GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

GENETIC TESTING AND COUNSELLING IN HEREDITARY CANCER

(HBOC; Lynch syndrome)

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GENETIC TESTING AND COUNSELLING IN HEREDITARY CANCER

(HBOC; Lynch syndrome)

The concept of hereditary cancer

Phenotypes and age-related penetrance

Limitations and pitfalls of genetic testing

Indications for testing symptomatic patients

Pre-test genetic counselling in symptomatic patients

Post-test genetic counselling in symptomatic patients

Presymptomatic genetic testing (PGT)

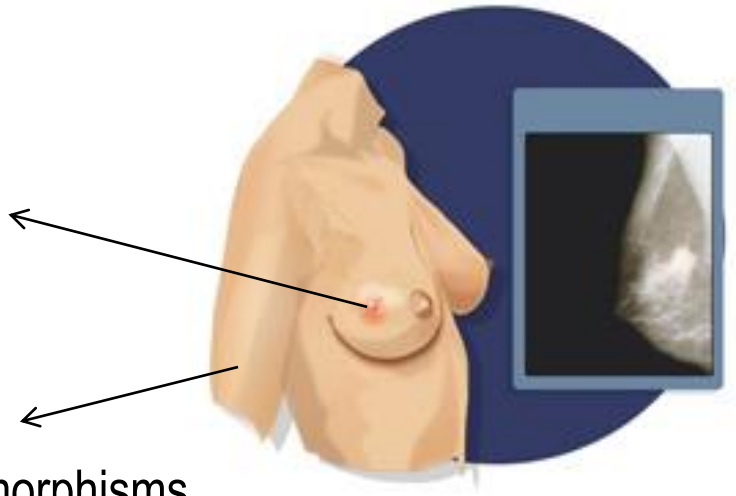
Patients' trajectories

Future trends

TWO REALMS OF CANCER GENETICS

In tumours (tumour DNA = somatic DNA):
Molecular pathology; tumourigenesis routes

- Genetic
- Epigenetic



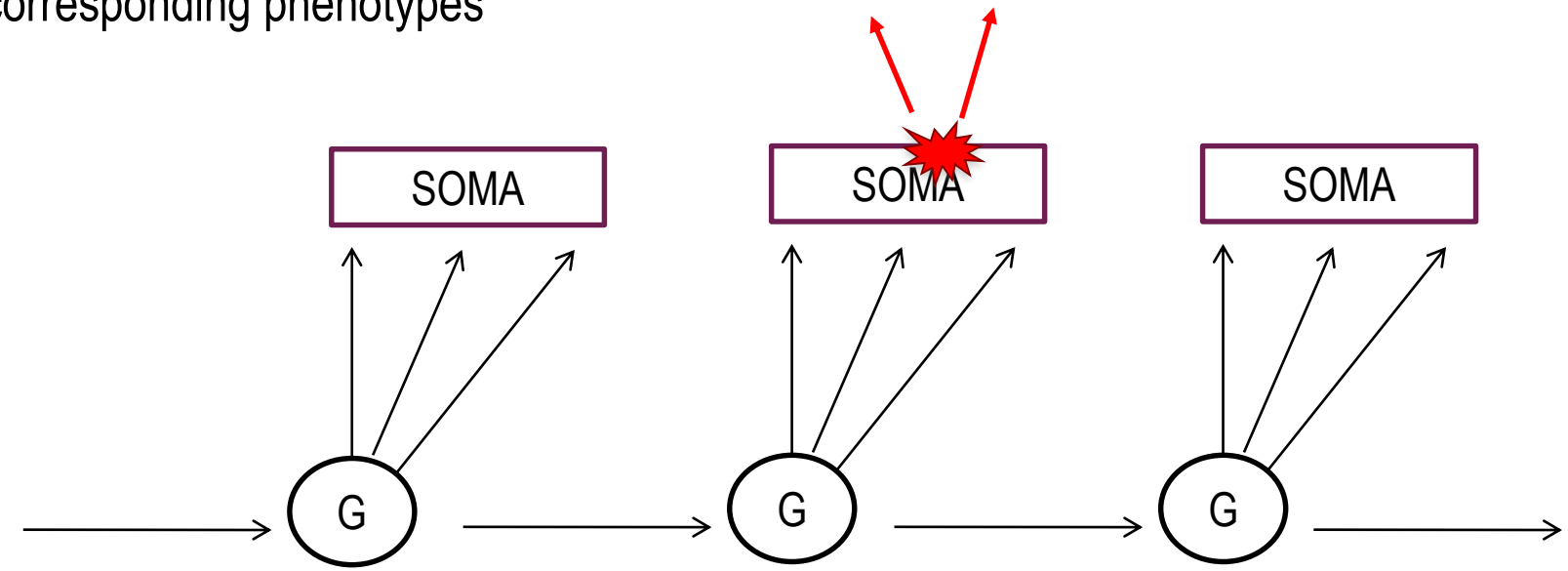
In patients (constitutional DNA = germline DNA):
Cancer risk profiling, from inherited mutations/polymorphisms

