons.[1] March 25, 2019

South Asian Journal of Cancer

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South Asian J Cancer. 2018 Apr-Jun; 7(2): 106–109.
doi: 10.4103/sajc.sajc_112_18

PMCID: PMC5909285
PMID: 29721474

Practical consensus recommendation on when to do BRCA testing

Purvish M. Parikh, J. Wadhwa,[1] S. Minhas,[2] A. Gupta,[3] S. Mittal,[4] S. Ranjan,[5] P. Mehta,[6] R. Singh,[7] S. P. Kataria,[8] S. Salim,[9] M. Ahmed,[10] and S. Aggarwal[2]

Broad question title

Question 1 - Will you do BRCA testing in all breast cancers under age 40 years?

Question 2 - Will you do BRCA testing for sporadic postmenopauasal triple negative breast cancer 55 years?

Question 3 - Will you go for extended germline mutation testing in triple negative 35-year-old female?

Question 4 - Will you do BRCA testing for postmenopausal breast cancer 60 years old with one maternal cousin having ovarian cancer Will you do BRCA testing for postmenopausal breast cancer 60 years old with one maternal cousin having ovarian cancer?

Question 5 - Will you do BRCA testing for postmenopausal breast cancer 60 years with one paternal cousin having prostate cancer or pancreatic cancer?

Update in oncology-X-2017

RECOMMENDATIONS BY THE PANEL

1	The expert panel recommended not to do BRCA testing in all breast cancers under the age of 40 years
2	BRCA testing should be done for all breast cancer patients above the age of 60 years.
3	Extended germline mutation testing (beyond BRCA) should be done fore triple negative young patients with breast cancer so as not to miss out on other syndromes.
4	The expert panel recommended BRCA testing in breast cancer patients with maternal family history of ovarian cancer.
5	BRCA testing is recommended in selected cases with breast cancer who have paternal family history of prostate or pancreatic cancer (based on published guidelines)

South Asian J Cancer. 2018 Apr-Jun; 7(2): 106–109.

BENEFITS OF A MOLECULAR DIAGNOSIS

- For the patient
- Identify risk of cancer in other organ (ovary; uterus, CRC) for secondary prevention (BRCA; PTEN, and all syndromic BC genes; MMR genes)
- Refine risk of recurrence (CHEK2, ATM)
- Individualised drugs (olaparib in BRCA-linked ovarian cancer)
- Individualised therapy (avoid radiotherapy in TP53)

- For the patient's relatives
- Prevention of cancer if mutation present (surveillance; surgery)
- Reassurance (population risk; or really?) if mutation absent
- Primary prevention in future offspring
- (pregestational diagnosis, prenatal diagnosis)

Screening for BRCA mutated women

- Clinical Breast examination, beginning at age 25.
- Mammogram once per year, beginning at age 30.
- Breast MRI once per year, beginning at age 25 .
- "Breast awareness," beginning at age 18, which involves paying attention to changes in breasts and may include regular breast self-exams.

Prevention and screening in *BRCA* mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening†

S. Paluch-Shimon[1], F. Cardoso[2], C. Sessa[3], J. Balmana[4], M. J. Cardoso[2], F. Gilbert[5] & E. Senkus[6], on behalf of the ESMO Guidelines Committee*

Table 1. Prevention and screening strategies for specific mutations

	Screening	Prevention/risk reduction
Li Fraumeni Syndrome - *p53* mutation	1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI at age 20–75. If MRI is not available, mammography may be considered [V] 3) Colonoscopy every 5 years from the age of 25 or as clinically indicated 4) Annual dermatological and neurological examination 5) Consider annual whole-body MRI and 6-monthly complete blood count	1) Avoid ionising radiation, e.g. CT 2) Consider offering PGD before pregnancies 3) Consider risk-reducing mastectomy
PTEN/Cowden Syndrome	1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI and/or mammogram at age 30–75 [V] 3) Annual endometrial ultrasound ± biopsies from age 30–35	1) Consider risk-reducing mastectomy 2) Consider risk-reducing hysterectomy 3) Consider offering PGD before pregnancies
ATM mutation	1) Consider annual breast MRI (no evidence regarding the age of onset)	
Lynch Syndrome - *MLH1, MSH2,MSH6, EPCAM* and *PMS2* mutations	1) Annual colonoscopy from age 20–25 2) Annual neurological examination for screening of CNS tumours may be considered 3) Annual endometrial ultrasound ± biopsies from age 30–35 may be considered	1) Consider risk-reducing hysterectomy and RRSO after completion of childbearing
RAD51 mutation		1) Consider RRSO after the age of 45
BRIP1 mutation		1) Consider RRSO after the age of 45
PALB2 mutation	1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI from age 20–29 3) Annual breast MRI and/or mammogram at age 30–75 [V]	1) Consider risk-reducing mastectomy

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CHEK2 mutation	1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI from age 20–29 3) Annual breast MRI and/or mammogram at age 30–75 [V]	
STK11 mutation (Peutz–Jeghers Syndrome)	1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI from age 20–29 3) Annual breast MRI and/or mammogram at age 30–75 [V] 4) Upper endoscopy and colonoscopy every 2–3 years from late teens 5) Screening for pancreatic cancer with EUS or MRI from the age of 30 6) Annual testicular examination from childhood 7) Routine annual gynaecological surveillance 8) Counselling to reduce lung cancer risk	1) Consider risk-reducing mastectomy
CDH1 mutation	1) Clinical breast examination every 6–12 months starting from age 20–25 [V] 2) Annual breast MRI from age 20–29 3) Annual breast MRI and/or mammogram at age 30–75 [V]	1) Consider risk-reducing mastectomy

MRI, magnetic resonance imaging; CT, computed tomography; PGD, pre-implantation genetic diagnosis; CNS, central nervous system; RRSO, risk-reducing salopingo-oophorectomy; EUS, endoscopic ultrasound.

