Genetic Counselling in Breast Cancer

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CANCER RESEARCH INSTITUTE

CANCER ECHO UM 25 Feb 2021

Outline

- Cancer genetics principles
- Mainstreaming vs conventional genetic testing
- Testing criteria and risk models
- Guiding principles to tests – types of tests (direct to consumer tests)
- Interpreting results and post test counselling
- Cascade or predictive testing
- Risk Management

Clinical Application

In oncology, the two dominant applications are:

1) the assessment of **somatic** alterations in tumors to **inform prognosis** and/or **targeted therapeutics**;

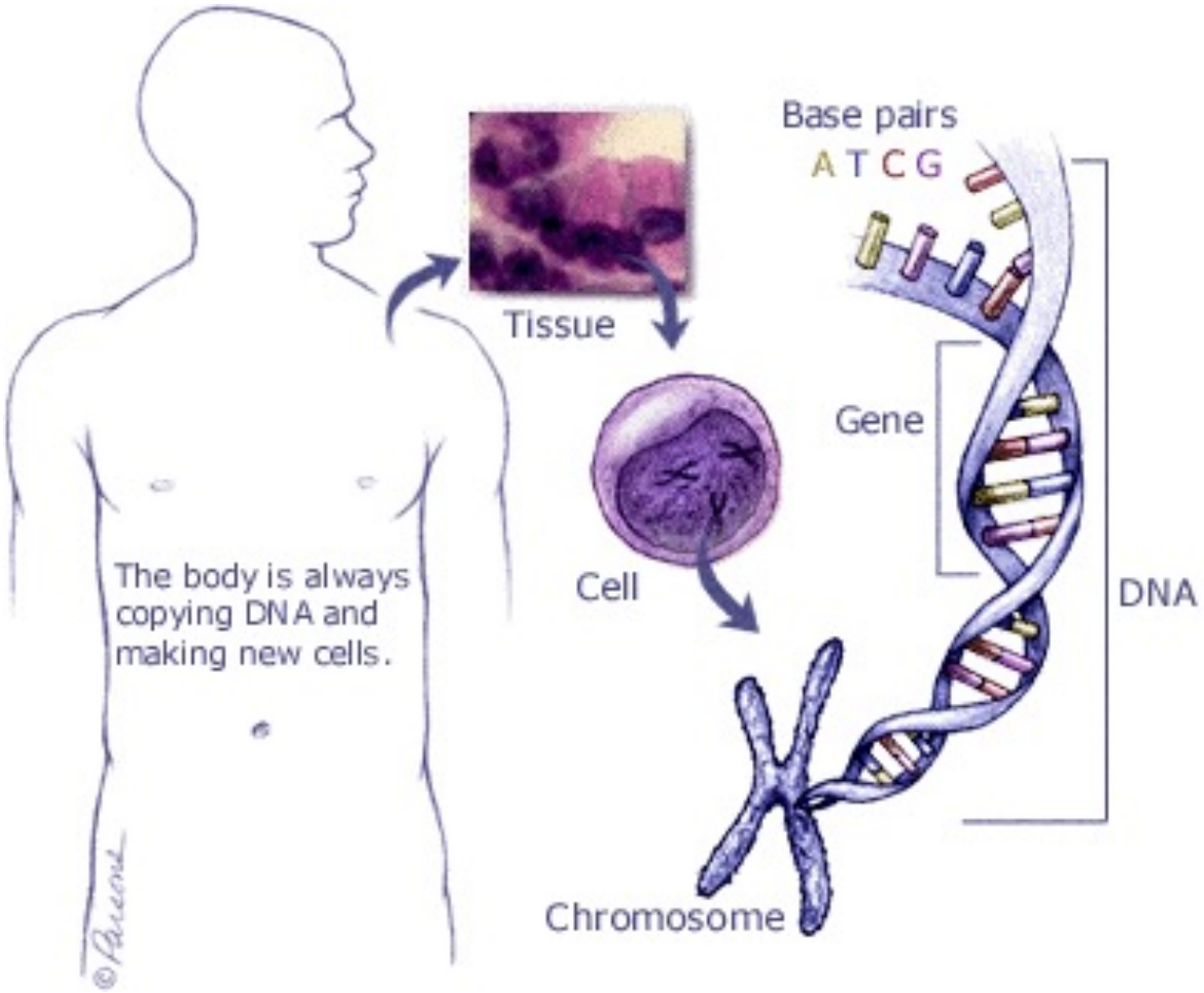
2) the assessment of the **germline** to identify **cancer risk, targeted therapeutics and treatments**

Cancer Genetics Principles

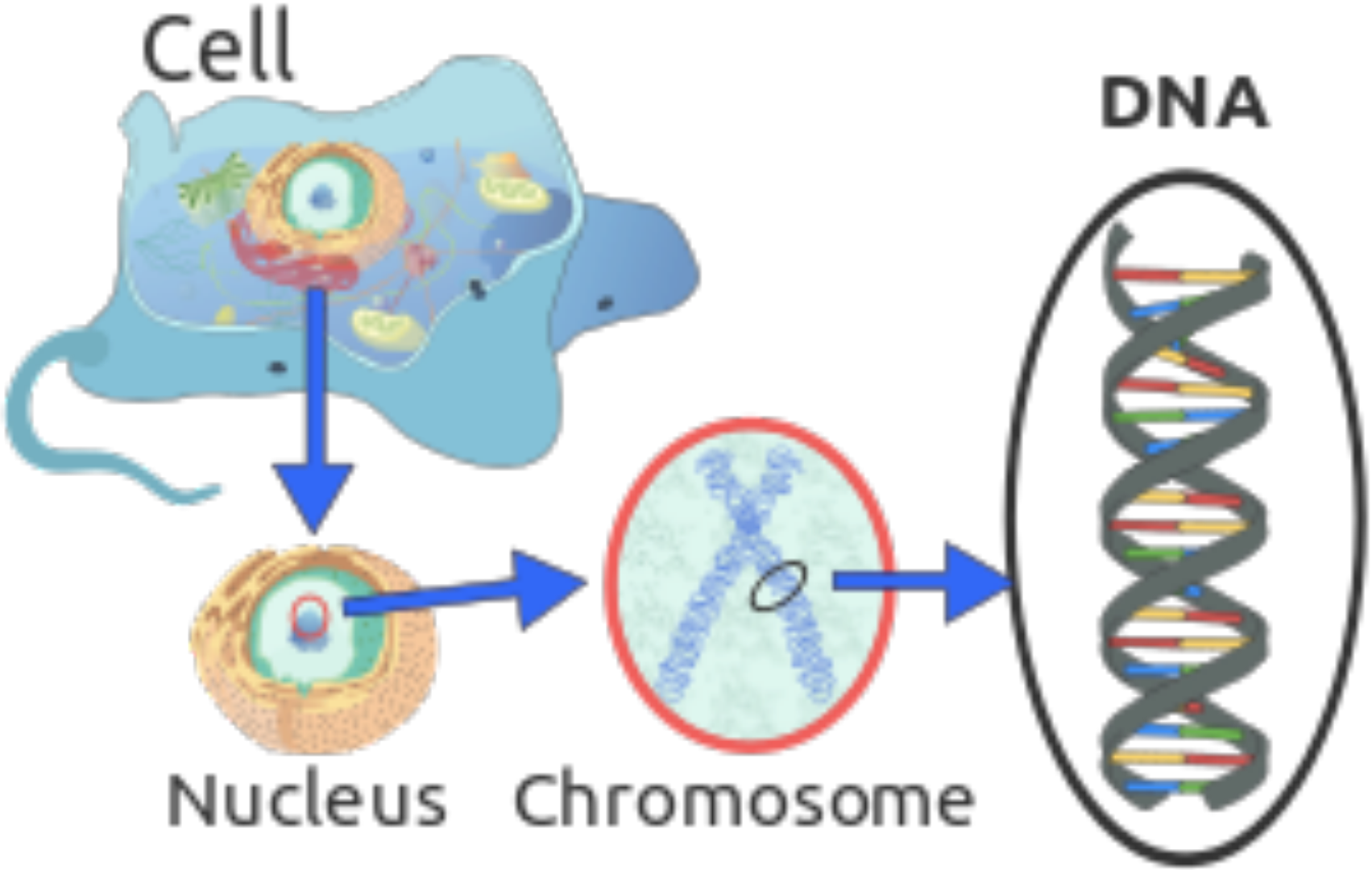
- What are genes
- Wildtype vs mutants
- Somatic vs Germline mutation
- Oncogenes and tumour suppressor genes
- Application in cancer

- Homologous Recombinant Deficiency (HRD)
- Traditional vs Mainstreaming of Genetic testing

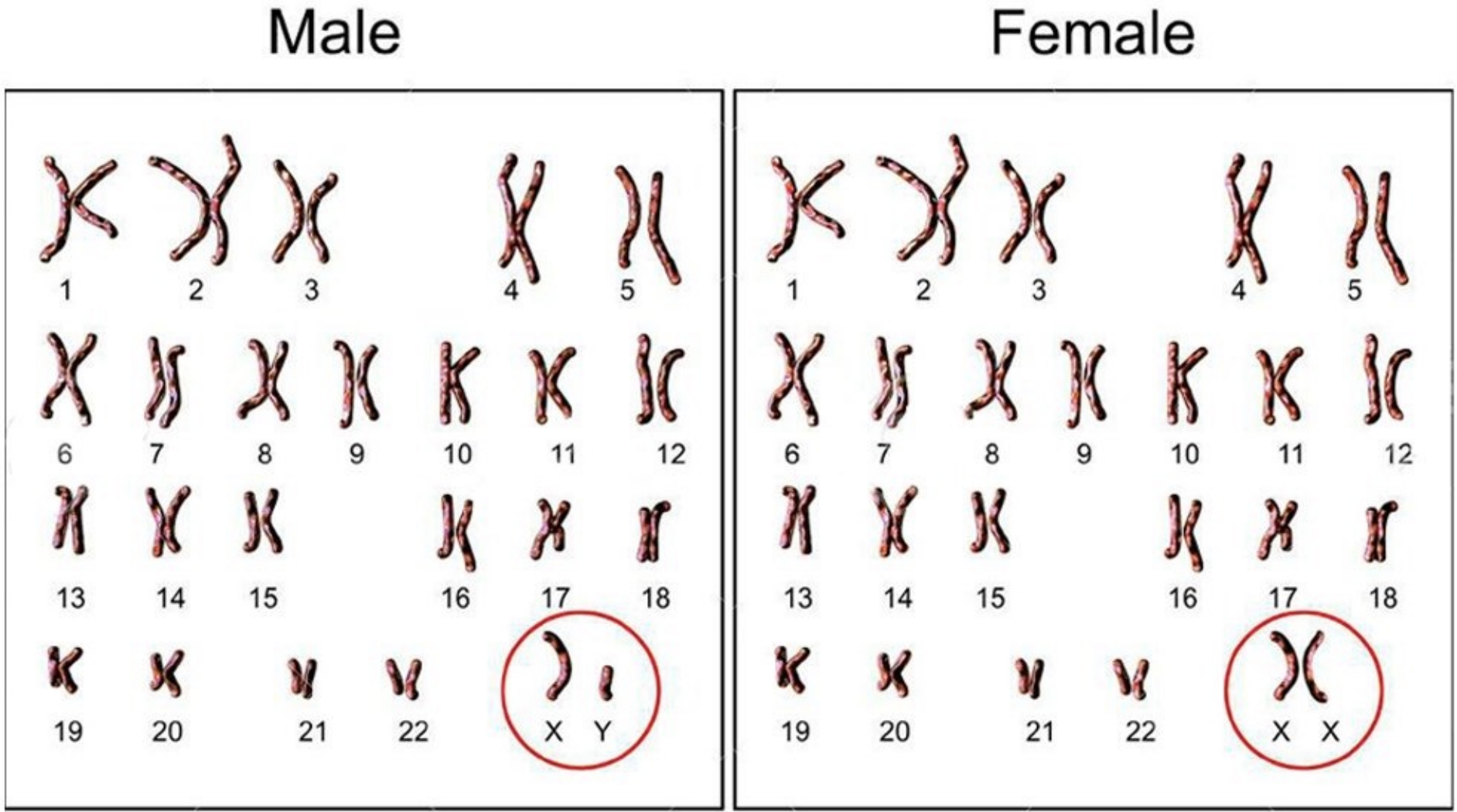
Genes in perspective

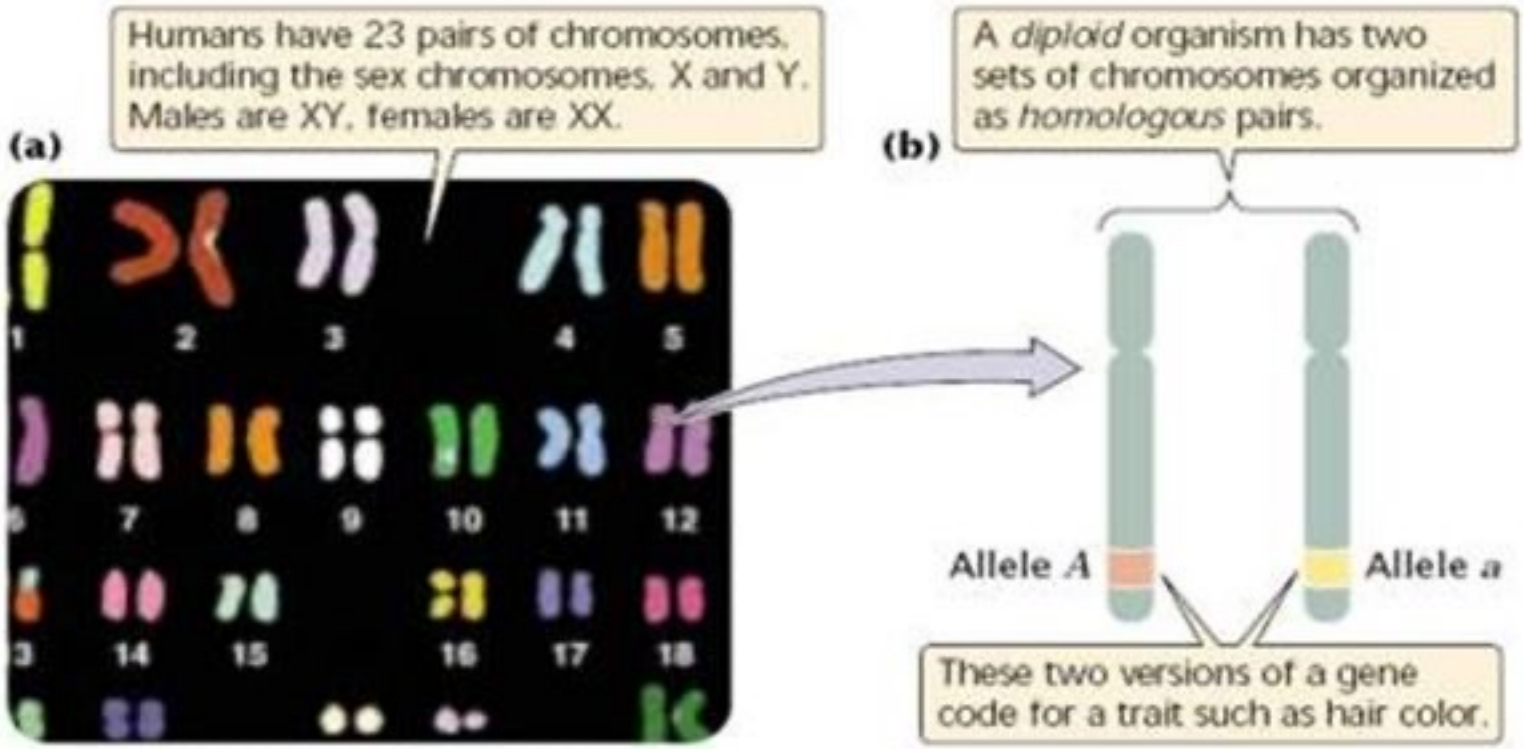


http://pathology.jhu.edu/pc/BasicCauses.php?area=ba

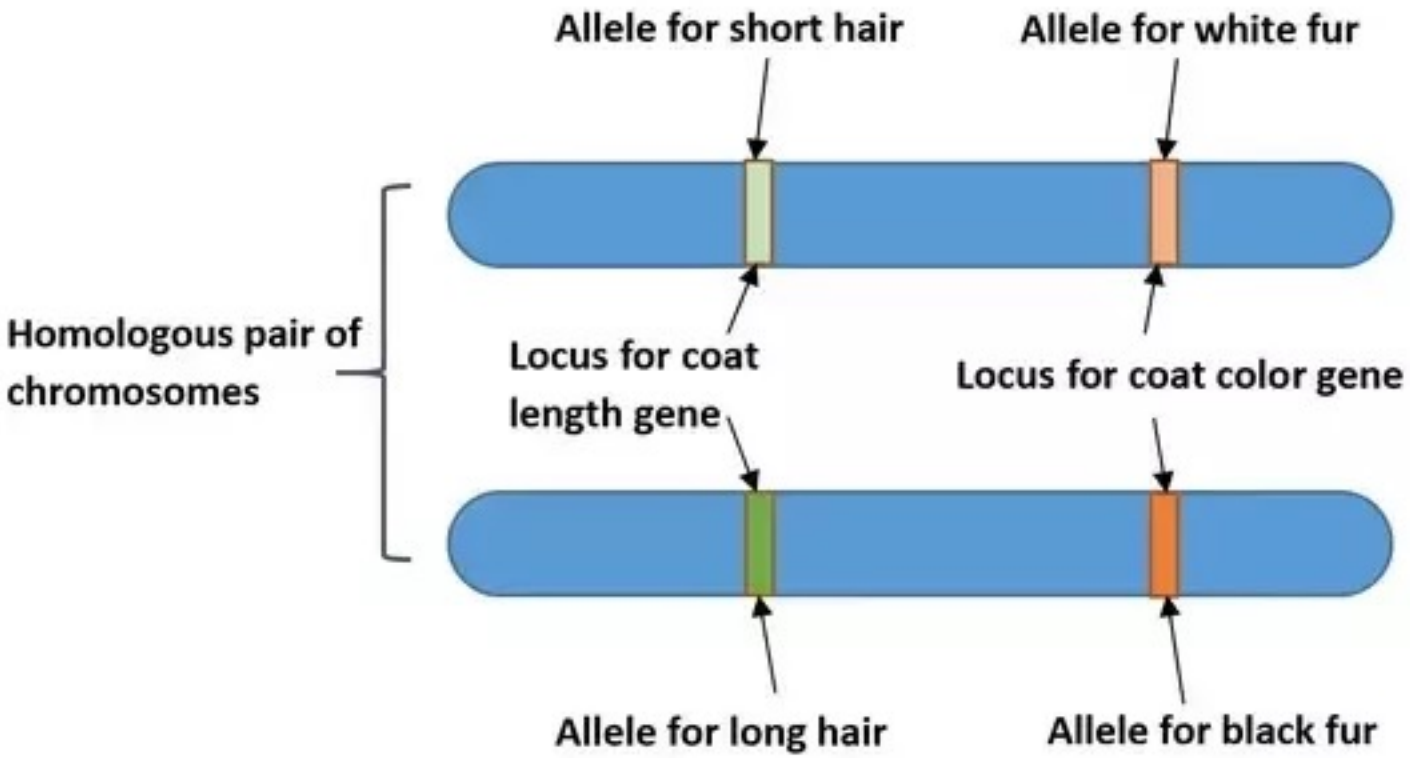

Cell
DNA
Nucleus
Chromosome

Karyotype (23 pairs of chromosomes)



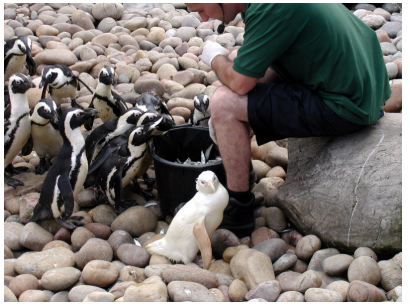

Humans have 23 pairs of chromosomes, including the sex chromosomes, X and Y. Males are XY, females are XX.
(a)
1
2
3
4
5
7
8
9
10
11
12
14
15
16
17
18
(b)
A *diploid* organism has two sets of chromosomes organized as *homologous* pairs.
Allele *A*
Allele *a*
These two versions of a gene code for a trait such as hair color.