Cartoon free of rights, found on Google Images.

GERMLINE AND SOMA

Germline cells produce egg or sperm, so germ line genetic changes can be transmitted to offspring, via a fertilised egg

Somatic cells carry the genetic changes present in the germline and express the corresponding phenotypes

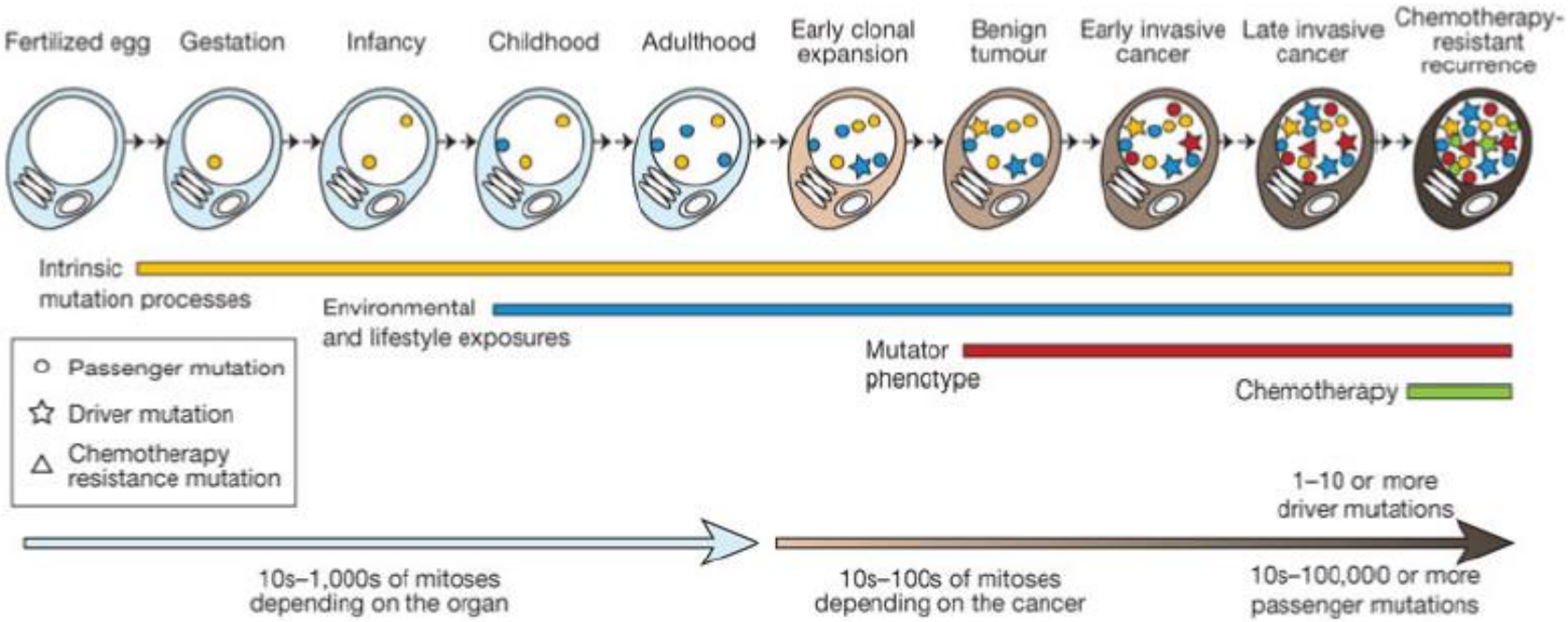


Cartoon by Prof Marc Abramowicz.

THE CONCEPT OF HEREDITARY CANCER

In **sporadic** cancer, (epi)genetic changes are somatic only

Most cancers



In **hereditary** cancer, a genetic mutation is present in the fertilized egg, and all subsequent cells

Small minority of cancers

HEREDITARY *VERSUS* 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*

*Knudson AG, PNAS 1971.

THE CONCEPT OF HEREDITARY CANCER

A small fraction of patients are born with a biological predisposition to some cancers, e.g., to:

- Breast and ovarian cancer