GENETIC TESTS : History of test development

Developed by Myriad Genetic Laboratories in 1999

↓

Patent protected predominant genetic test for BRCA1 and 2 till 2013

↓

In 2013: US supreme court ruled that genes were naturally occurring and cannot be patented

↓

University based gene mutation panel
Other private laboratories:
Ambry genetics
Gene Dx

Test Limitations

- **Sequences that can be read only in the forward or reverse direction.**
- **Less frequent polymorphisms.**
- **Inversions or regulatory mutations, and insertions without duplication will not be detected.**
- **Turn around time 1- several weeks**

MyriadGeneticLaboratories.Testing Options. My support 360. https://mysupport360.com /genetic-testing/genetic-testing-process/

Centogene

- A worldwide leader in the field of genetic diagnostics for rare hereditary diseases

- Cento MD (Mutation Database)

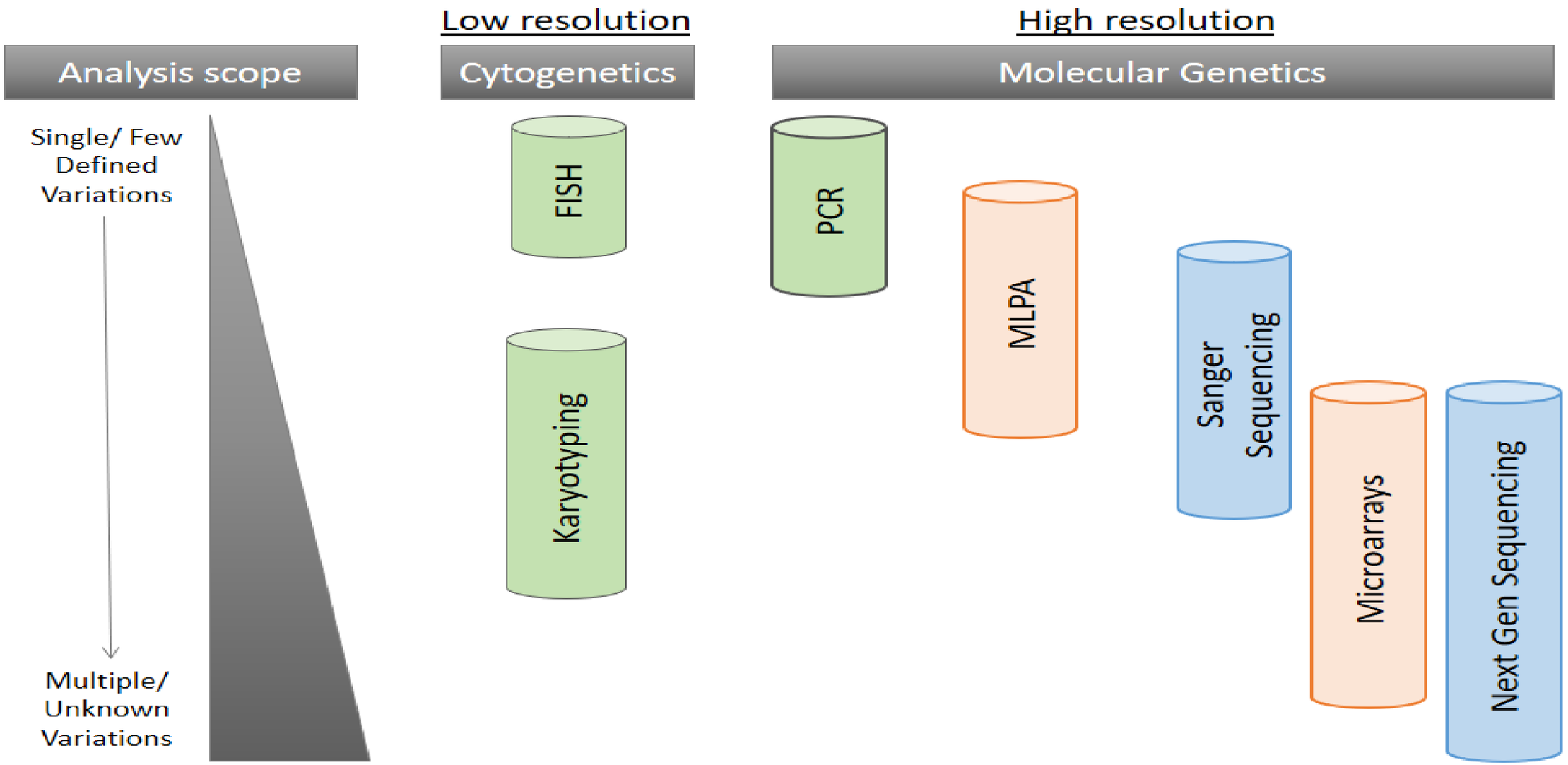
  - Bridges the gap between genetic variants and clinical interpretation
  - Follows American College of Medical Genetics and Genomics (ACMG) guidelines for variant classification
  - Access to more than 5.2 million variants , based on clinically diagnosed individuals worldwide.
  - Significant number (58%) of unpublished relevant variants from a worldwide cohort of patients.