Definitely not human



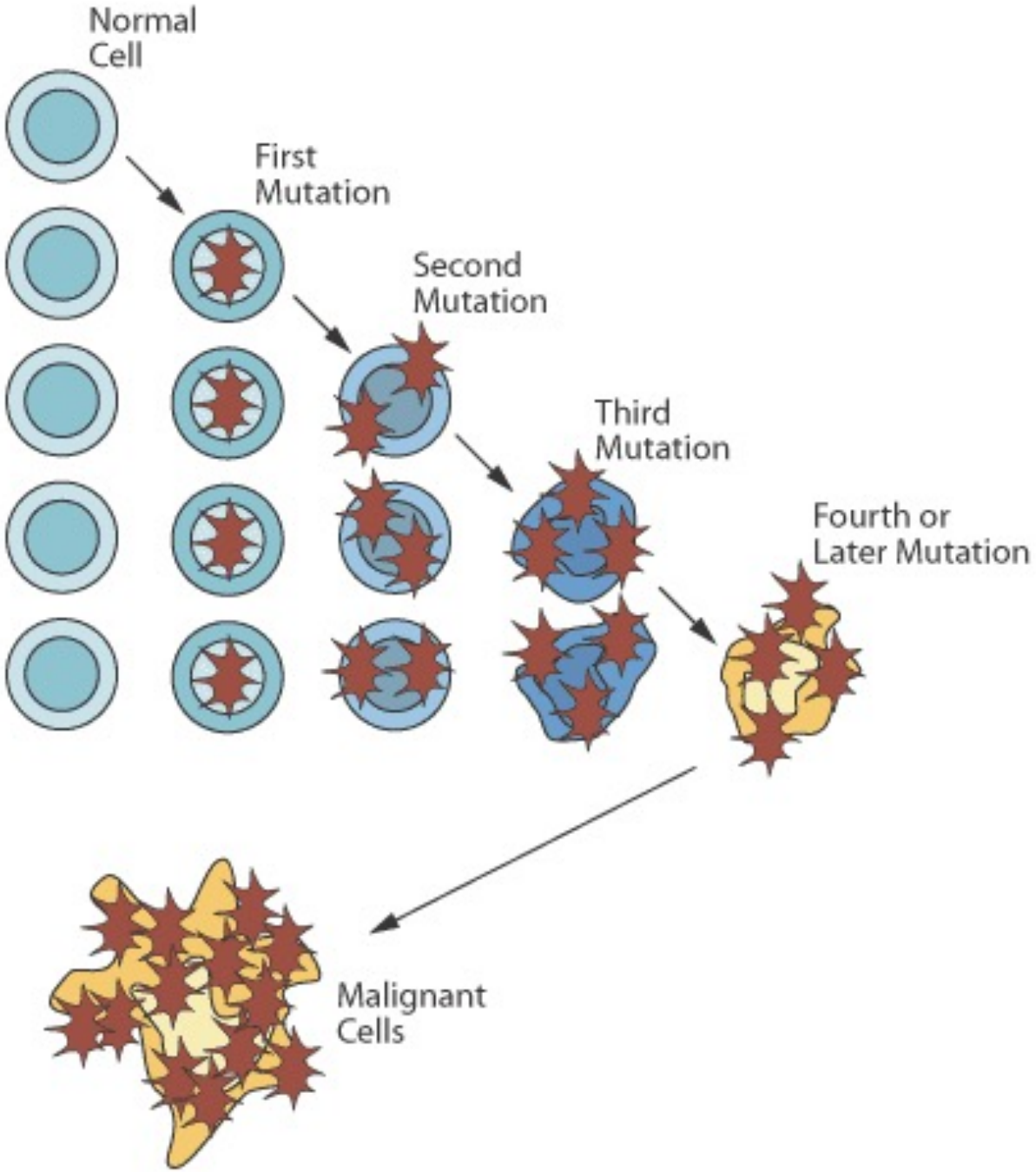
Wild type

- The **allele that encodes** the **phenotype most common in a particular natural population** is known as the **wild type** allele. It is often designated, in genetic shorthand, as **"+"**.
- Any form of that allele other than the wild type is known as a **mutant** form of that allele.
- Wild type penguins wear tuxedos. Albino mutants look white.



http://www.bio.miami.edu/dana/dox/wildtype.html#:~:text=The%20allele%20that%20encodes%20the,mutant%20form%20of%20that%20allele.&text=Wild%20type%20tigers%20have%20orange%20fur%20and%20black%20stripes.

Cancer is a Genetic Disease



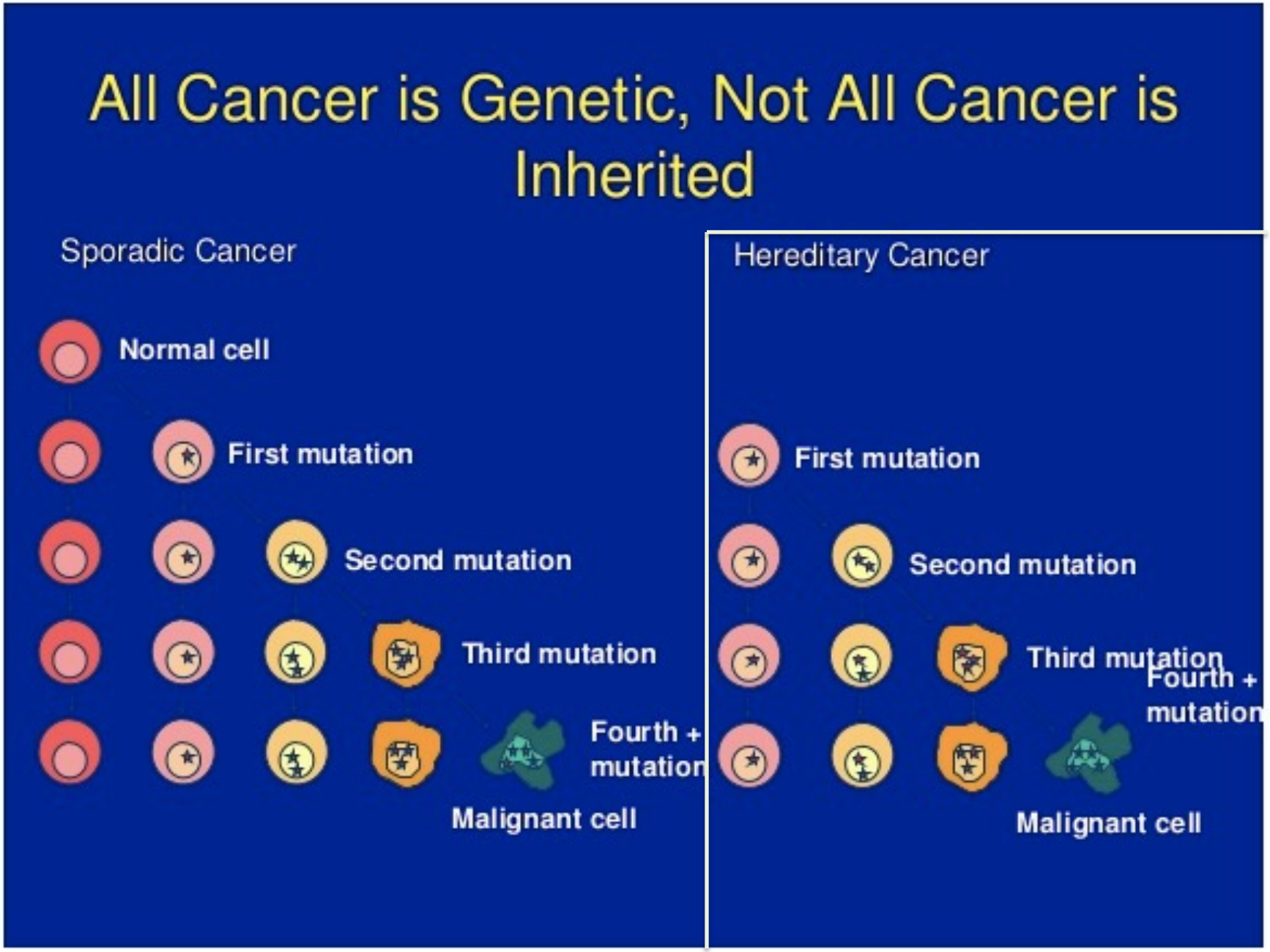
Two- Hit Theory of Cancer Causation

Normal cells typically have two undamaged chromosomes; one inherited from our mother and the other from our father. Each chromosome contains thousands of genes some of which are responsible for controlling cancer.

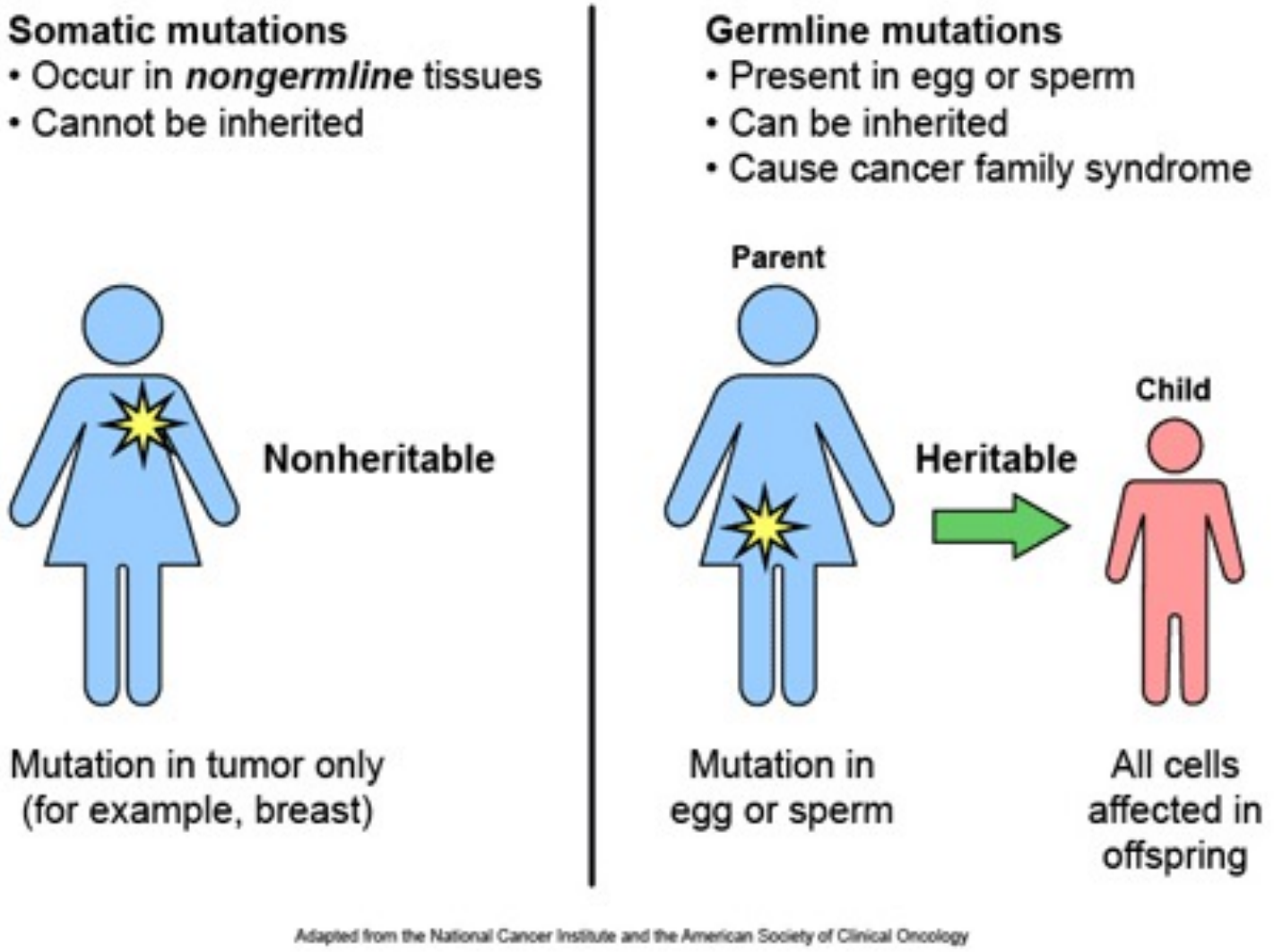
NON-HEREDITARY CANCER *By Chance – Most Common*

HEREDITARY CANCER *Passed Through Family – Rare*

All Cancer is Genetic, Not All Cancer is Inherited

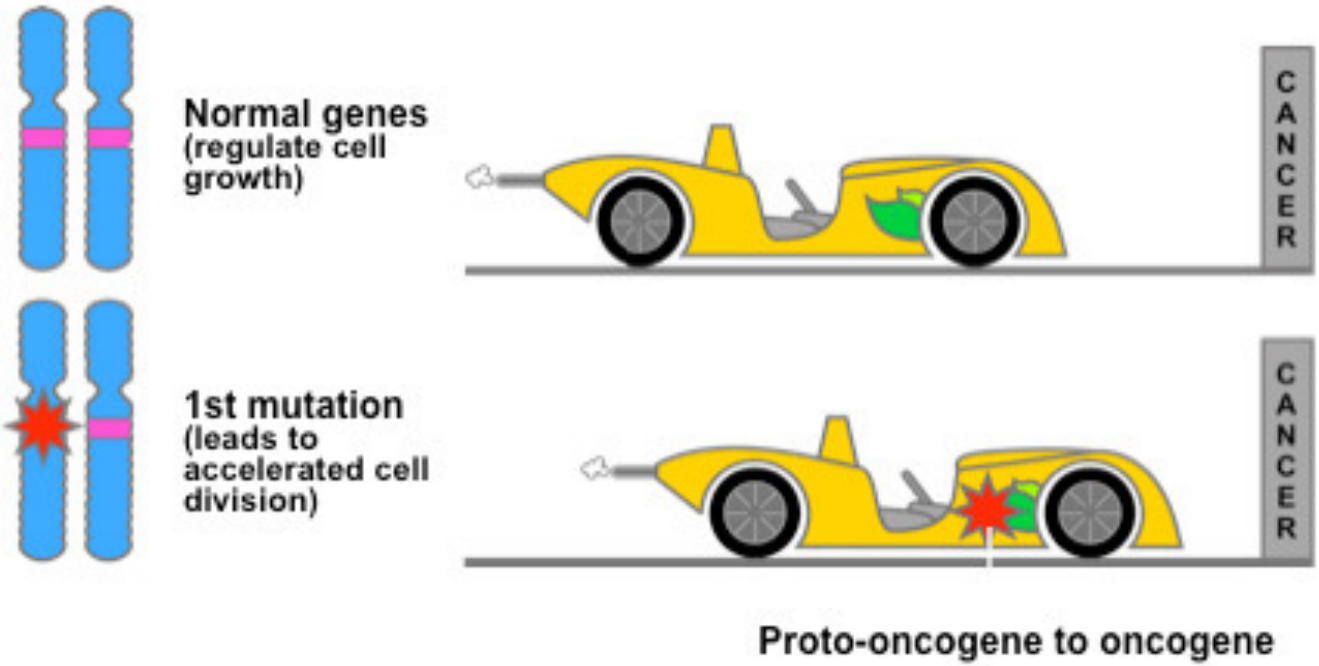


Somatic vs Germline Mutation



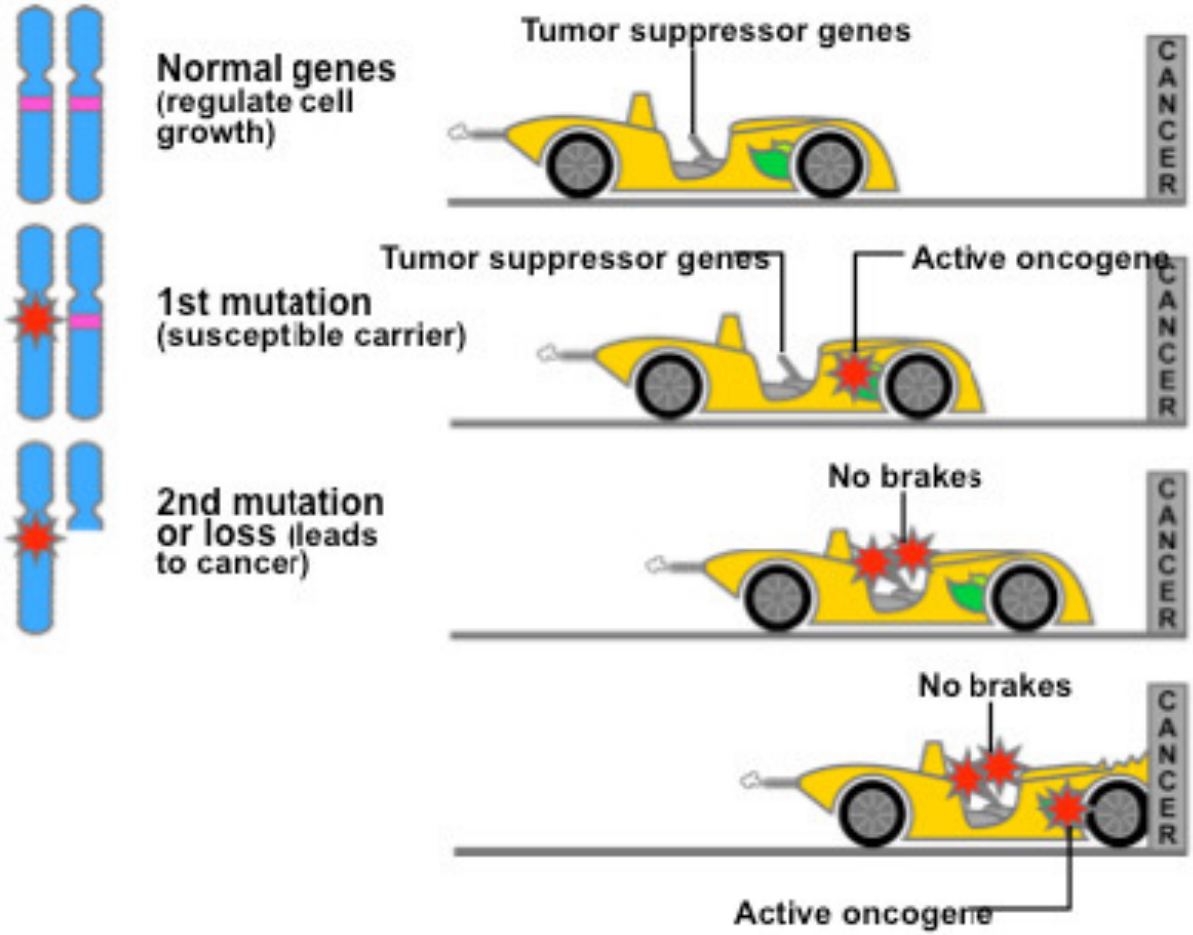
http://www.stjude.org/stjude/v/index.jsp?vgnextoid=5817b5b36e70c210VgnVCM1000001e0215acRCRD