- Colon and endometrium cancer
- Multiple Endocrine Neoplasia
- Other types of cancer patterns

The biological predisposition is inherited and can, in turn, be transmitted to offspring

The cause of the predisposition is a genetic change present in the patient's germline and in all of his somatic cells

- Occasional mosaic patients

The germline genetic change is heterozygous (one copy of a gene)
=> autosomal dominant pattern of familial predisposition

HEREDITARY CANCERS ARE A MINORITY

A germline, heterozygous genetic change (one copy of a gene) with (almost) dominant inheritance is found in:

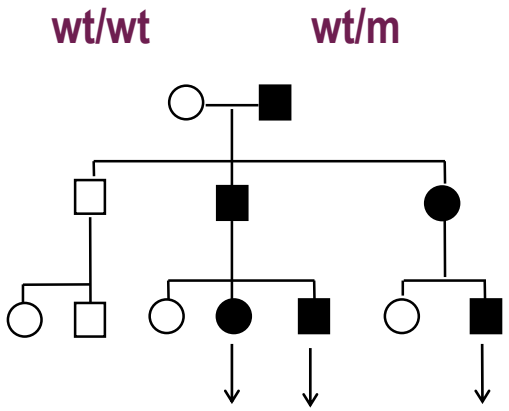
- 5% of colorectal cancers
- 5-10% of breast cancers
- 20% ovarian cancers (epithelial carcinomas)*

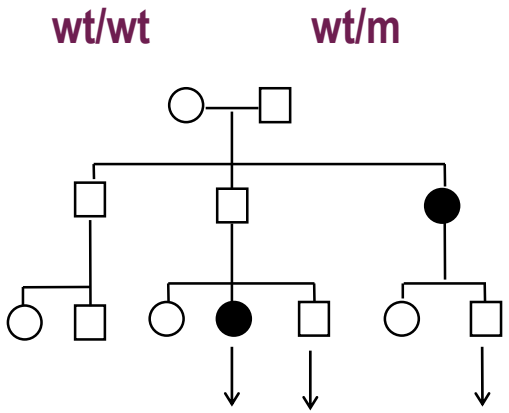
*Hennessy BT, *et al.* J Clin Oncol 2012; Alsop K, *et al.* J Clin Oncol 2012; 30(21): 2654-63.