Centogene

- **CentoCard** ®
  - A unique **CE-labeled filter card** product for sample collection
  - Samples collected on CentoCard ® are easy to handle
    - Dried samples are stable, can be mailed in regular post
    - Collected samples are not sensitive to temperature over time and not considered as biohazard
  - Reusable for future analysis
  - Barcode labeled filter cards, ensure accurate tracking and easy monitoring through CentoPortal.

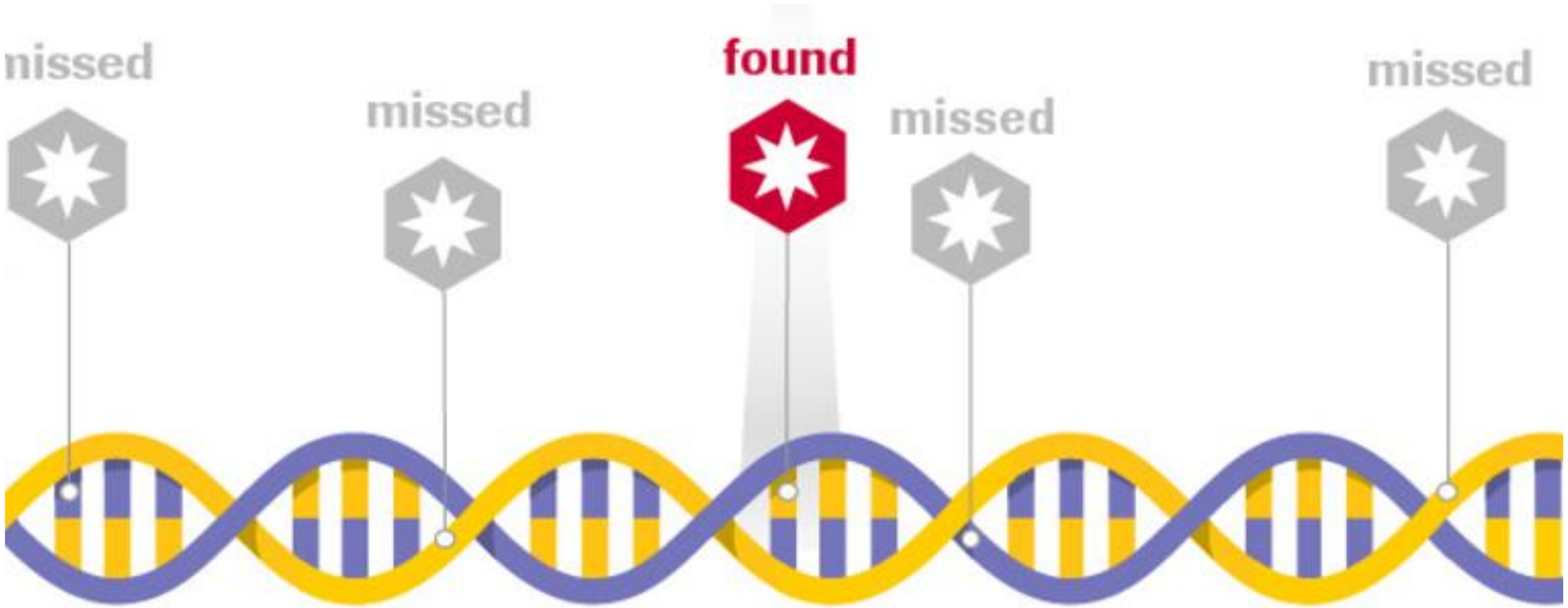
- Genetic counselling services.

Genetic Diagnostics



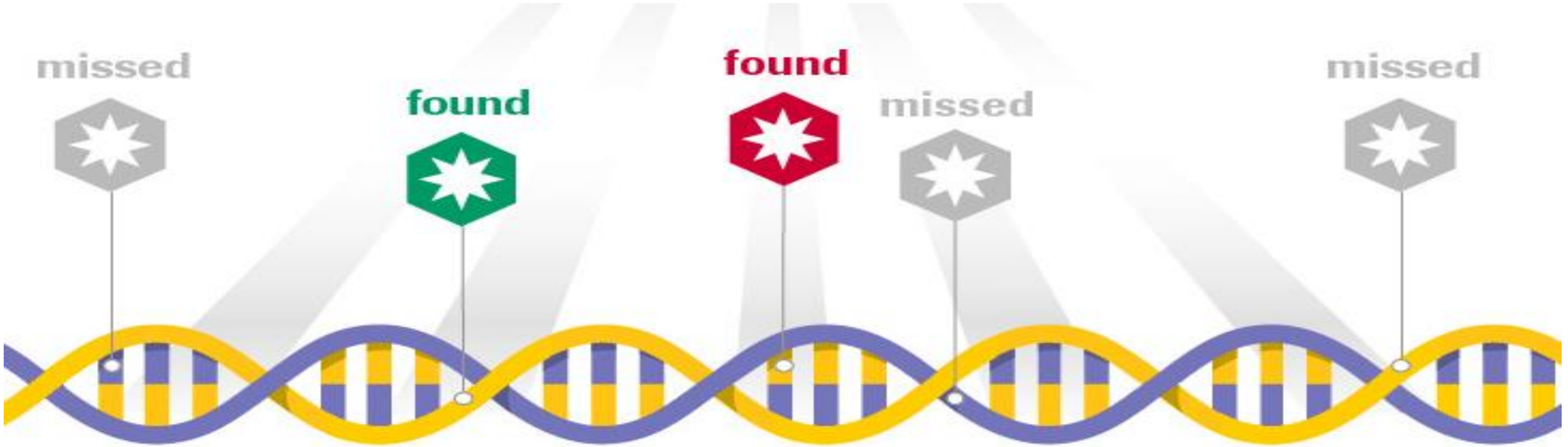
Single-marker molecular test

- Identifies only one gene (E.g., GATA2 in MDS)
- Other genes causing the same disease will not be identified