Proto-oncogene to Oncogene



Proto-oncogene to oncogene

Tumour suppressor gene



https://cisncancer.org/research/what_we_know/advances/oncogenes.html

Oncogenes and Tumour suppressor genes

Oncogenes

- **Turn on**
- Aka Proto-oncogene
- Chromosome rearrangements (Philadelphia chrom in CML)
- Gene duplication
- **Acquired**

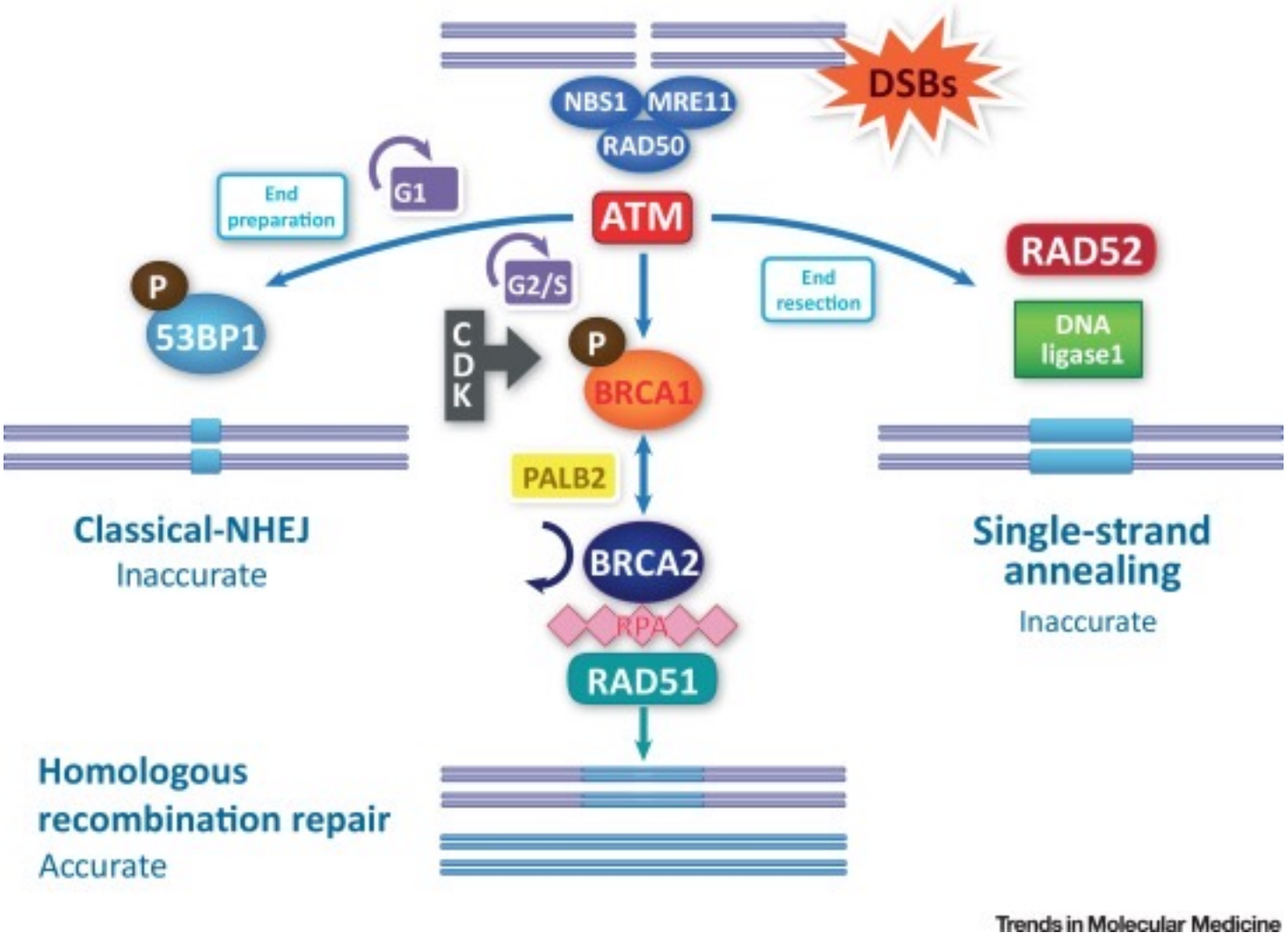
Tumour suppressor genes

- **Turn off**
- Slow down cell division
- **Repair DNA mistakes, (eg HRR genes)**
- Tell cells when to die (*apoptosis* or *programmed cell death*).
- **Inherited eg BRCA1/2, p53**
- **Acquired eg p53**

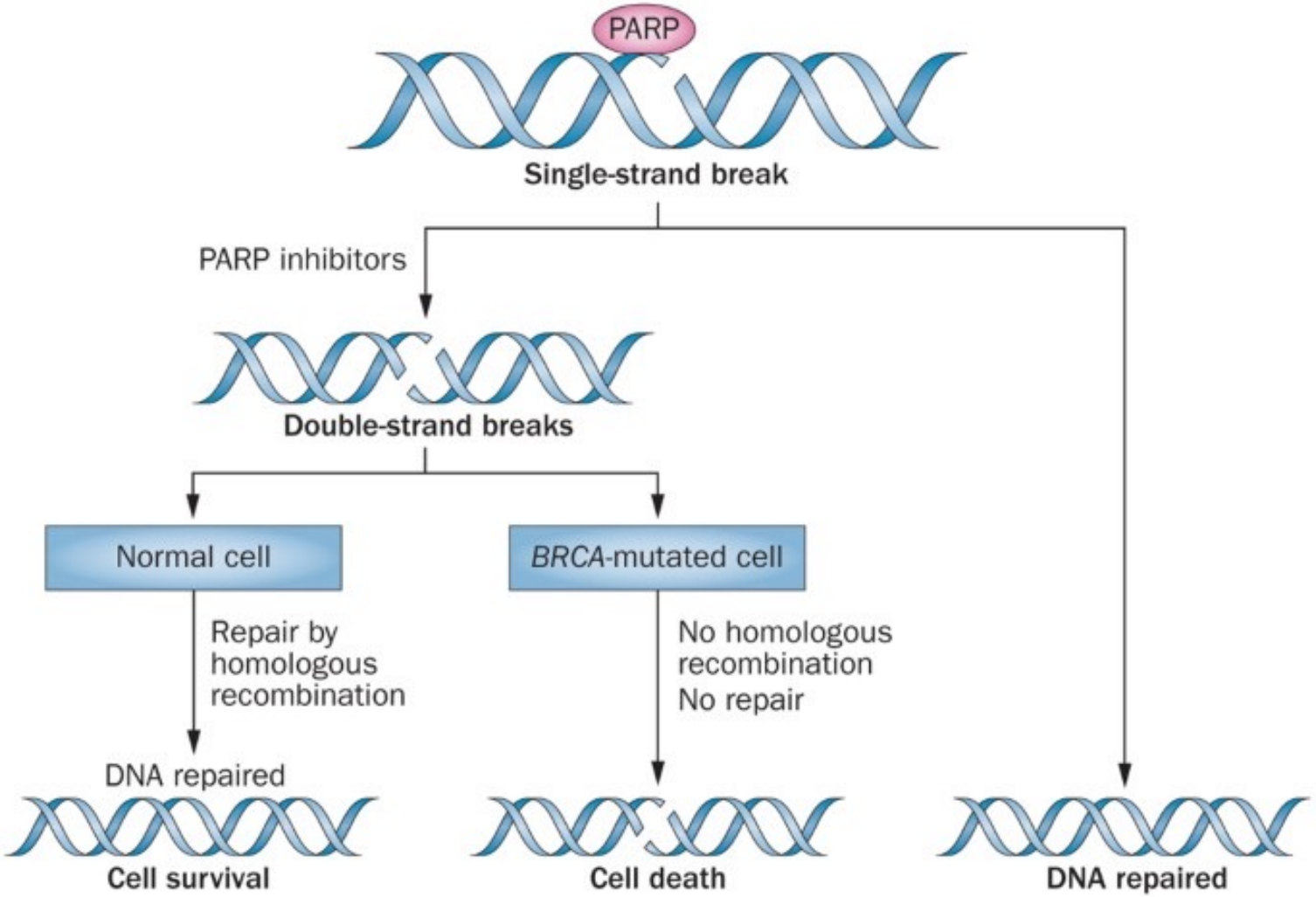
Homologous Recombinant Repair

- HRR is a DNA repair pathway of clinical interest due to the sensitivity of HRR deficient cells to **poly(ADP-ribose) polymerase (PARP) inhibitors**, and **platinum-containing chemotherapy**.

Homologous Recombination Repair



poly ADP ribose polymerase (**PARP**)

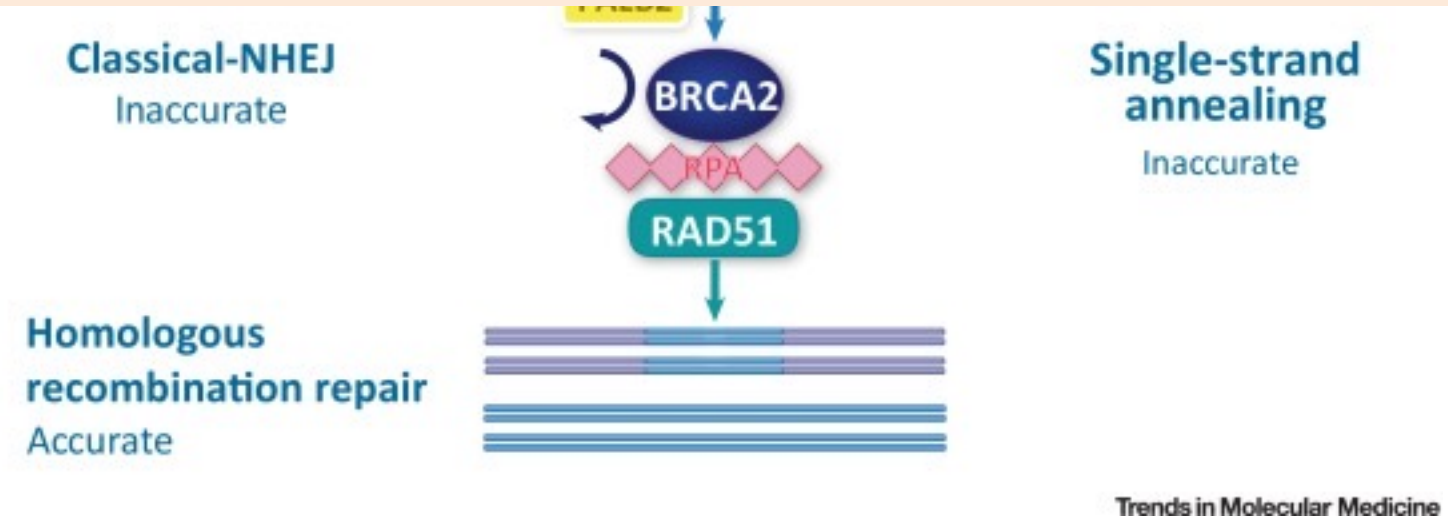


Homologous recombinant repair deficiency (HRD)

- Assays measuring **homologous recombination deficiency (HRD)** caused by a broader range of mechanisms than *BRCA1/2* loss.
- Tests identify **somatic mutations** in *BRCA1/2* and other **HRR-related genes** and detect the presence of **genomic scars** indicative of HRD.

Homologous Recombination Repair

- Genes that are directly or indirectly implicated in HRR include :
- ***BRCA1*, *BRCA2*, *CHEK2*, *ATM*, *PALB2*, *FANCA*, and *RAD51D,*** among others.



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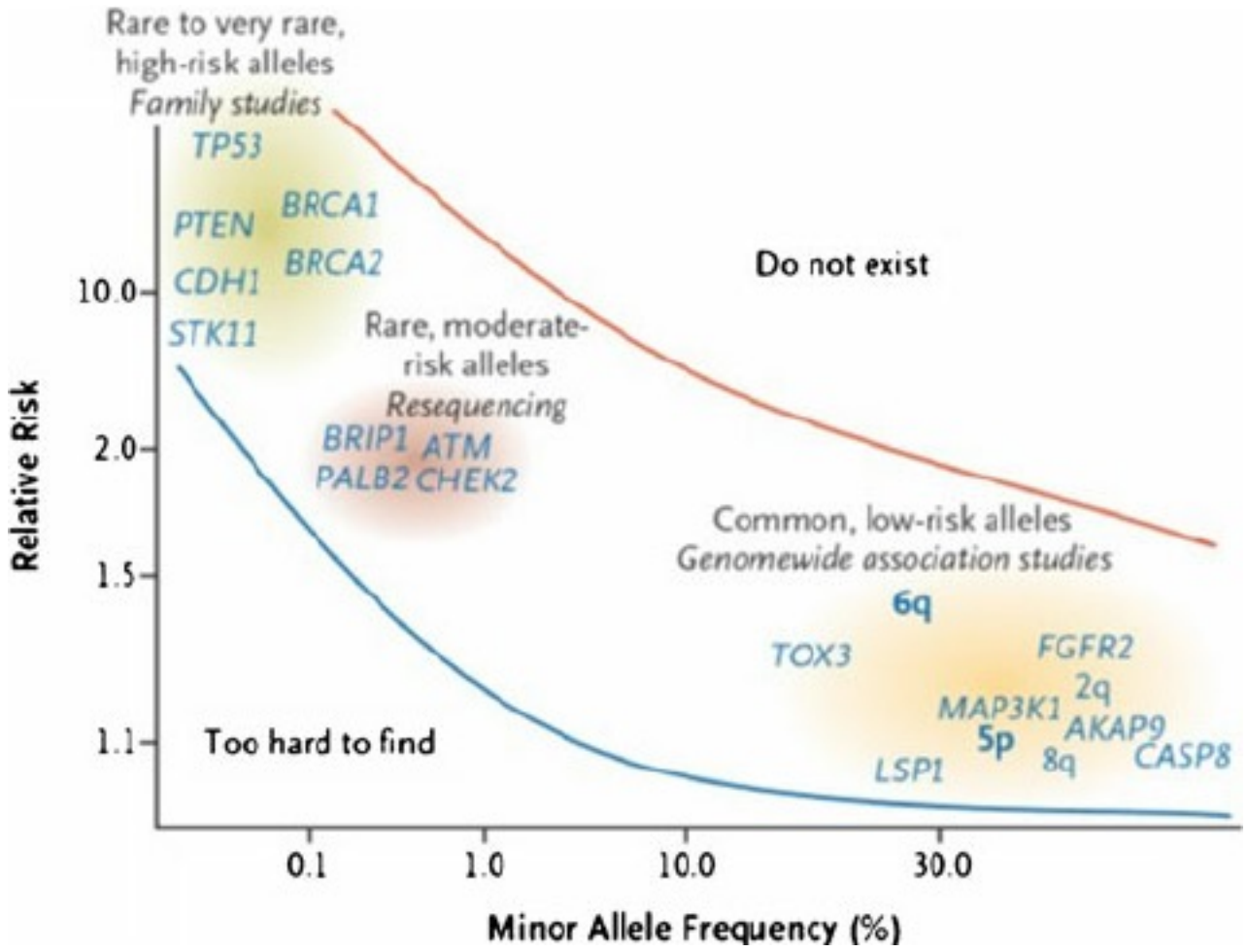
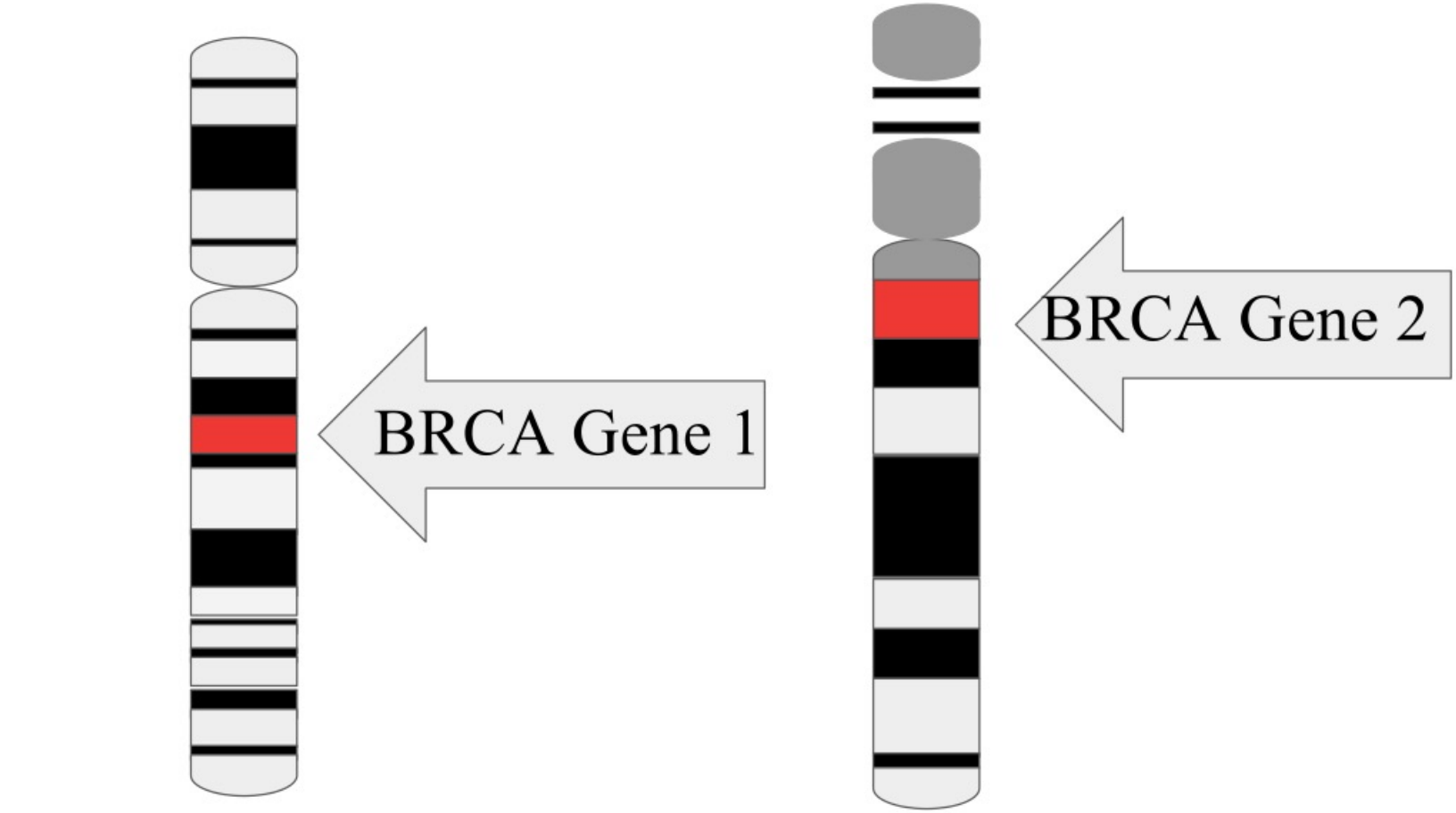
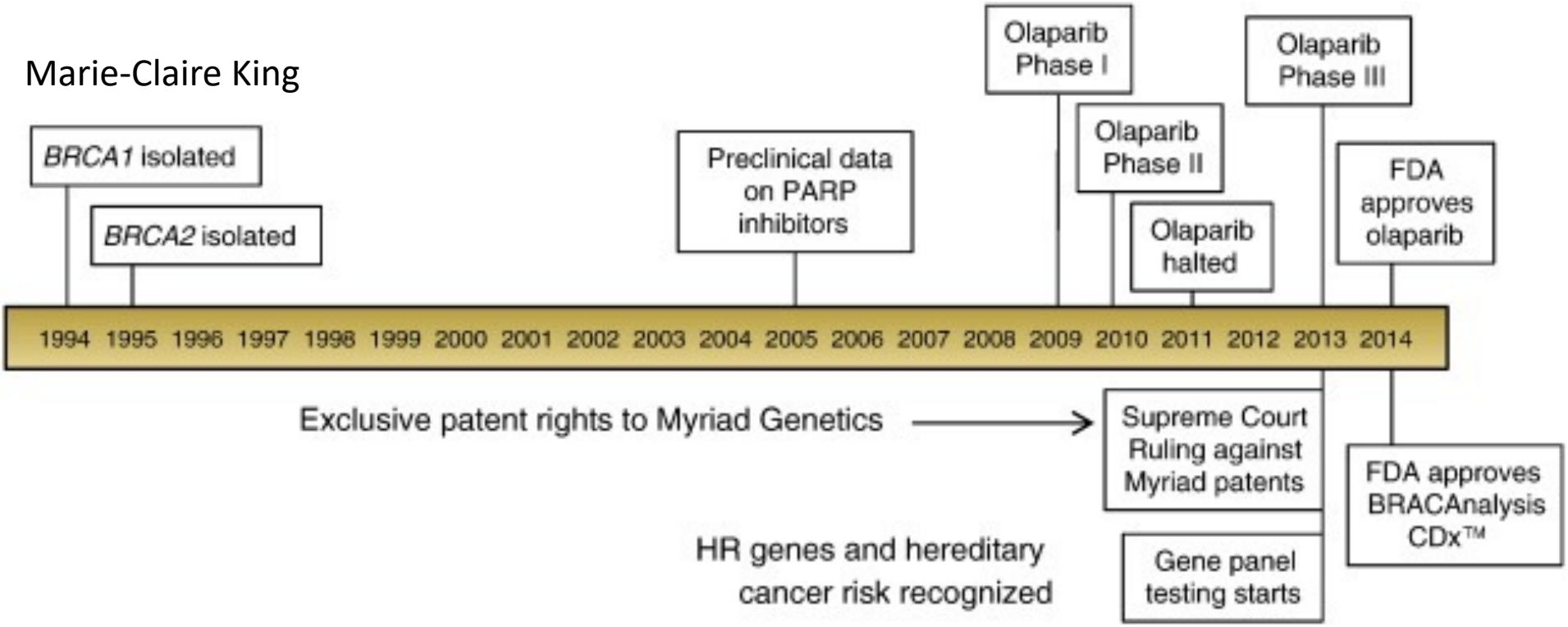