MENDELIAN AUTOSOMAL DOMINANT INHERITANCE

Autosomal dominant (AD) phenotype

AD phenotype with female-restricted expression





Each offspring of a mutation carrier has a 50% chance of inheriting the mutation

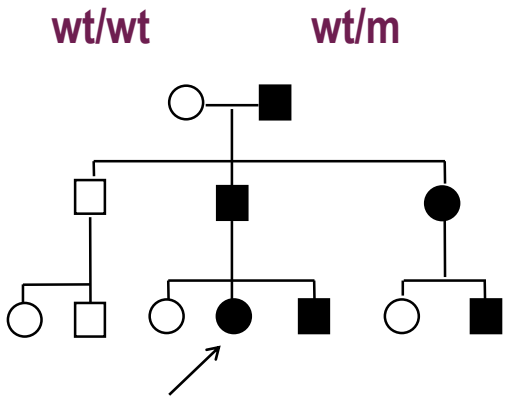
wt, wild-type allele; m, allele with genetic variant (mutation).

Cartoons by Prof Marc Abramowicz.

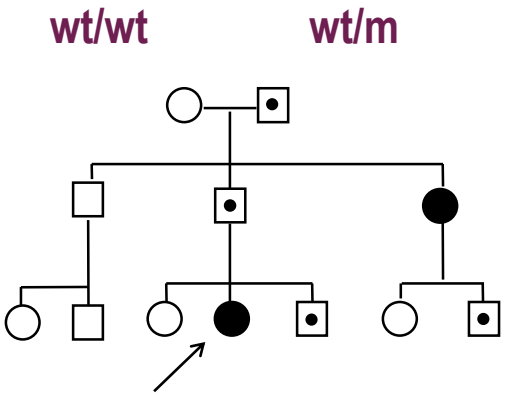
ASYMPTOMATIC CARRIERS OF A MUTATION

Autosomal dominant (AD) phenotype

AD phenotype with female-restricted expression



Arrow indicates proband
= propositus = index case
= individual by whom family comes to medical attention



- Dot indicates mutation in unaffected carrier

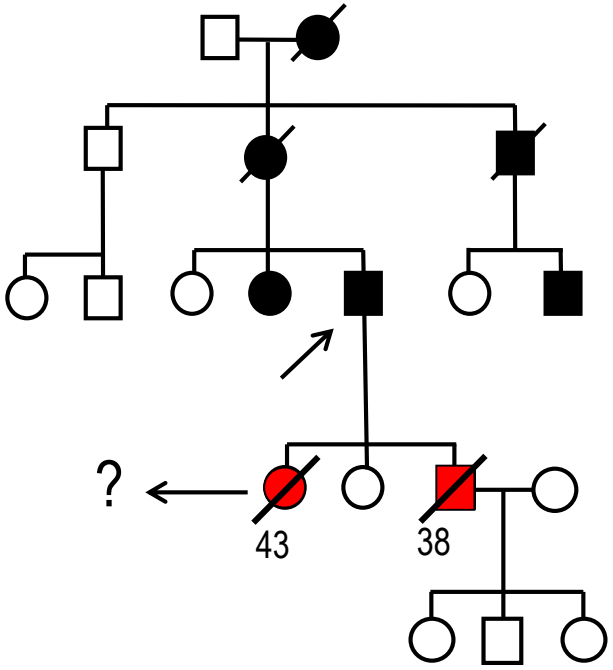
All carriers, males like females, may transmit mutation

Each offspring of carrier has a 50% chance of inheriting mutation

wt, wild-type allele; m, allele with genetic variant (mutation).

Cartoons by Prof Marc Abramowicz.