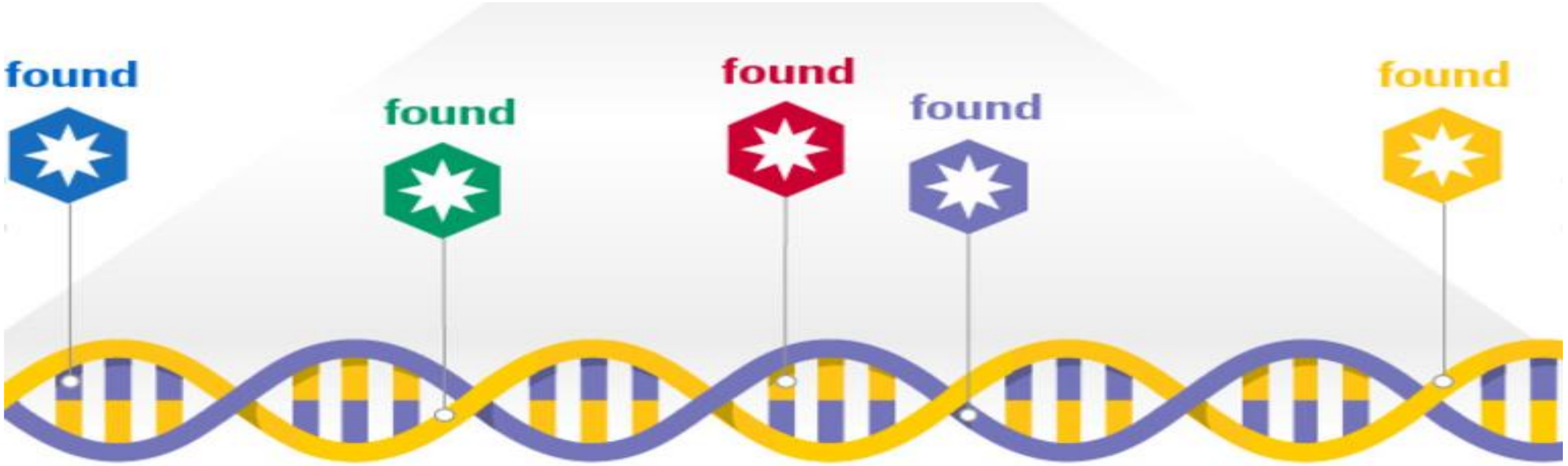
“Hot-spot”

- Multi-gene assay
- Includes the most commonly occurring mutations
  (E.g., TET2, Tp53, RUNX1, ASXL1 for MDS)
- Will miss the less commonly pathogenic mutation analysis



Comprehensive Gene Profiling

- Whole Genome / Exome
- Most of the pathogenic genetic alterations are identified