Rare to very rare, high-risk alleles
Family studies
TP53
PTEN
BRCA1
BRCA2
CDH1
STK11
Do not exist
Rare, moderate-risk alleles
Resequencing
BRIP1
ATM
PALB2
CHEK2
Common, low-risk alleles
Genomewide association studies
6q
TOX3
FGFR2
2q
MAP3K1
AKAP9
5p
8q
CASP8
LSP1
Too hard to find
Relative Risk
10.0
2.0
1.5
1.1
0.1
1.0
10.0
30.0
Minor Allele Frequency (%)


BRCA Gene 1
BRCA Gene 2
Chromosome 17
Chromosome 13

BRCA Timeline

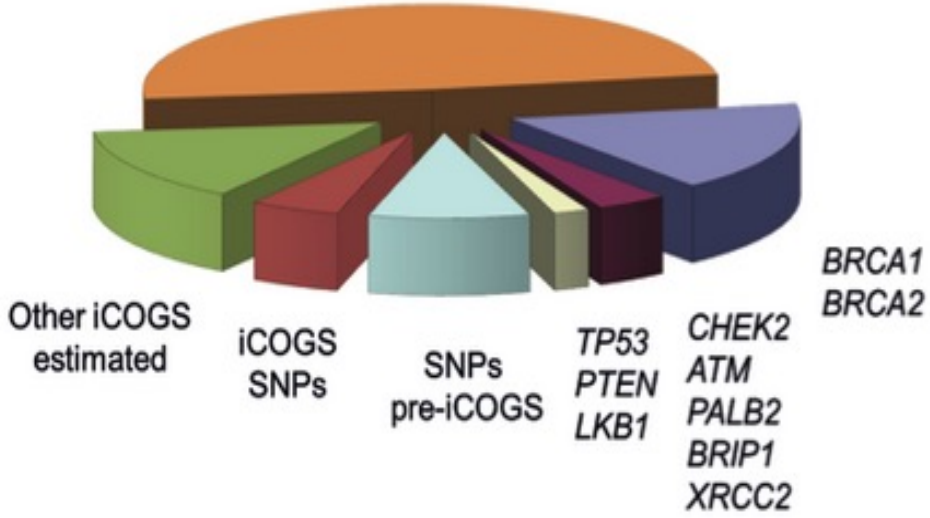
Marie-Claire King



Estimated explained familial risk for breast cancer (~ 30% of BC patients)

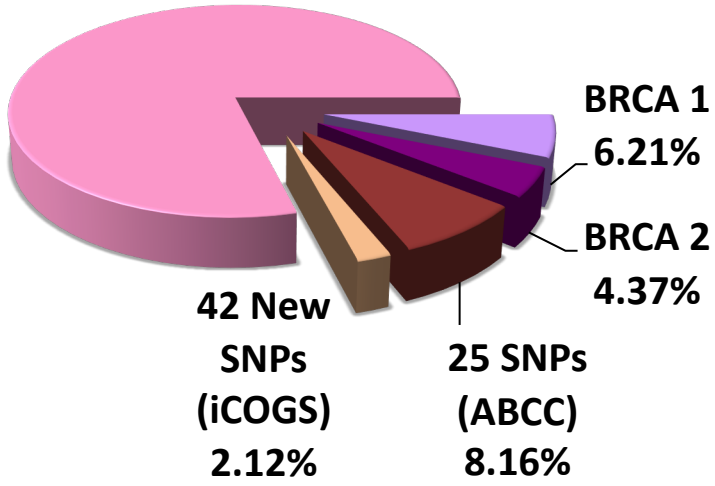
Caucasian (BCAC)

Unexplained: 50%



Asian: Malaysia (MyBRCA)

Unexplained: 79%



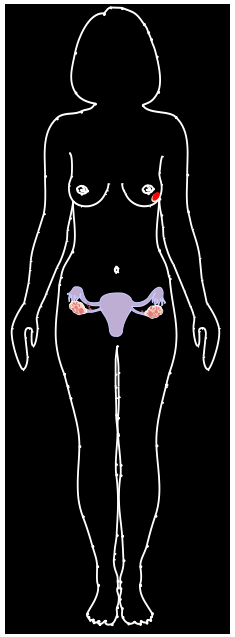
//www.nature.com/icogs/primer/common-variation-and-heritability-estimates-for-breast-ovarian-and-prostate-cancers/

Hereditary Breast Cancer Syndromes

Hereditary Breast and Ovarian Cancer Syndromes

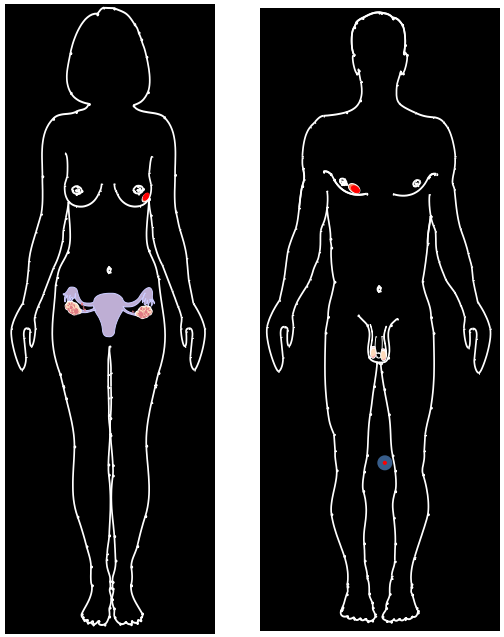
Hereditary Breast cancer and ovarian cancer syndrome	**BRCA1 (17q11)**	**Breast cancer,** • High risk (50–70%); 3-4th decade • Triple Negative BC, • Medullary Carcinoma **Ovarian cancer, high risk (40–50%)** • Average age 38.6 years

Type of cancer	**Risk by Age 70**
Breast – initial	57-65%
Breast - second	3% per year (30% at 10 years)
Ovarian	40%
Prostate	None to 2-3 fold increase
Male breast cancer	1%
Colon	Slight increase
Pancreatic cancer	1-4%



Hereditary breast cancer and ovarian cancer syndrome	**BRCA2 (13q12-q13)**	**Breast cancer, high risk (45-50 %)** **Ovarian cancer, intermediate risk (18%)** **Prostate cancer** **Pancreatic cancer** **Melanoma**

Type of cancer	**Risk by age 70**
Breast-initial	45-49%
Breast-second	3% per year
Ovarian	18% (>50 years)
Prostate	7.5-39%
Male breast cancer	6%
Pancreatic	2-7%



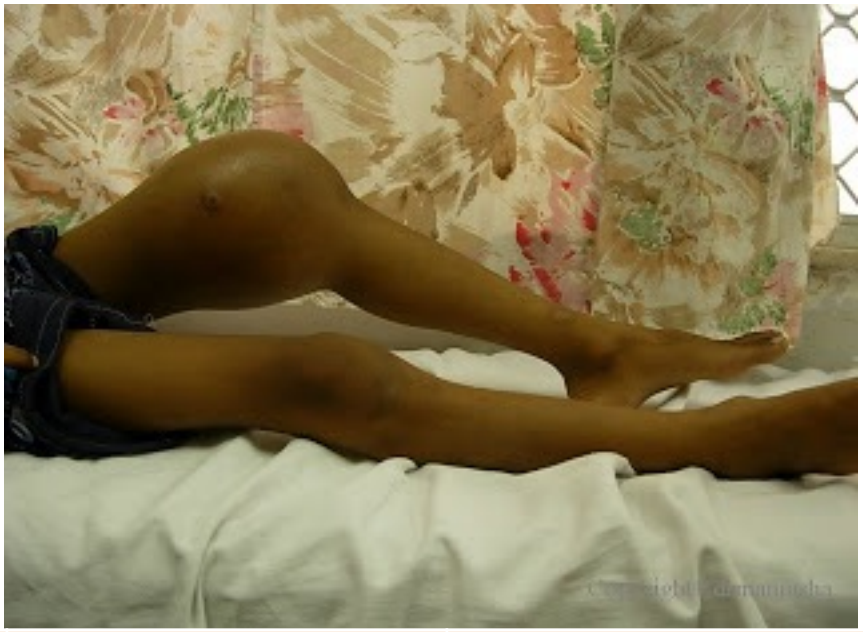
Li Fraumeni Syndrome (TP53)

Sarcoma,**L**eukemia, **A**drenocortical, **B**reast

Breast cancer

- Less than 50 years
- More likely to be **triple positive**

May be associated **malignant phyllloides**



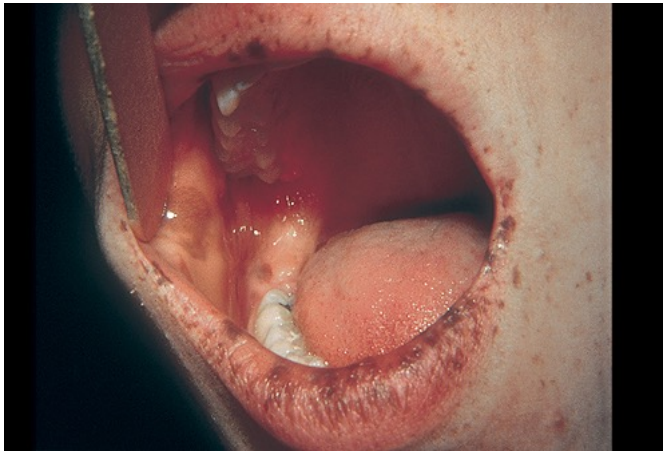
Adrenocortical cancer

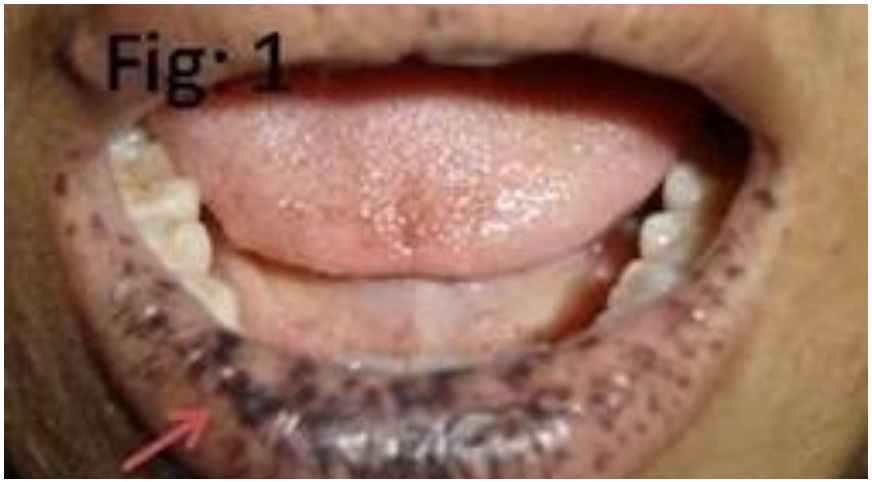
- 50-80% of ACC in childhood

Sarcoma

Li–Fraumeni syndrome	**TP53** (17p13.1)	High penetrance for breast cancers at young age Risk of soft-tissue sarcomas and osteosarcomas, brain tumours, leukaemia and adrenocortical carcinoma

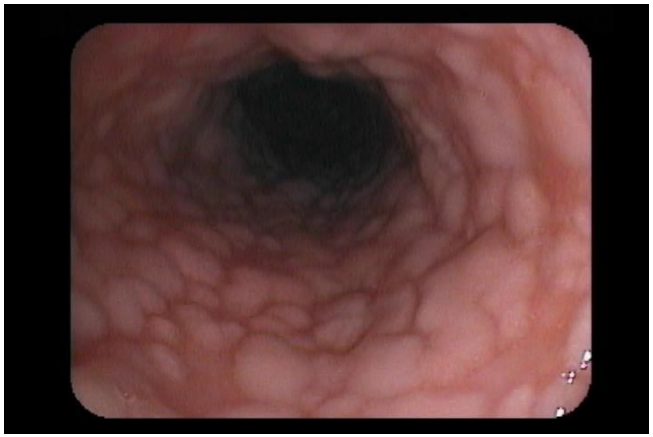
Peutz Jegher (STK11)

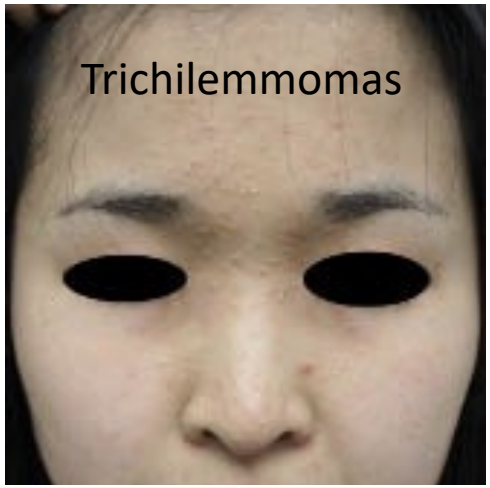


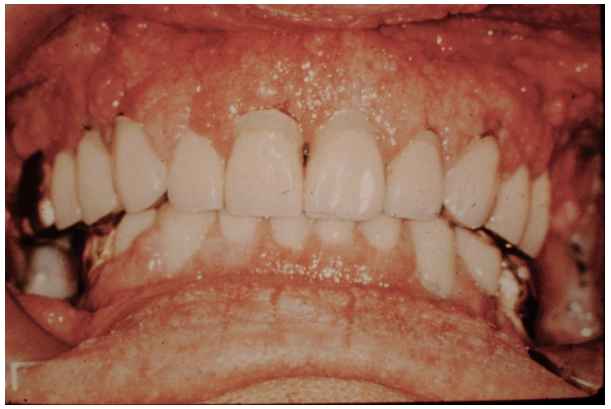


Peutz–Jeghers syndrome (175200)	STK11 (19p13.3)	Melanocytic macules of the lips, buccal mucosa and digits Multiple gastrointestinal hamartomatous polyps Increased risk of various neoplasms (**breast, testis, pancreas and cervix**)

Cowden's Syndrome (PTEN)







Cowden syndrome	**PTEN** (10q23.31)	Increased risk of developing neoplasms (**breast cancer**, thyroid carcinoma, endometrial carcinoma and others) **Hamartomatous polyps** of the gastrointestinal tract **Mucocutaneous** lesions
Bannayan–Riley–Rivalcaba syndrome (Paediatric age)	**PTEN** (10q23.31)	Breast cancer Meningioma Follicular cells tumours of the thyroid (Macrocephaly)

Lynch Syndrome

Lynch cancer family syndrome II (114400)	MSH2 (2p22–p21), MSH3 (5q11–q12), MSH6 (2P16), MLH1 (3p21.3), PMS1 (2q31–q33), PMS2 (7p22)	Increased risk of **endometrial carcinoma and colorectal carcinoma** High risk of multiple primary malignant neoplasms, including **breast, ovarian,** gastrointestinal and genitourinary carcinomas, sarcomas, glioblastoma and leukaemia

CHEK2 mutations (Li–Fraumeni 2 syndrome?)	**CHEK2** (22q12.1)	Breast cancer, intermediate risk (,twofold) Sarcomas Brain tumours
PALB2	**PALB2**/FANCN (16p12)	PALB2/FANCN and BRIP1/FANCJ: moderate risk of **breast cancer** development
Familial-linitis-plastic type gastric cancer and lobular breast carcinomas syndrome	**CDH1** (16q22.1)	**Gastric cancer** **Lobular breast cancer**

Louis–Bar syndrome	**ATM** (11q22.3)	Lymphoma Cerebellar ataxia Immune deficiency Glioma Medulloblastoma Breast cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Breast Cancer Risk Genes — Association Analysis in More than 113,000 Women

Breast Cancer Association Consortium*

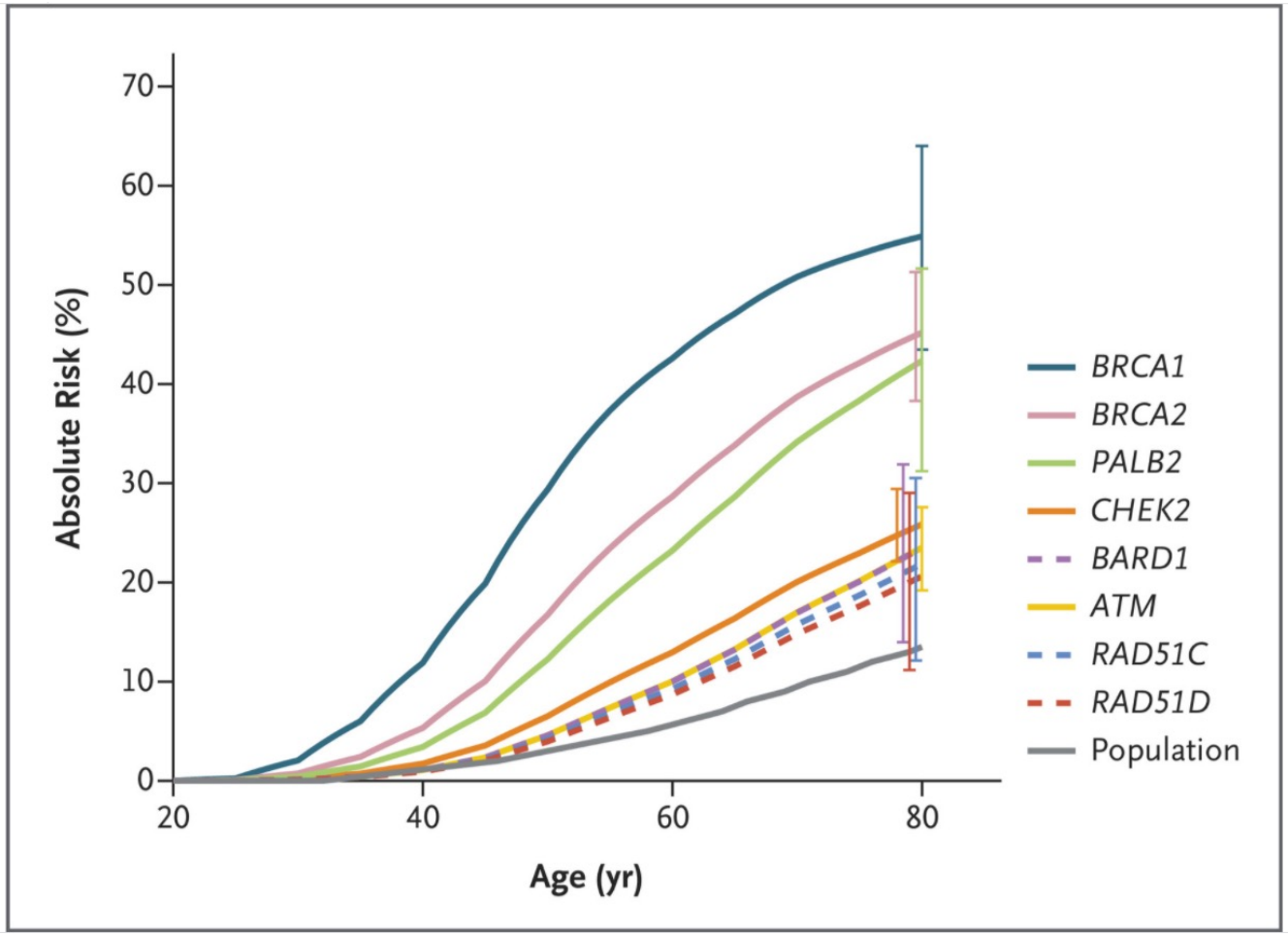


Figure 3. Estimated Absolute Risk of Breast Cancer Associated with Protein-Truncating Variants in 8 Genes.