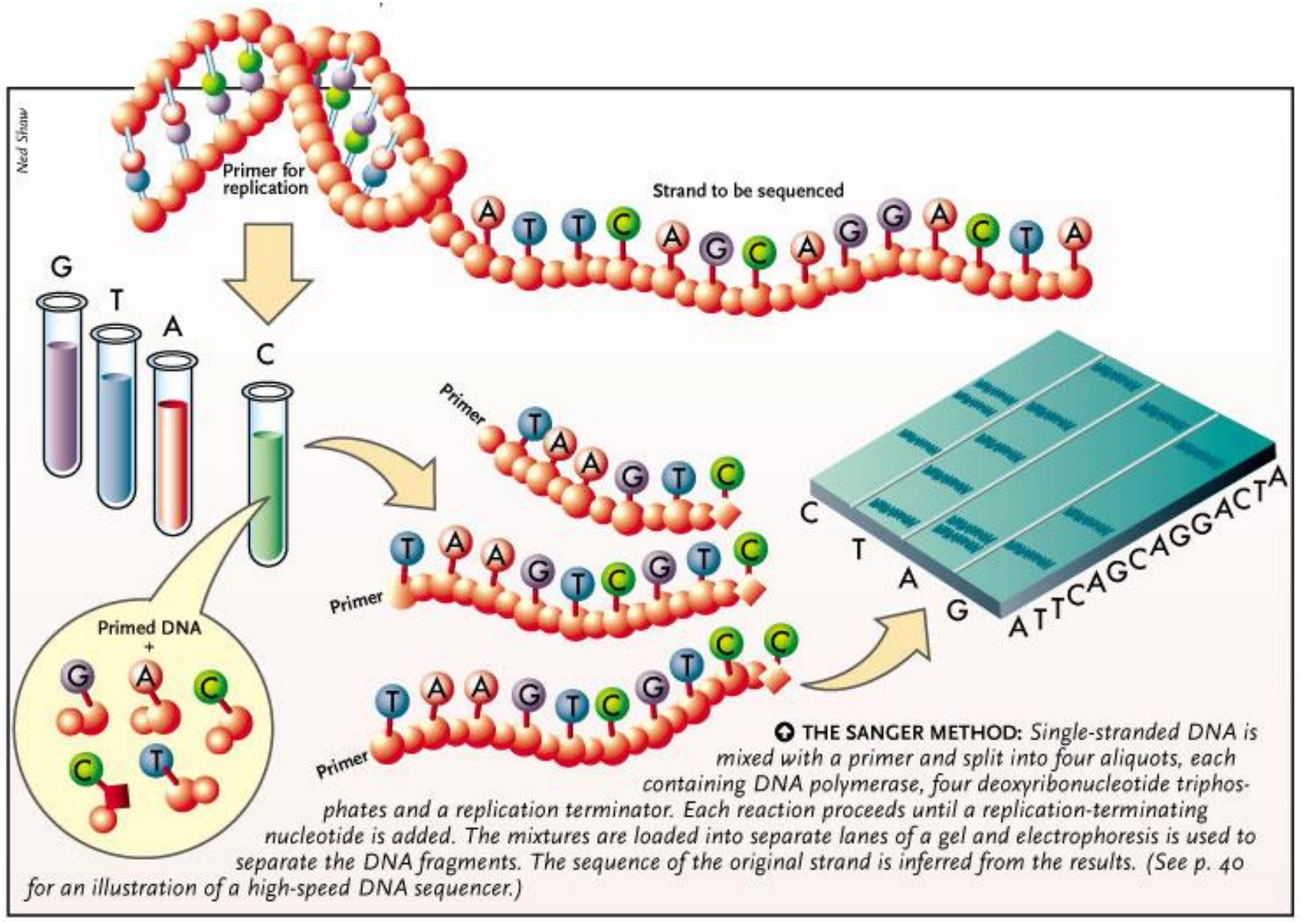


Sanger Sequencing

- Gold Standard sequencing method

- The Sanger method has **separate steps** for
  - Sequencing,
  - Separation (by electrophoresis) and
  - Detection

- **Disadvantages**
  - Difficult to automate the sample preparation
  - Limited in throughput, scalability and resolution



Next Generation Sequencing (NGS)

- Also known as high-throughput sequencing
- Enables a broad range of applications:
  - Sequence DNA and RNA much more **quickly** and **cheaply**
  - Rapidly sequence whole genome / Exome
  - Zoom in to **deeply sequence target regions (increased read depth)**
  - Helps in identifying **rare hereditary and somatic variants**

Next Generation Sequencing (NGS) uses massive parallel sequencing to generate the DNA (or RNA) sequences of many genes simultaneously

cgagatttcac
tagtagcccg
cggagatcgagcc
acgggatcgaata

List of identified gene variants

Interpretation

(likely) pathogenic gene variants, sometimes also unclear variants (VUS)

With new knowledge and new classifying software:
updated interpretation
and possibly new diagnosis

Interpretation

List of identified

gene variants

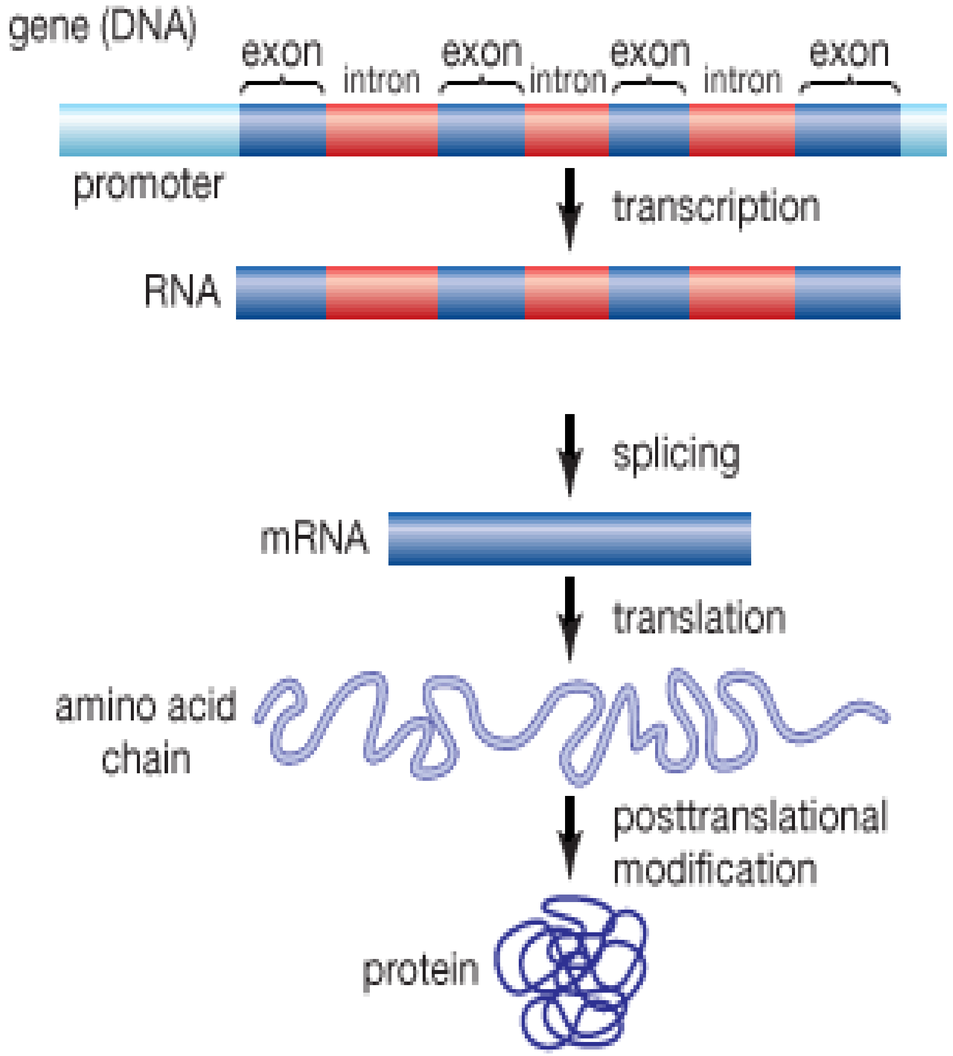
Exons

- Genes are made up of alternating regions of
  - Introns (noncoding sequences) and
  - **Exons (coding sequences)**

- There are ~21,000 exons in human genome

- Exons constitute ~1-2% of the genome

- Mutations in genes in about **6,800 exons** are known to cause various diseases.

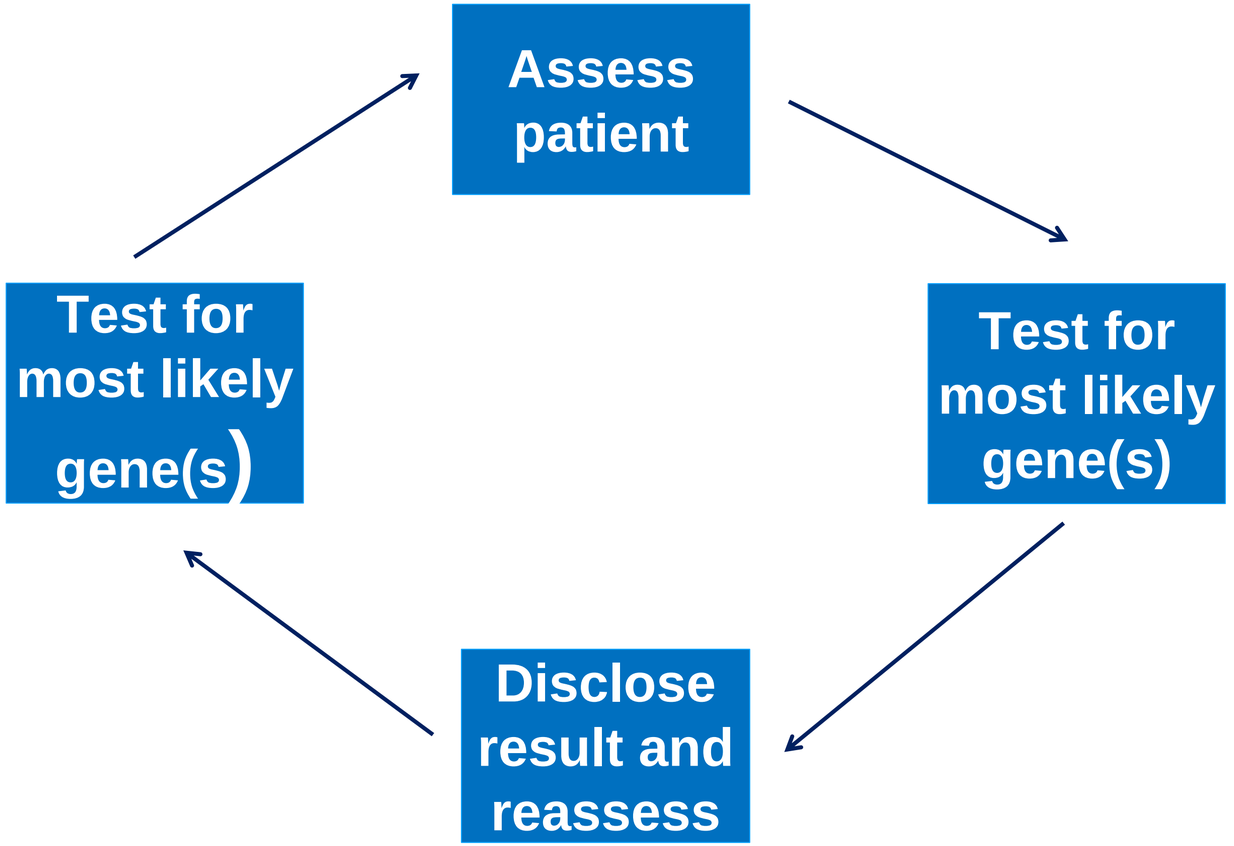


Advantages of Clinical Exome Sequencing (CES) versus Whole Genome Sequencing (WGS)

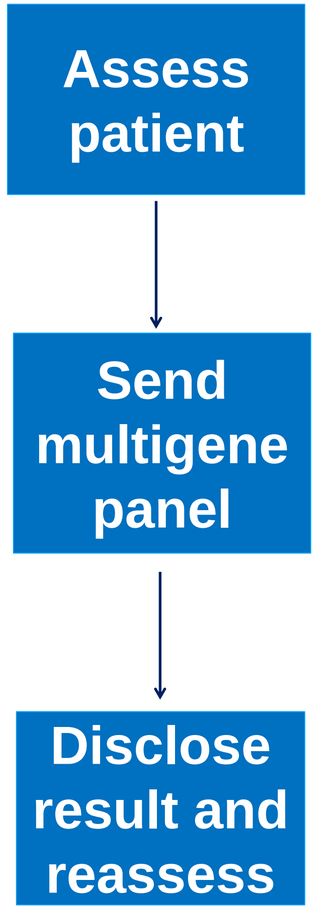
- Whole Genome Sequencing (WGS) analyses introns (non coding regions) & Exons (Coding regions) of the gene
  - Large data after NGS
  - Costlier than Exome sequencing
  - May confuse interpretation.