Shown are absolute risks of breast cancer through 80 years of age associated with protein-truncating variants in 8 genes that had significant evidence of an association with breast cancer overall, on the basis of estimated odds ratios from population-based studies. The absolute risk was not calculated for TP53 because of the wide 95% confidence interval for the odds ratio and the known association with a substantial risk of childhood cancer. Baseline absolute risks were derived from population incidences in the United Kingdom in 2016.[6] The I bars indicate 95% confidence intervals.

February 4, 2021
N Engl J Med 2021; 384:428-439
DOI: 10.1056/NEJMoa1913948

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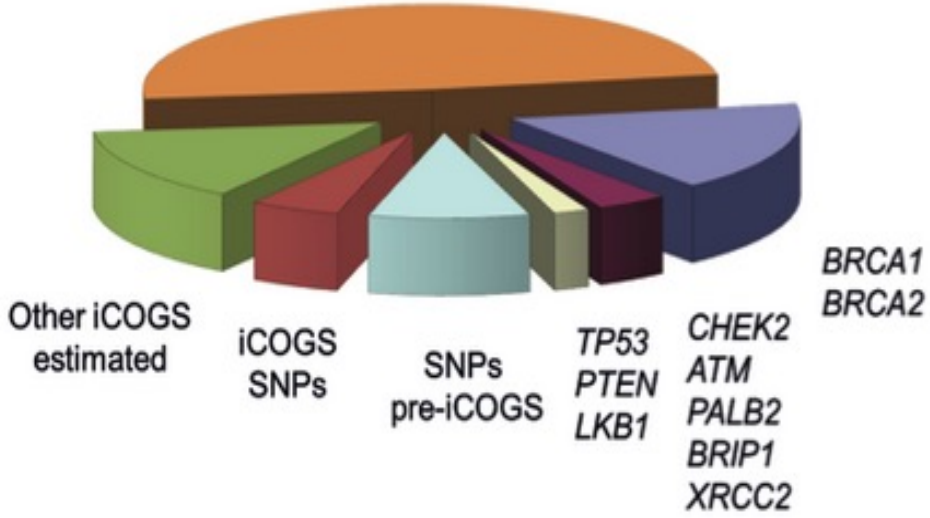

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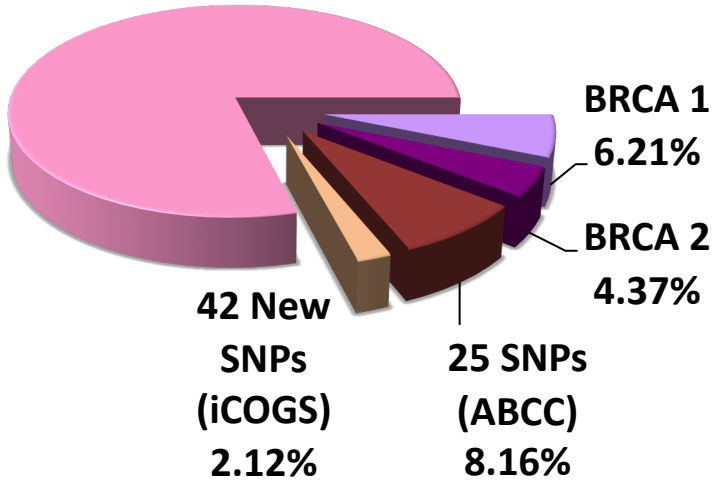

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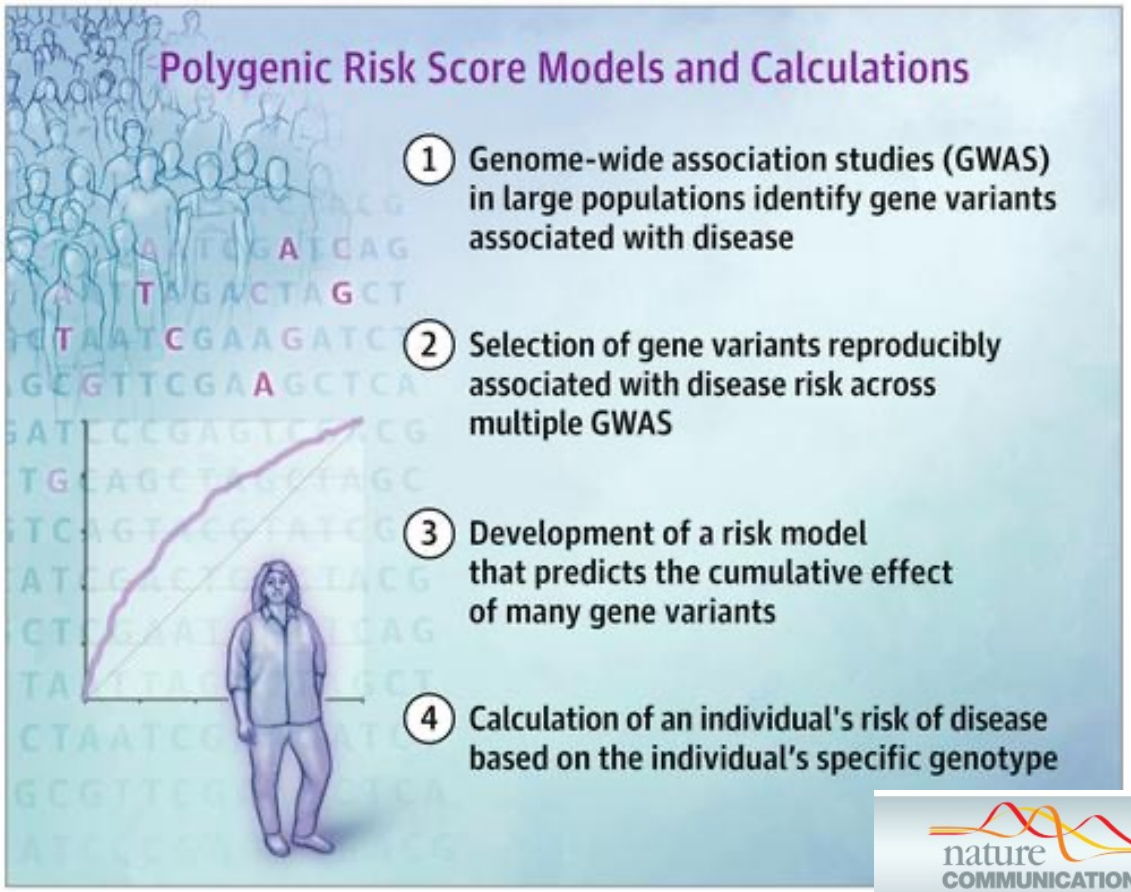
What Are Polygenic Scores and Why Are They Important?

JAMA (IF 45.540) **Pub Date : 2019-05-14** , *DOI: 10.1001/jama.2019.3893*

Leo P. Sugrue, Rahul S. Desikan



nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-17680-w OPEN

European polygenic risk score for prediction of breast cancer shows similar performance in Asian women

Weang-Kee Ho et al.#

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Traditional

HEREDITARY CANCER RISK IDENTIFIED

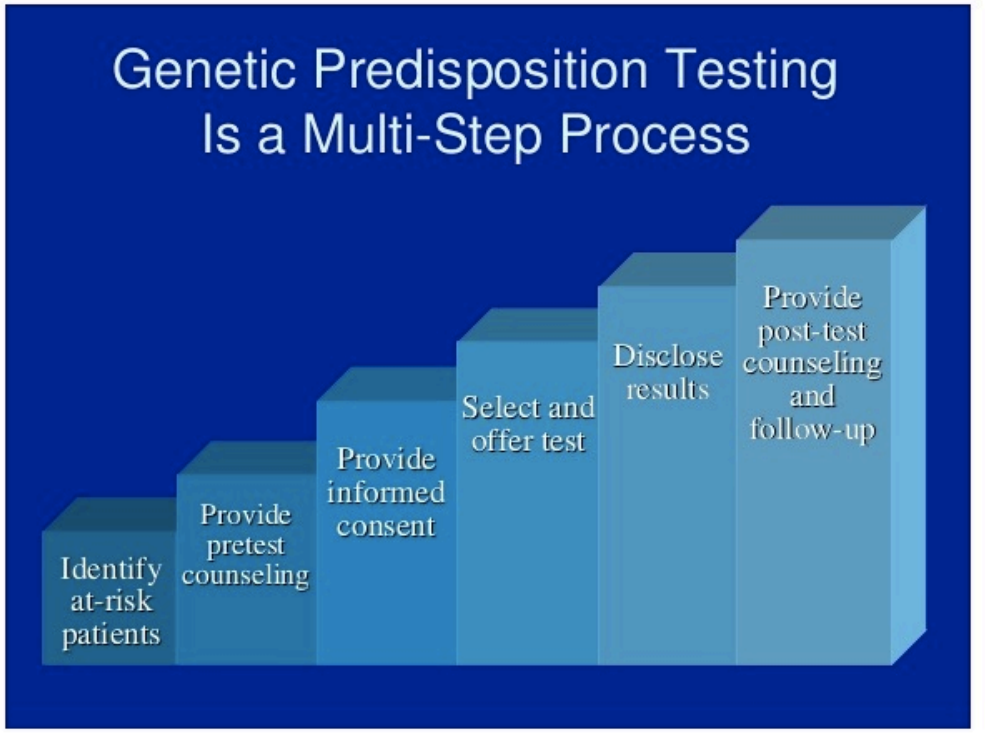
PATIENT REFERRED TO CLINICAL GENETICS SERVICE

PRE-TEST GENETIC COUNSELLING

BRCA GENETIC TESTING

POST-TEST GENETIC COUNSELLING

CANCER RISK

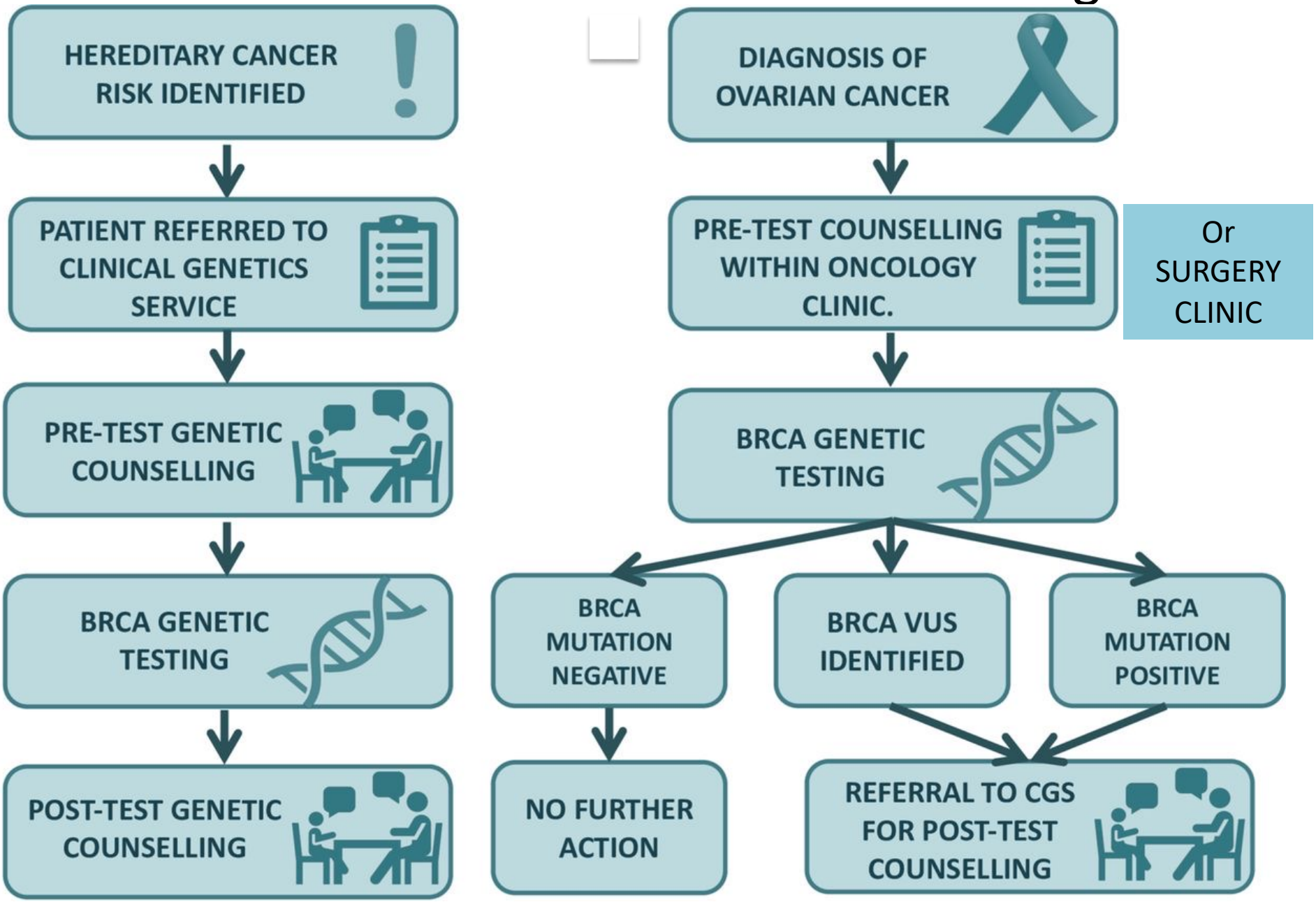


https://ijgc.bmj.com/content/30/2/221

BUT

- **Systematic underuse and inappropriate use** of BRCA testing over the past 2 decades, with consequent lost opportunities for improved cancer management and cancer prevention.[14-26]
- A recent US study estimated that only **20%** of eligible individuals are being offered testing, with more than a million eligible individuals not having testing between 2000 and 2010.[27] It is further estimated that only **30% of patients with breast cancer and 10% of unaffected individuals with BRCA mutations** in the United States have been identified.[28]
- These challenges and outcomes have been similar in many other countries.[14-26]
- HRR genes are a therapeutic target

Traditional vs. Mainstreaming



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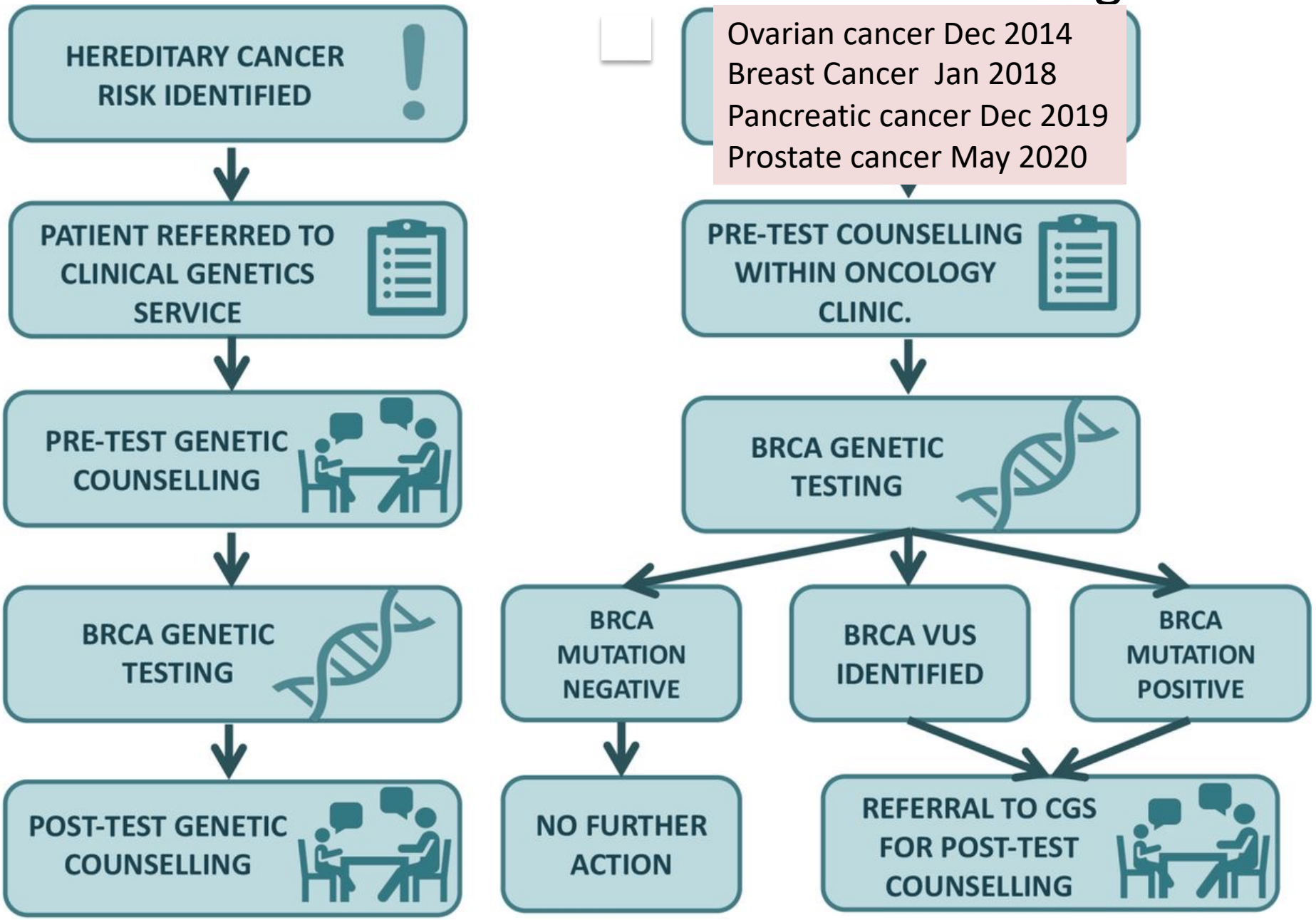
Traditional vs. Mainstreaming



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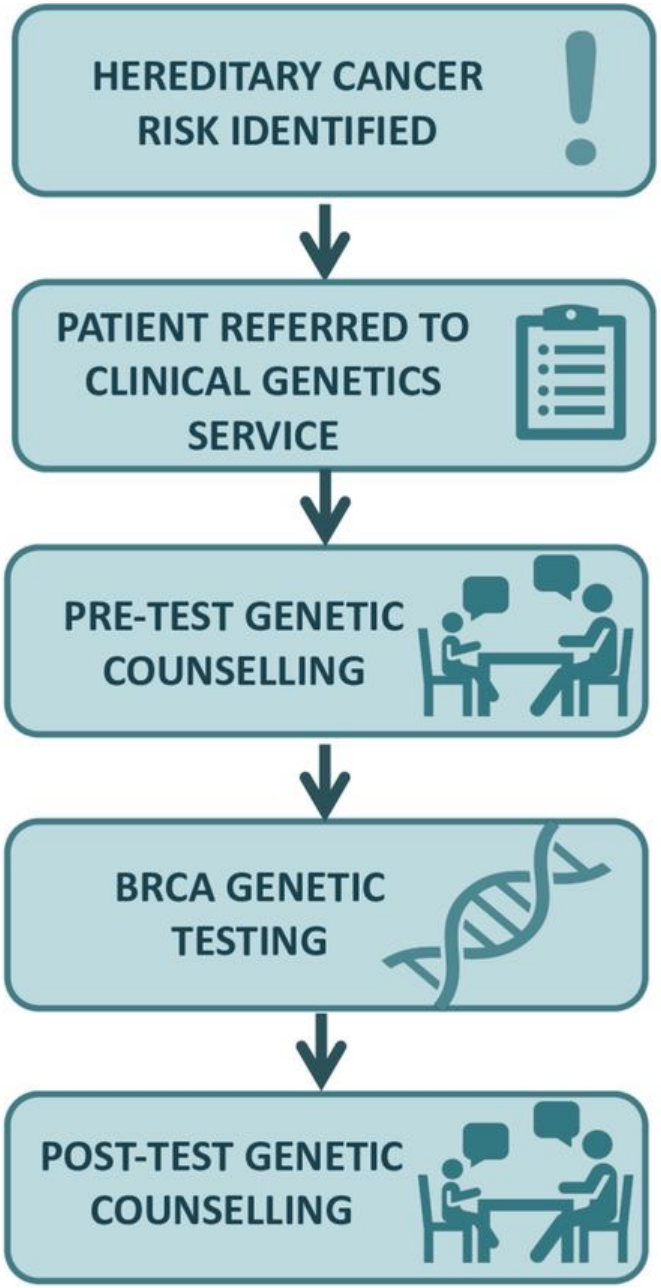
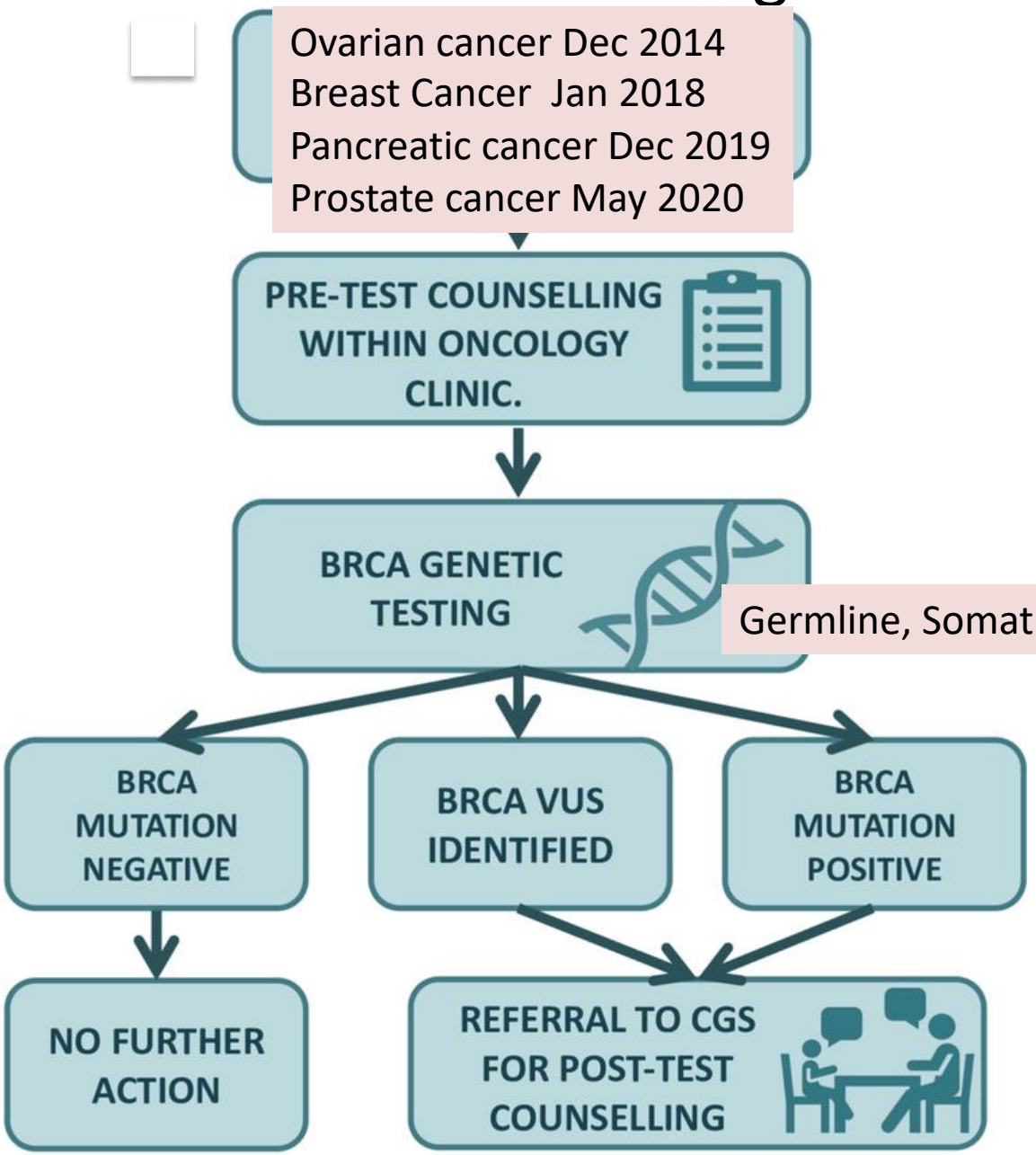
Traditional vs. Mainstreaming





https://ijgc.bmj.com/content/30/2/221

From: **Evaluation of Cancer-Based Criteria for Use in Mainstream BRCA1 and BRCA2 Genetic Testing in Patients With Breast Cancer**

JAMA Netw Open. 2019;2(5):e194428. doi:10.1001/jamanetworkopen.2019.4428

To improve BRCA testing, the Mainstreaming Cancer Genetics (MCG) Programme has been developing simplified eligibility criteria and testing access processes.[29] Ovarian cancer was addressed first, simplifying eligibility to all women with epithelial ovarian cancer, as the BRCA mutation rate is more than 10% within this group. A mainstream test access model was validated in which patients with ovarian cancer were directly approved for BRCA testing by their cancer team, with patients who were BRCA mutation-positive rather than all patients having an appointment for genetics consultation. The mainstream model has proved to be popular, efficient, and cost-effective and more than 1000 patients with ovarian cancer have had BRCA testing through the mainstream access model in the **Royal Marsden National Health Service Foundation Trust**.[7]

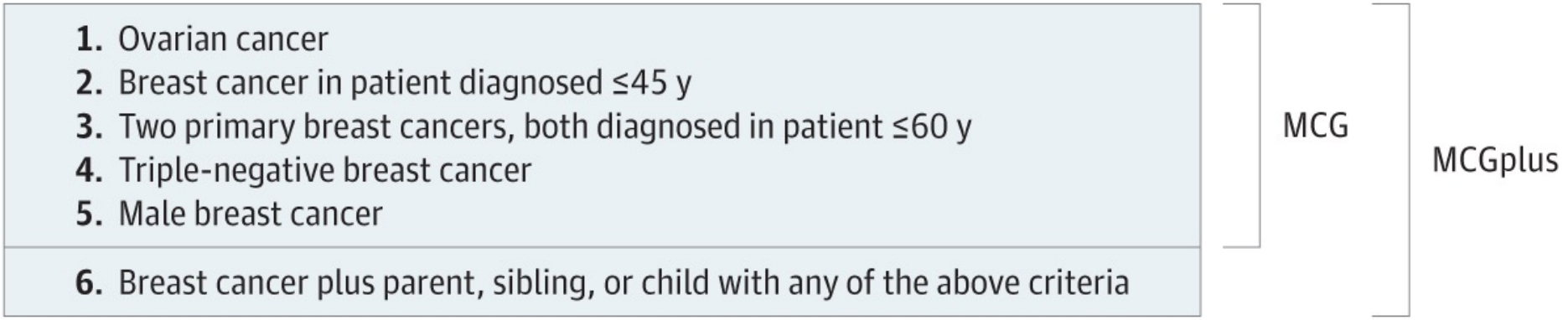


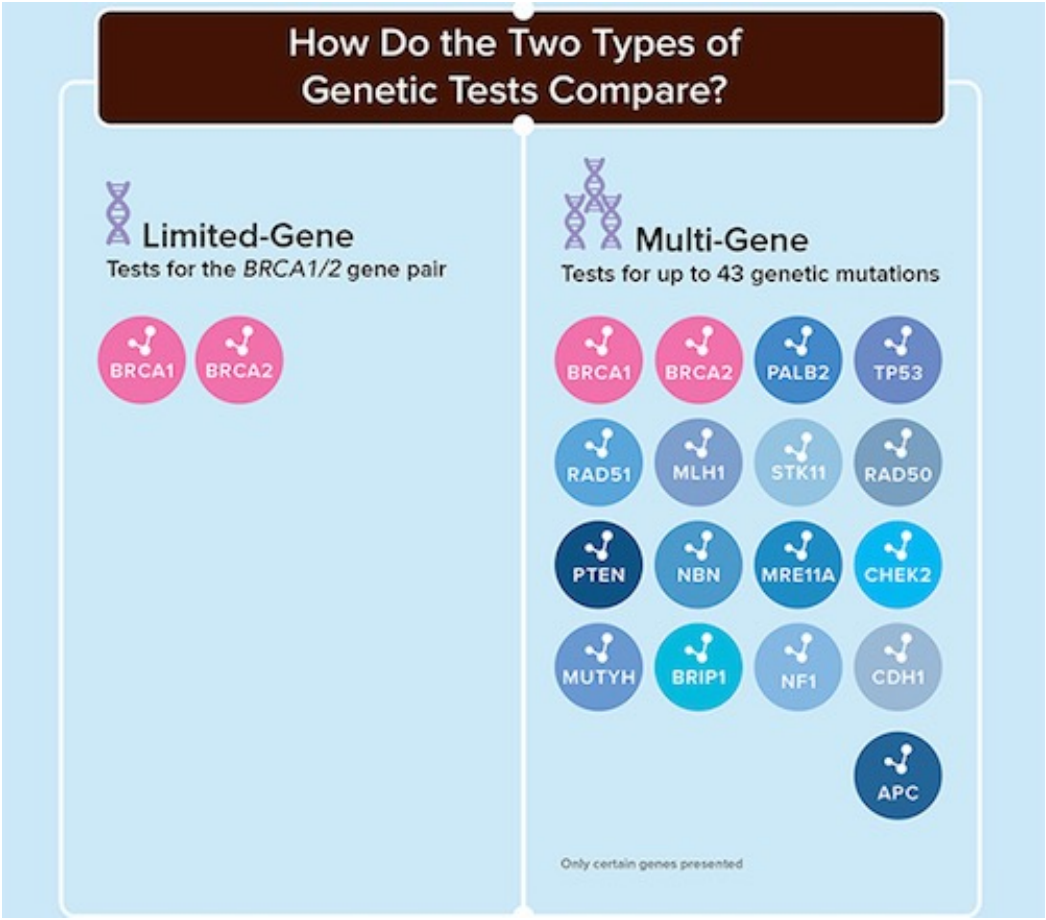
Figure Legend:

Mainstreaming Cancer Genetics (MCG) Criteria MCG includes criteria 1 through 5; MCGplus includes criteria 1 through 6. Ovarian cancer indicates epithelial ovarian cancer.

Which test

Germline or Somatic

Germline testing



https://www.breastlink.com/blog/nimmi-s-kapoor-md-gene-tests-asbs/

Germline tests available
~USD 250 =~ RM1000
direct to consumer price

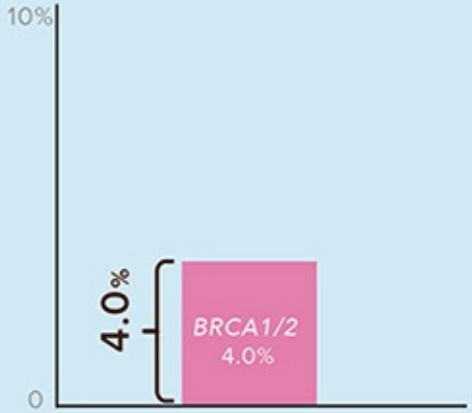
Multi-Gene Testing Nearly DOUBLES Detection Rate

BREASTLINK STUDY

A total of 966 patients were tested based on family history and NCCN genetic testing guidelines.

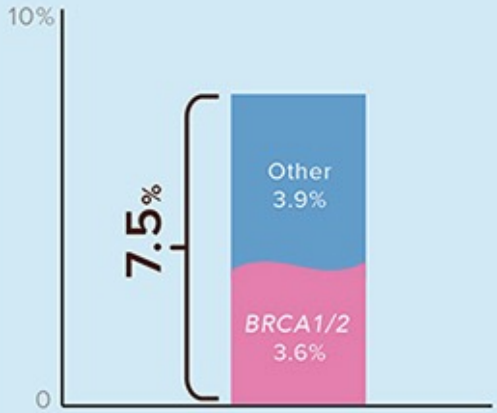
Mutations Detected:

Limited-Gene
629 patients



Total Detected: **4.0%**

Multi-Gene
337 patients



Total Detected: **7.5%**

Somatic HRD tests

Test name	Test description	Biomarkers detected	FDA-approved usage as companion diagnostic
myChoice CDx (Myriad Genetics)	–Determines GIS score –Positive HRD status defined as positive GIS score or t*BRCA*1/2 mutations –NGS on FFPE tumor tissue	–*BRCA1* and *BRCA2* SNVs, insertions, deletions, and large rearrangements –GIS measuring LOH, TAI, and LST	Niraparib: HRD or *BRCA1/2* positivity for patients with advanced ovarian cancer previously treated with ≥ 3 chemotherapy regimens Olaparib: HRD *or BRCA1/2* positivity when used in combination with bevacizumab as frontline maintenance therapy in patients with advanced ovarian cancer in complete or partial response to first-line platinum-based chemotherapy
FoundationOne CDx (Foundation Medicine)	–Determines LOH score –Positive HRD status defined as t*BRCA* positive and/or LOH high –NGS on FFPE tumor tissue	*BRCA1* and *BRCA2* alterations HRR genes: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L* alterations	Rucaparib: positivity for germline or somatic *BRCA1/2* alterations for patients with advanced ovarian cancer previously treated with ≥ 2 lines of chemotherapy[a] Olaparib: –Positivity for germline or somatic *BRCA1/2* alterations in patients with advanced ovarian cancer in complete or partial response to first-line platinum-based chemotherapy –Germline or somatic HRR gene–mutated metastatic CRPC in patients who have progressed following treatment with enzalutamide or abiraterone

CRPC, castration-resistant prostate cancer; FFPE, formalin-fixed paraffin-embedded; GIS, genomic instability score; HRD, homologous recombination deficiency; HRR, homologous recombination repair; LOH, loss of heterozygosity; LST, large-scale state transition; NGS, next-generation sequencing; SNV, single-nucleotide variant; TAI, telomeric allelic imbalance; t*BRCA*, tumor *BRCA*.
[a]Assay can also be used to analyze HRD status for rucaparib maintenance therapy in recurrent ovarian cancer.

In Malaysia, HRD somatic testing offered by one lab ~ RM 4K.