- Clinical Exome Sequencing(CES) analyses only the coding regions
  - Simplified interpretation versus whole genome sequencing
  - Cheaper and faster than genome sequencing.

Revolution of genetic testing



New approach?



Why do Multigene testing ?

- **More cost effective** (for the testing) to do multigene rather than serial testing
- **Patients (and providers!) can get testing fatigue**
- **The same cancer can be seen with different genes mutations**
  - Ovarian cancer in both *BRCA1/2* and Lynch
  - Uterine cancer in Lynch and Cowden
  - Breast in Li-Fraumeni and *BRCA1/2*
- **Isn’t more better?**

Risk reducing strategies for BRCA mutation but without a diagnosis of breast cancer

- Increased surveillance
- Chemoprevention (eg, tamoxifen citrate, raloxifene hydrochloride)
- Surgical intervention (ie, bilateral mastectomy, bilateral salpingo-oophorectomy)
- If hereditary breast cancer syndrome: screening of family members with indicated risk factors.

Women with breast cancer DX and +ve BRCA mutation:
Survival benefits of surgical intervention+ chemotherapy is well documented

Moyer VA et al. US Preventive Task Force. Ann Intern Med. 2014;160(4):271-281

Grignol et al. J Am Coll Surg. 2016;222(5):906-914.

Prophylactic surgery: Recommendations

- Risk-reducing bilateral - salpingo-oophorectomy (RRSO) in BRCA mutation carriers.
  - BRCA1 mutation: To undergo RRSO by age 35-40 or once the completion of childbearing.
  - BRCA2 mutation: Can delay surgery until their 50s.
- Prophylactic Mastectomy
  Prophylactic mastectomy (PM) results in up to a 97% risk reduction of contralateral breast cancer (CBC).

Bayratkar S, Arun B. BRCA mutation genetic testing implications in the Unitedd States. The Breast. 2017;224-232

Risk Reducing Salpingo-Oophorectomy and the risk of breast cancer

	No Prior Breast Cancer		
	Total	**BRCA1**	**BRCA2**
Total Participants	1,370	869	501
HR (95% CI)	0.54 (0.37-0.79)	0.63 (0.41-0.96)	0.36 (0.16-0.82)

RRSO and the risk of ovarian cancer

	Breast cancer prior		
	Total	**BRCA1**	**BRCA2**
Total Participants	1060	684	376
HR (95% CI)	0.14 (0.04-0.59)	0.15 (0.04-0.63)	No cancer events