Cancer Genetics Principles

- What are genes
- Wildtype vs mutants
- Somatic vs Germline mutation
- Oncogenes and tumour suppressor genes
- Application in cancer
- Homologous Recombinant Deficiency (HRD)
- Traditional vs Mainstreaming of Genetic testing

Outline

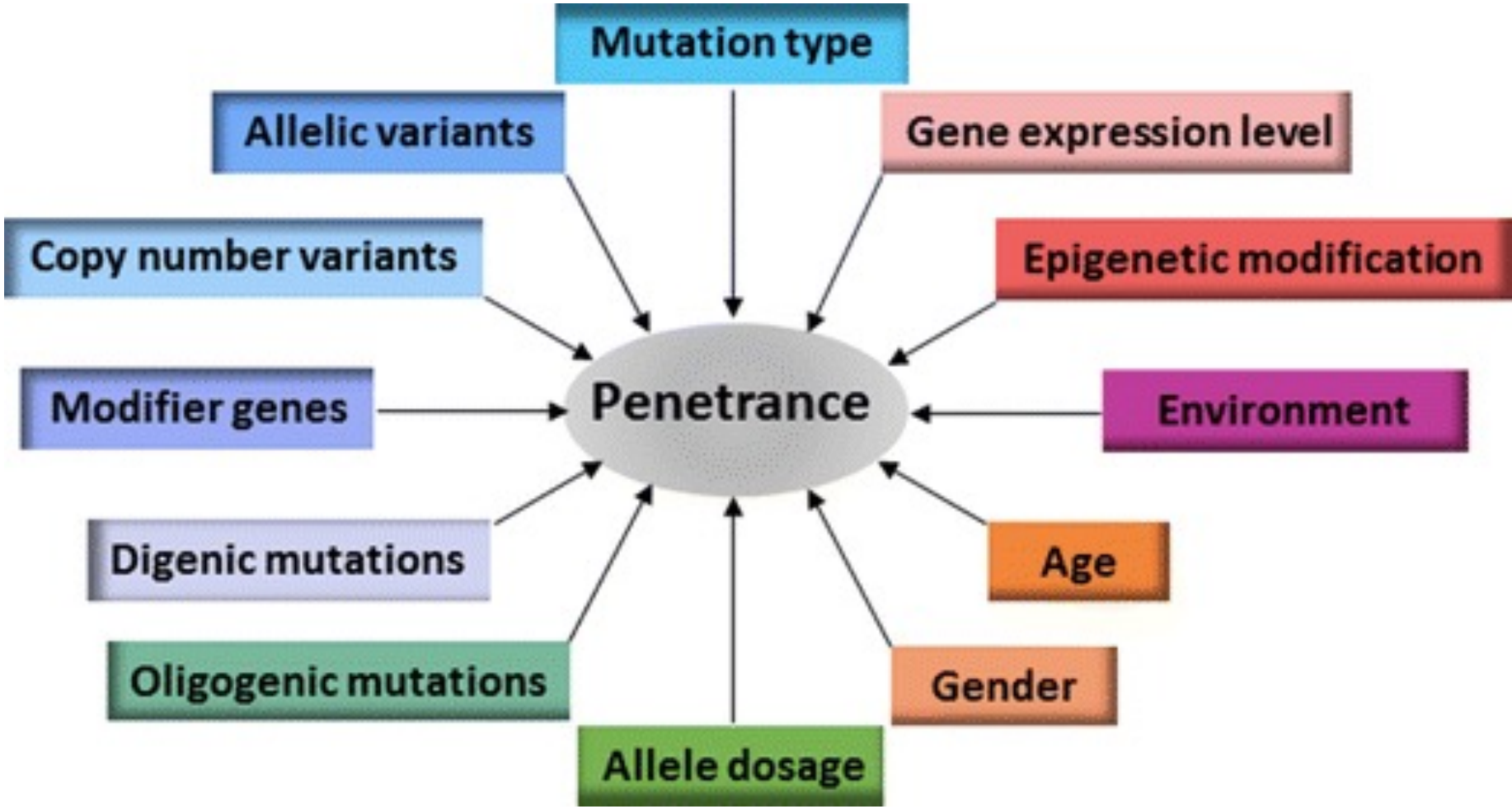
- Cancer genetics principles
- Mainstreaming vs conventional genetic testing
- Testing criteria and risk models
- Guiding principles to tests – types of tests (direct to consumer tests)
- Interpreting results and post test counselling
- Cascade or predictive testing
- Risk Management

Risk Management of Carriers

Outline

- Penetrance
- Affected vs unaffected
- Prognosis of previous cancer

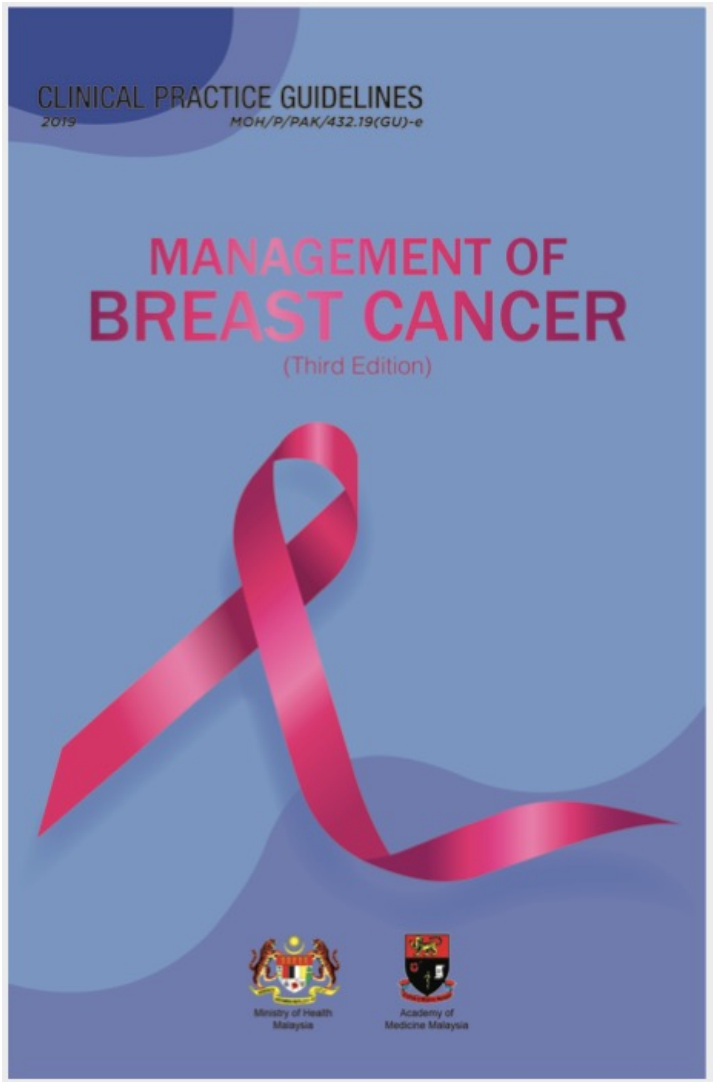
Incomplete penetrance

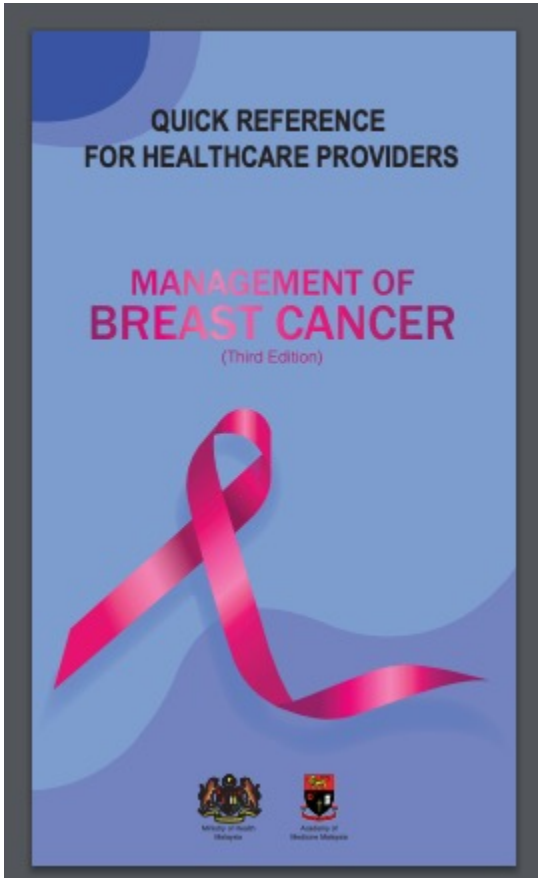


Levels of Penetrance Risk

Breast cancer risk	Genes
High risk: 10- to 20-fold relative risk	BRCA1 (17q21) BRCA2 (13q12.3) TP53 (17p13.1)
Intermediate risk: two- to fourfold relative risk	CHEK2 (22q12.1) ATM (11q22.3) CDH1 (16q22.1) PTEN (10q23.31) BRIP/FANCJ (17q22) PALB2/FANCN (16p12)
Possible low risk: < twofold	FANCA (16q24.3) FANCE (6p22–p21)

Tan et al. J Clin Pathol 2008;61:1073–1082. doi:10.1136/jcp.2008.057950


CLINICAL PRACTICE GUIDELINES
2019
MOH/P/PAK/432.19(GU)-e
MANAGEMENT OF
BREAST CANCER
(Third Edition)
Ministry of Health
Malaysia
Academy of
Medicine Malaysia


QUICK REFERENCE
FOR HEALTHCARE PROVIDERS
MANAGEMENT OF
BREAST CANCER
(Third Edition)


KANSER
PAYU DARA
menyerang
1 dalam 32 orang
Mungkinkah ANDA?

Recommendation 31

- Intensive screening of BRCA carriers and high risk individuals should be vigilantly performed and adhered to recommended guidelines.
- Screening of women with pathogenic/likely pathogenic variants in BRCA1 and BRCA2 should be conducted from age 30 to 49 years with both magnetic resonance imaging and mammography. Those 50 years and above, screening with mammography should be done.

Table 7. Summary of recommendations on screening for women with no personal history of breast cancer

Age (years)	Average risk of breast cancer[1]	Moderate risk of breast cancer[2]	High risk of breast cancer (but with a 30% or lower probability of being a BRCA or TP53 carrier)[3]	Known BRCA1 or BRCA2 carrier
20 - 29	Do not offer mammography	Do not offer mammography	Do not offer mammography	Do not offer mammography
	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI
30 - 39	Do not offer mammography	Do not offer mammography	Consider annual mammography	Annual MRI and consider annual mammography
	Do not offer MRI	Do not offer MRI	Do not offer MRI	
40 - 49	Do not offer mammography	Annual mammography	Annual mammography	Annual mammography and annual MRI
	Do not offer MRI	Do not offer MRI	Do not offer MRI	
50 - 59	Mammography	Consider annual mammography	Annual mammography	Annual mammography
	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI unless dense breast
60 - 69	Mammography as part of population screening	Mammography as part of population screening	Mammography as part of population screening	Annual mammography
	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI unless dense breast
70+	Mammography as part of population screening	Mammography as part of population screening	Mammography as part of population screening	Mammography as part of population screening

[1]Lifetime risk of developing breast cancer is <17%.

[2]Lifetime risk of developing breast cancer is at least 17% but <30%. This is likely to include individuals with pathogenic/likely pathogenic variants in PALB2 regardless of family history of breast cancer and, individuals with pathogenic/likely pathogenic variants in ATM and CHEK2 and at least one first degree relative affected by breast cancer. Individuals with pathogenic/likely pathogenic variants in ATM or CHEK2 and no close family history of breast cancer is considered to be of low/moderate risk of breast cancer (i.e. <17% lifetime risk).

[3]Lifetime risk of developing breast cancer is at least 30%. This is likely to include individuals with pathogenic/likely pathogenic variants in PALB2 and strong family history of breast cancer, or individuals where BOADICEA or other risk prediction tools suggest a high risk based on family history of breast cancer.

Adapted: National Institute for Health and Clinical Excellence. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. London: NICE; 2018

No role for ovarian cancer screening

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast and Ovarian

Version 3.2019 — January 18, 2019

NCCN.org

Continue

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Version 2.2021 — November 20, 2020

Dec. 4, 2019. The National Comprehensive Cancer Network® (NCCN®) announced publication of the newest genetic risk assessment recommendations for breast, ovarian and pancreatic cancers. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 1.2020

PANCREATIC CANCER SCREENING

- **For individuals considering pancreatic cancer screening, the panel recommends that screening be performed in experienced high-volume centers, ideally under research conditions. The panel recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening.**
- **Consider screening using annual contrast-enhanced MRI/MRCP and/or EUS, with consideration of shorter screening intervals, based on clinical judgment, for individuals found to have worrisome abnormalities on screening. The panel emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention.**

- **For all individuals with pathogenic/likely pathogenic germline variants in *STK11***
  - **Consider pancreatic cancer screening beginning at age 30–35 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).**

- **For all individuals with pathogenic/likely pathogenic germline variants in *CDKN2A***
  - **Consider pancreatic cancer screening beginning at age 40 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).**

- **For individuals with pathogenic/likely pathogenic germline variants in one of the other pancreatic cancer susceptibility genes (*ATM, BRCA1, BRCA2, MLH1, MSH2, MSH6, EPCAM, PALB2, TP53*), see GENE-A.**
  - **Consider pancreatic cancer screening beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same side of (or presumed to be from the same side of) the family as the identified pathogenic/likely pathogenic germline variant.[d]**
  - **The panel does not currently recommend pancreatic cancer screening for carriers of mutations in genes other than *STK11* and *CDKN2A* in the absence of a close family history of exocrine pancreatic cancer.**

Hereditary Pancreatitis Genes

- **For individuals with pathogenic/likely pathogenic variants in *PRSS1* or other hereditary pancreatitis genes AND a clinical phenotype consistent with hereditary pancreatitis[e]**
  - **Consider pancreatic cancer screening 20 years after onset of pancreatitis, or at age 40 years, whichever is earlier.**

[d] Abe T, et al. J Clin Oncol 2019;37:1070-1080.

[e] The panel recognizes that patients with hereditary pancreatitis (sometimes caused by pathogenic germline variants in *PRSS1*, *SPINK1*, and other genes) have increased lifetime risks of pancreatic cancer. The clinical significance of pathogenic germline variants in these genes is unclear, when such variants are identified in individuals lacking a clinical history of pancreatitis. As such, the panel recommends germline testing for *PRSS1*, *SPINK1*, and other pancreatitis genes in individuals with a personal and/or family history of exocrine pancreatic cancer only if there is a personal and/or family history suggestive of hereditary pancreatitis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2021
Genetic Testing Process

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
BRCA1	• **Evidence for increased risk:** Very strong (with predisposition to triple negative disease) • **Absolute risk:** >60%[20-24] • **Management:** See *BRCA* Pathogenic Variant-Positive Management	• **Evidence for increased risk:** Very strong • **Absolute risk:** 39%-58%[25] • **Management:** See *BRCA* Pathogenic Variant-Positive Management	**Pancreatic cancer** • **Evidence for increased risk:** Strong • **Absolute risk:** ≤5% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A. **Prostate cancer** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: There have been a few case reports of Fanconi-like conditions in individuals with two *BRCA1* pathogenic variants.[27,28]		
BRCA2	• **Evidence for increased risk:** Very strong (with predisposition to ER+ disease) • **Absolute risk:** >60% [20-24] • **Management:** See *BRCA* Pathogenic Variant-Positive Management	• **Evidence for increased risk:** Very strong • **Absolute risk:** 13%-29%[25] • **Management:** See *BRCA* Pathogenic Variant-Positive Management	**Pancreatic cancer** • **Evidence for increased risk:** Very strong • **Absolute risk:** 5-10% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A. **Prostate cancer and Melanoma** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: Counsel for risk of autosomal recessive condition in offspring.		

NCCN Guidelines Version 1.2021
Prostate Cancer Early Detection

NCCN Guidelines Index
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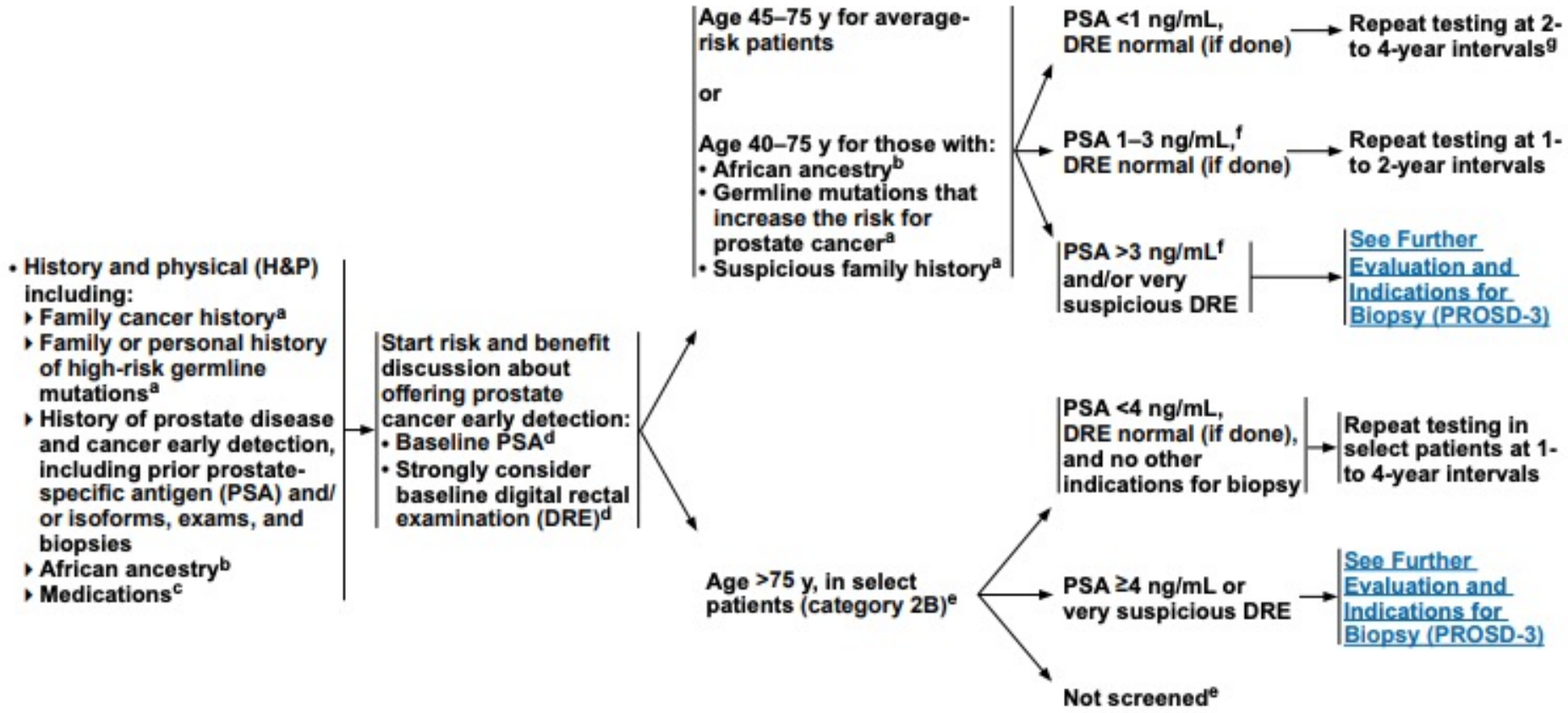
Discussion

BASELINE EVALUATION | **RISK ASSESSMENT** | **EARLY DETECTION EVALUATION**



See footnotes on PROSD-2A.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Risk-reducing strategies

Recommendation 32

- Risk-reducing surgeries should be discussed and offered to women with pathogenic/likely pathogenic variants in BRCA1 and BRCA2 genes.

i) Risk-reducing surgery

- **Bilateral risk-reducing mastectomy**

Risk-reducing mastectomy (RRM) remains the most effective strategy for reducing breast cancer risk. A meta-analysis showed that prophylactic bilateral mastectomy reduced the risk for breast cancer (RR=0.11, 95% CI 0.04 to 0.32) but not all-cause mortality.[124, level II-2] Another systematic review also showed 90 - 95% risk reduction.[125, level II-2]

Multidisciplinary consultations are recommended prior to surgery and should include discussions of the risks and benefits of surgery and option of breast reconstruction. Psychosocial effects of RRM should also be addressed.

For carriers of pathogenic/likely pathogenic variants of PALB2, ATM and CHEK2, there is currently insufficient evidence for RRM and these individuals are managed based on family history.[25]

- **Contralateral risk-reducing mastectomy**

Carriers of pathogenic/likely pathogenic variants of BRCA1 and BRCA2 have increased risk of developing contralateral breast cancer. A prospective study showed average cumulative risks by age 70 years of 83% (95% CI 69 to 94) for BRCA1 and 62% (95% CI 44 to 79.5) for BRCA 2.[126, level II-2] BRCA 1 particularly has higher risks as the majority of tumours would not receive endocrine therapy.[127, level III] Further risk factors for contralateral breast cancer within BRCA carriers include early age of first breast cancer diagnosis (<50 years) with increasing numbers of first-degree relatives with breast cancer at a young age.[127, level III; 128, level II-2]

Contralateral risk-reducing mastectomy reduces risk of contralateral breast cancer by over 90% in BRCA1 and BRCA2 carriers[129, level II-2] and is associated with 48 - 63% survival advantage.[129 - 130, level II-2]

For carriers of pathogenic/likely pathogenic variants of PALB2, ATM and CHEK2, there is currently insufficient evidence for increased risk to contralateral breast cancer.

- **Risk-reducing bilateral salpingo-oophorectomy**

Risk-reducing bilateral salpingo-oophorectomy (RRSO) remains the **most effective risk reduction strategy** for the prevention of BRCA1- and BRCA2-associated ovarian, fallopian tube and peritonial cancers.
A Cochrane systematic review of moderate quality primary papers showed RRSO reduced risk of gynaecological cancers in both BRCA1 and BRCA2.[131, level II-2]

Pre-menopausal high risk women are most likely to benefit from RRSO, but also most likely to experience side effects from surgery, including loss of fertility, loss of sexual function and increased osteoporosis. Thus, RRSO is advised after completion of childbearing and from the age of **35 - 40 years old.**
Notably, whereas earlier meta-analyses suggested that RRSO may reduce the risk of breast cancer, two recent studies presented strong evidence suggesting that the previous reports may have been subject to ascertainment bias. Correction for this bias suggested that **RRSO provided no or minimal protective effect on breast cancer risk.**[132 - 133, level II-2]

- In high risk women, evidence has shown that risk-reducing surgeries and chemoprevention are effective in reducing the risk of developing breast cancers.

Chemoprevention

• Selective estrogen receptor modulators

A long-term RCT on tamoxifen as chemoprevention (20 mg for five years) for moderate and high risk women (as determined using the Tyrer Cuzick Model) found a reduction in the occurrence of all breast cancers in the tamoxifen group compared with placebo group (HR=0.71, 95% CI 0.60 to 0.83). After 20 years of follow-up, the estimated risk of developing all types of breast cancer was **12.3% (95% CI 10.1 to 14.5) in the placebo group compared with 7.8% (95% CI 6.9 to 9.0**) in the tamoxifen group; hence the **NNT for five years to prevent one breast cancer in the next 20 years was 22 (95% CI 19 to 26).**[134, level I]

A higher incidence of deep vein thrombosis in women receiving tamoxifen compared with placebo was seen in the first 10 years of follow-up (OR=1.87, 95% CI 1.11 to 3.18). Although not significant, there were more endometrial cancers in the tamoxifen group, but only for the first five years of active treatment.[134, level I]

Women on tamoxifen should stop tamoxifen two months before trying to conceive or six weeks before elective surgery.[1]

- **Aromatase inhibitors**

In an RCT of anastrozole as chemoprevention in post-menopausal high risk women (as determined using the Tyrer Cuzick Model), after a median follow-up of five years, **fewer women in the anastrozole group developed breast cancer compared with placebo group (HR=0.47, 95% CI 0.32 to 0.68**). The predicted cumulative incidence of all breast cancers after seven years was 5.6% in the placebo group and 2.8% in the anastrozole group, suggesting that **36 women (95% CI 33 to 44) would need to be treated with anastrozole to prevent one cancer in seven years of follow-up**.[135, level I]
Anastrozole was not associated with an increased risk of other cancers particularly gynaecological cancers, nor any thromboembolic or vascular events. A contraindication for anastrozole use was severe osteoporosis.[135, level I]

- **Oral contraceptives**

For female carriers of pathogenic/likely pathogenic variants in BRCA1 or BRCA2, use of oral contraceptive **could reduce the risk of ovarian cancer, with no significant increase in risk to breast cancer.**[118]

COLLEGES OF THE ACADEMY

Colleges of the Academy

College of Anaesthesiologists

- Office Bearers 2017 - 2018
- Special Interest Groups 2011 - 2012
- Total Intravenous Anaesthesia (Pocket Reference)
- Continuous Spinal Anaesthesia Workshop 2012
- 3rd National DayCare Conference Surgery 2014
- Berita Anestesiologi

College of Dental Specialists

- Council 2017-2018

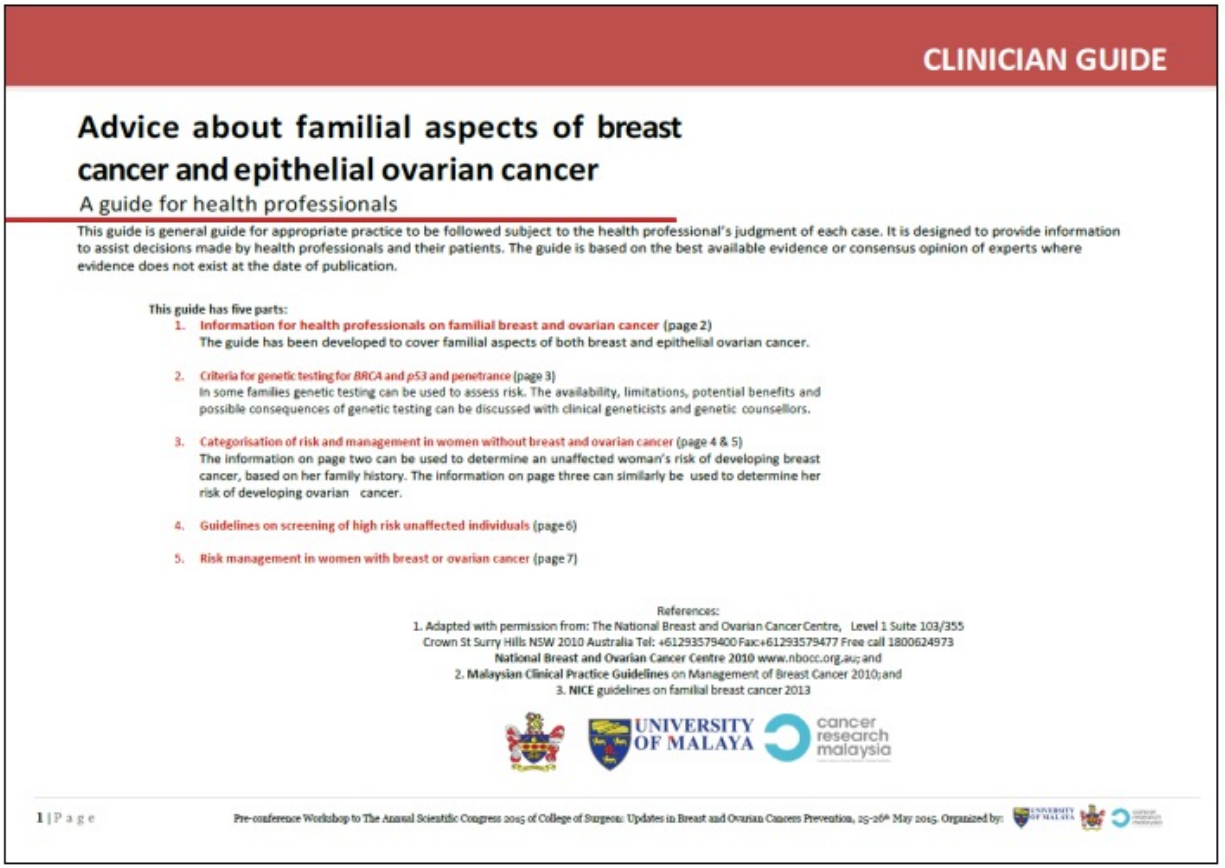
College of Emergency Physicians

- Office Bearers 2017-2019

College of Obstetricians and Gynaecologists

- Council 2015 - 2017

Breast Chapter



CLINICIAN GUIDE

Advice about familial aspects of breast cancer and epithelial ovarian cancer

A guide for health professionals

This guide is general guide for appropriate practice to be followed subject to the health professional's judgment of each case. It is designed to provide information to assist decisions made by health professionals and their patients. The guide is based on the best available evidence or consensus opinion of experts where evidence does not exist at the date of publication.

This guide has five parts:

1. Information for health professionals on familial breast and ovarian cancer (page 2)
   The guide has been developed to cover familial aspects of both breast and epithelial ovarian cancer.
2. Criteria for genetic testing for *BRCA* and *p53* and penetrance (page 3)
   In some families genetic testing can be used to assess risk. The availability, limitations, potential benefits and possible consequences of genetic testing can be discussed with clinical geneticists and genetic counsellors.
3. Categorisation of risk and management in women without breast and ovarian cancer (page 4 & 5)
   The information on page two can be used to determine an unaffected woman's risk of developing breast cancer, based on her family history. The information on page three can similarly be used to determine her risk of developing ovarian cancer.
4. Guidelines on screening of high risk unaffected individuals (page 6)
5. Risk management in women with breast or ovarian cancer (page 7)

References:

1. Adapted with permission from: The National Breast and Ovarian Cancer Centre, Level 1 Suite 103/355 Crown St Surry Hills NSW 2010 Australia Tel: +61293579400 Fax:+61293579477 Free call 1800624973 National Breast and Ovarian Cancer Centre 2010 www.nbocc.org.au; and
2. **Malaysian Clinical Practice Guidelines** on Management of Breast Cancer 2010;and
3. **NICE** guidelines on familial breast cancer 2013

UNIVERSITY OF MALAYA cancer research malaysia

1 | Page

Pre-conference Workshop to The Annual Scientific Congress 2015 of College of Surgeon: Updates in Breast and Ovarian Cancers Prevention, 25-26th May 2015. Organized by:

Clinican Guide

Advice about familial aspects of breast cancer and epithelial ovarian cancer

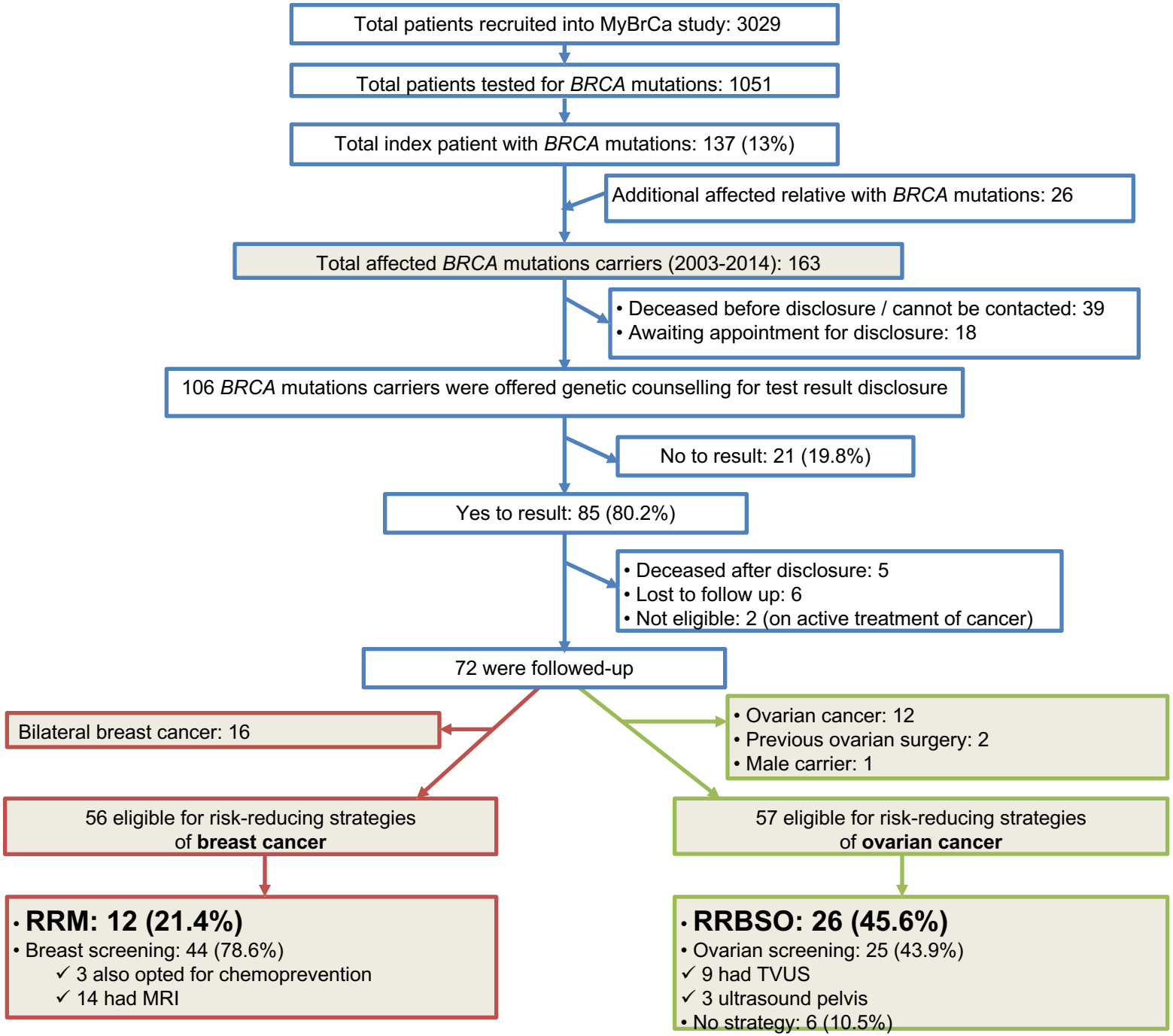
A guide for health professionals

UMMC Risk Management Clinic

- Since 2009
- Once a month
- Joint Breast Surgery/ Gyneoncology Clinic
  - Commitment from specialist to see patients
- CRM team on site

Role of team members

- Navigation → Breast care nurse team
- Breast cancer risk management → Breast surgeon team
- Ovarian cancer risk management → Gyne-oncologist team
- Breast Screening → Breast radiology team


Total patients recruited into MyBrCa study: 3029
Total patients tested for *BRCA* mutations: 1051
Total index patient with *BRCA* mutations: 137 (13%)
Additional affected relative with *BRCA* mutations: 26
Total affected *BRCA* mutations carriers (2003-2014): 163
• Deceased before disclosure / cannot be contacted: 39
• Awaiting appointment for disclosure: 18
106 *BRCA* mutations carriers were offered genetic counselling for test result disclosure
No to result: 21 (19.8%)
Yes to result: 85 (80.2%)
• Deceased after disclosure: 5
• Lost to follow up: 6
• Not eligible: 2 (on active treatment of cancer)
72 were followed-up
Bilateral breast cancer: 16
• Ovarian cancer: 12
• Previous ovarian surgery: 2
• Male carrier: 1
56 eligible for risk-reducing strategies of **breast cancer**
57 eligible for risk-reducing strategies of **ovarian cancer**
• **RRM: 12 (21.4%)**
• Breast screening: 44 (78.6%)
✓ 3 also opted for chemoprevention
✓ 14 had MRI
• **RRBSO: 26 (45.6%)**
• Ovarian screening: 25 (43.9%)
✓ 9 had TVUS
✓ 3 ultrasound pelvis
• No strategy: 6 (10.5%)

MDT (Medical Genetics Unit, Breast Surgery, Gyneoncology)

- On-site (every month)
- Discussion on new cases
- Type of mutation
- Risk Management Plan
- Psychosocial aspects (from genetic counsellor and breast nurse)
- **Occasional update on risk assessment clinic

Patient Decision Aids

- 2 Phd students
- Patient decision aids – Aid communication of risk and education
- Coach patient through decision making process

Phd Student: Ms Grace Yeoh

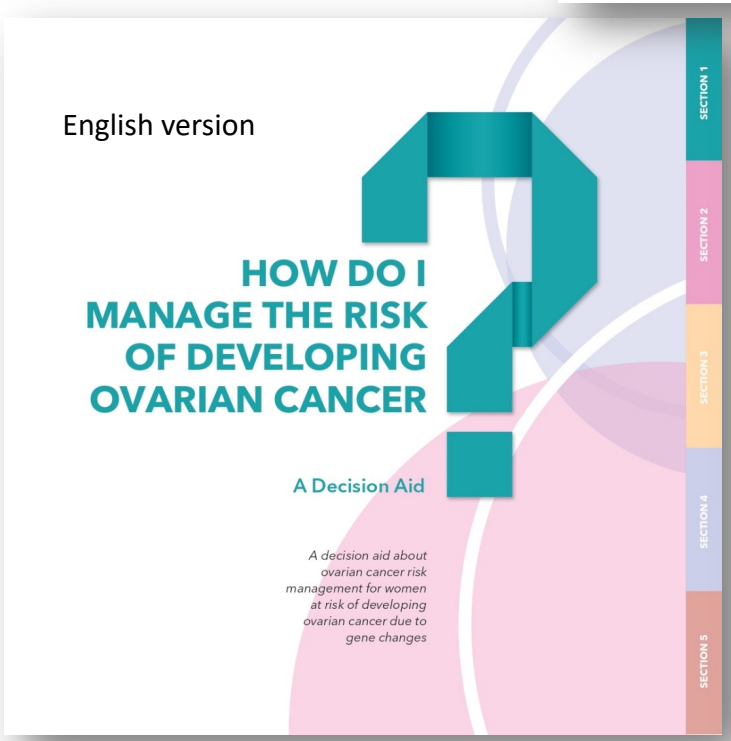
https://brcada.um.edu.my/

Phd Student: Ms Hamizah Sa'at

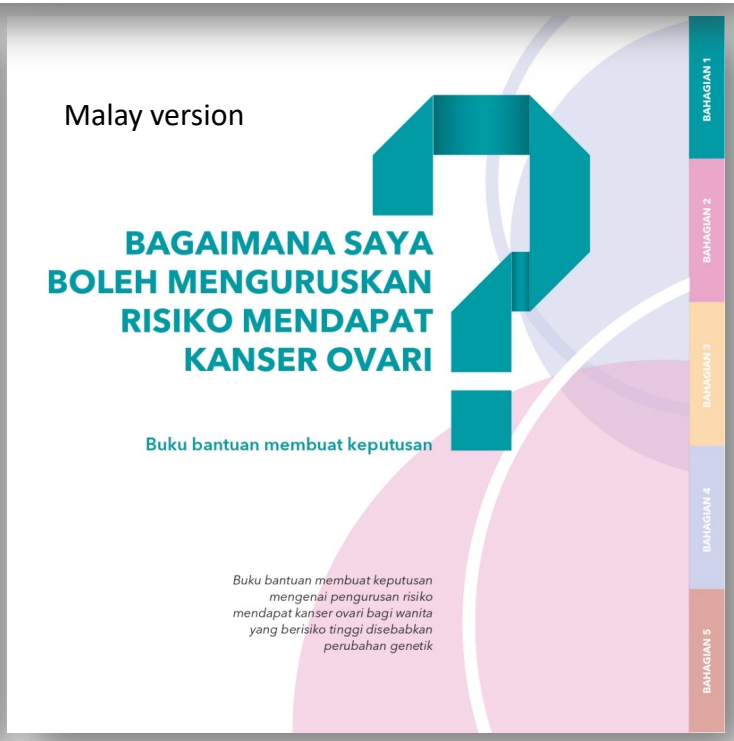
This decision aid is prepared by:

Ms Hamizah Hj Sa'at (PhD candidate, Faculty of Medicine, University of Malaya)
Prof Dr Nur Aishah Mohd Taib (Clinician expert in Hereditary Breast and Ovarian Cancer, Consultant Breast Surgeon, University Malaya Medical Centre)
Dr. Lee Yew Kong (Expert in Decision Aid, Faculty of Medicine, University of Malaya)

English version



Malay version



Familial Cancer
https://doi.org/10.1007/s10689-021-00232-6

ORIGINAL ARTICLE

Check for updates

The needs of Southeast Asian BRCA mutation carriers considering risk-reducing salpingo-oophorectomy: a qualitative study

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Malaysia- Genetic Clinic (Risk Assessment)

- HKL
- UMMC
- UKMMC
- Cancer Research Malaysia in SJMC
  - **MAGIC Trial** (Mainstreaming of Genetic Testing in Ovarian Cancer)
  - 22 sites across Malaysia

Conclusion

- Penetrance
- Affected vs unaffected
- Prognosis of previous cancer

- Strategies for screening and risk reduction

Outline

- Cancer genetics principles
- Mainstreaming vs conventional genetic testing
- Testing criteria and risk models
- Guiding principles to tests – types of tests (direct to consumer tests)
- Interpreting results and post test counselling
- Cascade or predictive testing
- Risk Management

THANK YOU

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CANCER RESEARCH INSTITUTE

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