PROSE Consortium

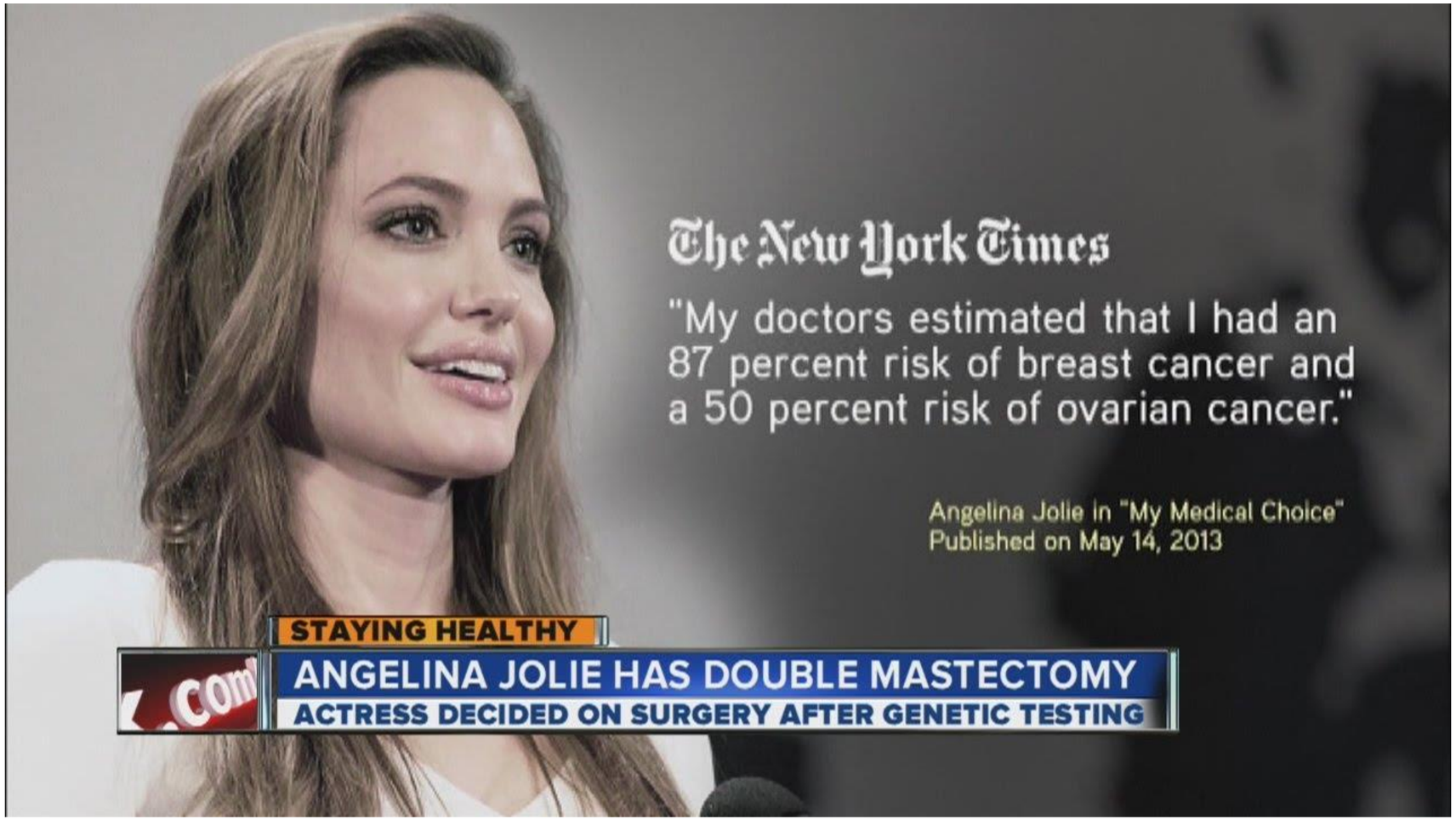
Domchek et al, *JAMA* 2010

RRSO and all-cause mortality

	All eligible women		
	All	**BRCA1**	**BRCA2**
Total Participants	2,482	1587	895
HR (95% CI)	0.40 (0.26-0.61)	0.38 (0.24-0.62)	0.52 (0.22-1.23)

Domchek et al, *JAMA* 2010

“Angelina Jolie effect”



Medications

- Tamoxifen.
  - Recommended as adjuvant in BRCA positive, ER+ breast cancers.
  - Reduces risk of contralateral breast cancer (CBC) by 40-70%.

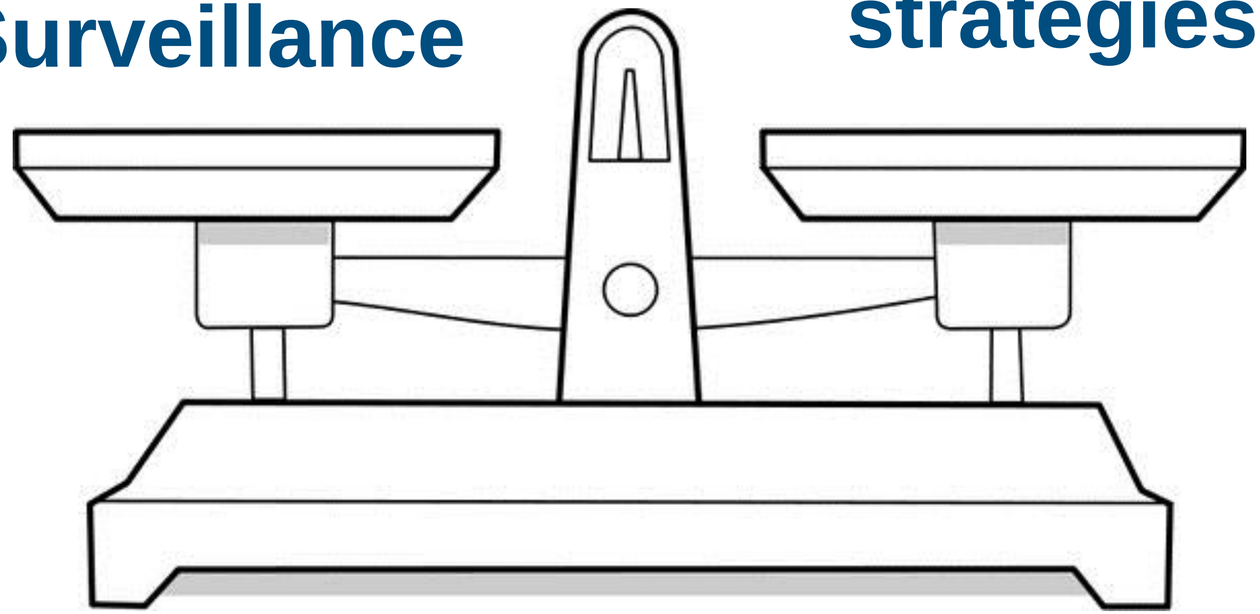
Bayratkar S, Arun B. BRCA mutation genetic testing implications in the Unitedd States. The Breast. 2017;224-232

Know the lifetime risk of breast cancer conferred by the mutation

Genetic counselling

Surveillance

Risk reduction strategies



Duties of a genetic counsellor

(1)Assesses personal and familial risk for disease.

(1)Explains the pros, cons, and limitations of genetic testing.

(1)Helps the patient understand the test results and make an informed decision

(1)Identifies potential strategies for risk reduction.

(2)Guides the patient through the emotional aspects of genetic testing, which have the potential to alter or even halt the diagnosis and treatment process .

Making the Best Decisions When You’re at High Risk for Breast or Ovarian Cancer. New York, NY: Prometheus Books; 2010.

Benefits of genetic counselling

- Decreased risk perception.
- Decreased intention for mutation testing among unlikely carriers.
- Decreased cancer-associated anxiety and depression

Genetic counselling and preventive strategies be carefully recommended to patients with less common mutations in the absence of strong consensus or official guidelines

Economopoulou et al. Cancer Treat Rev. 2015;41(1):1-8.

Conclusions

- Genetic testing can be very useful to patients and their family members
  - Both the prevent and to treat cancer.
- Genetic testing is continuously evolving.
- BRCA1 and BRCA2 mutations are the most commonly found and we have reasonable data on how to manage.
- New genetics tests are often less clear in terms of how to change patients care – and improve patient outcome.
- Variants of unknown significance should NOT be managed as mutations
- In the face of rising prophylactic mastectomies, we need to emphasize to patients how mutations in these genes are different from those in *BRCA1/2.*

Thank you!!!!