HEREDITARY COLORECTAL CANCER



Median age at diagnosis = 42 years
(*vs*. 67 years in general population)

3-5% of all CRC

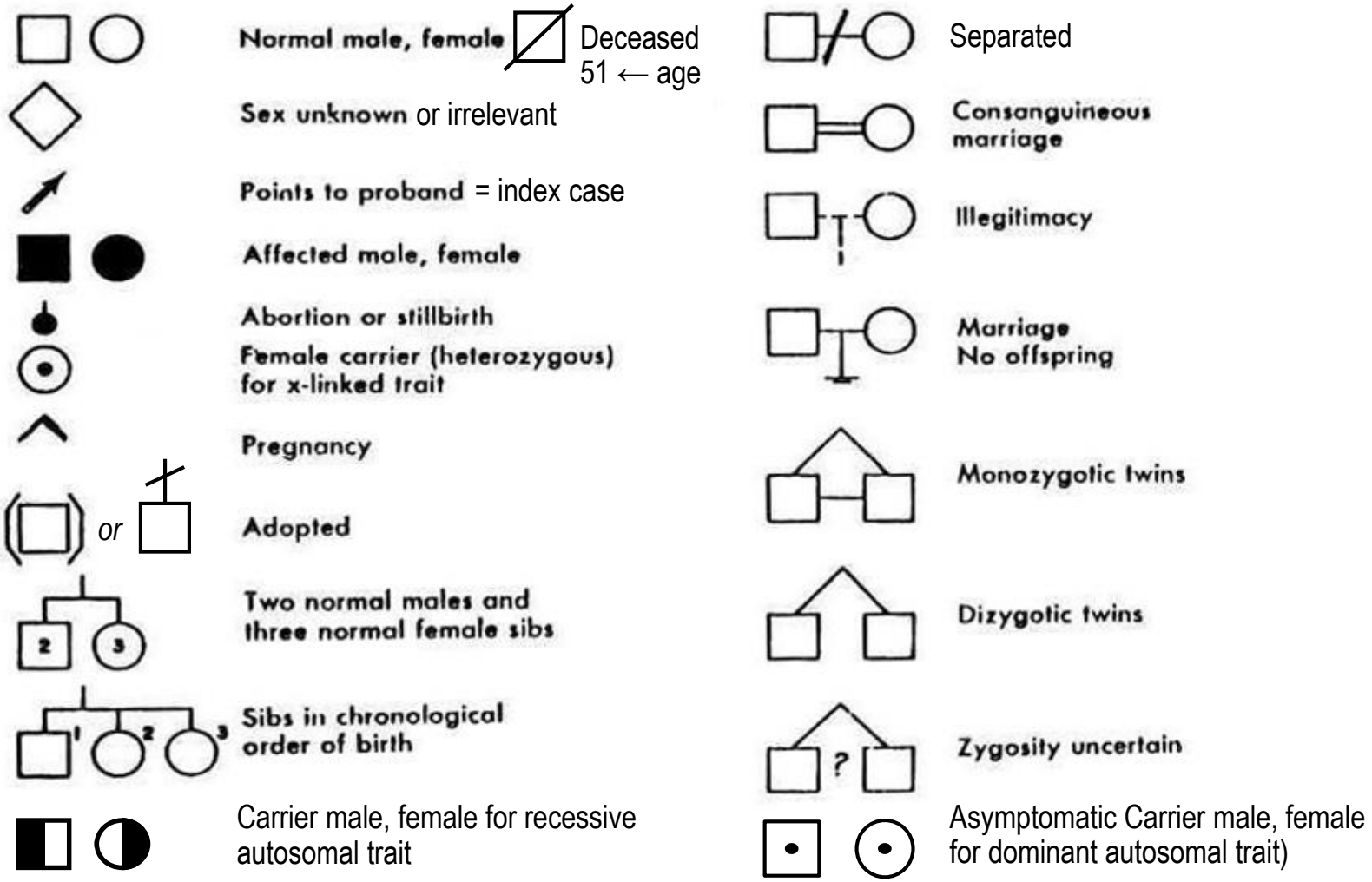
- HNPCC (4%)
- FAP (1%)

GENETIC CONSULT:

- Counsel affected patients
- Identify familial mutation in affected patient e.g., in father (arrow)
- Genetic counselling in children

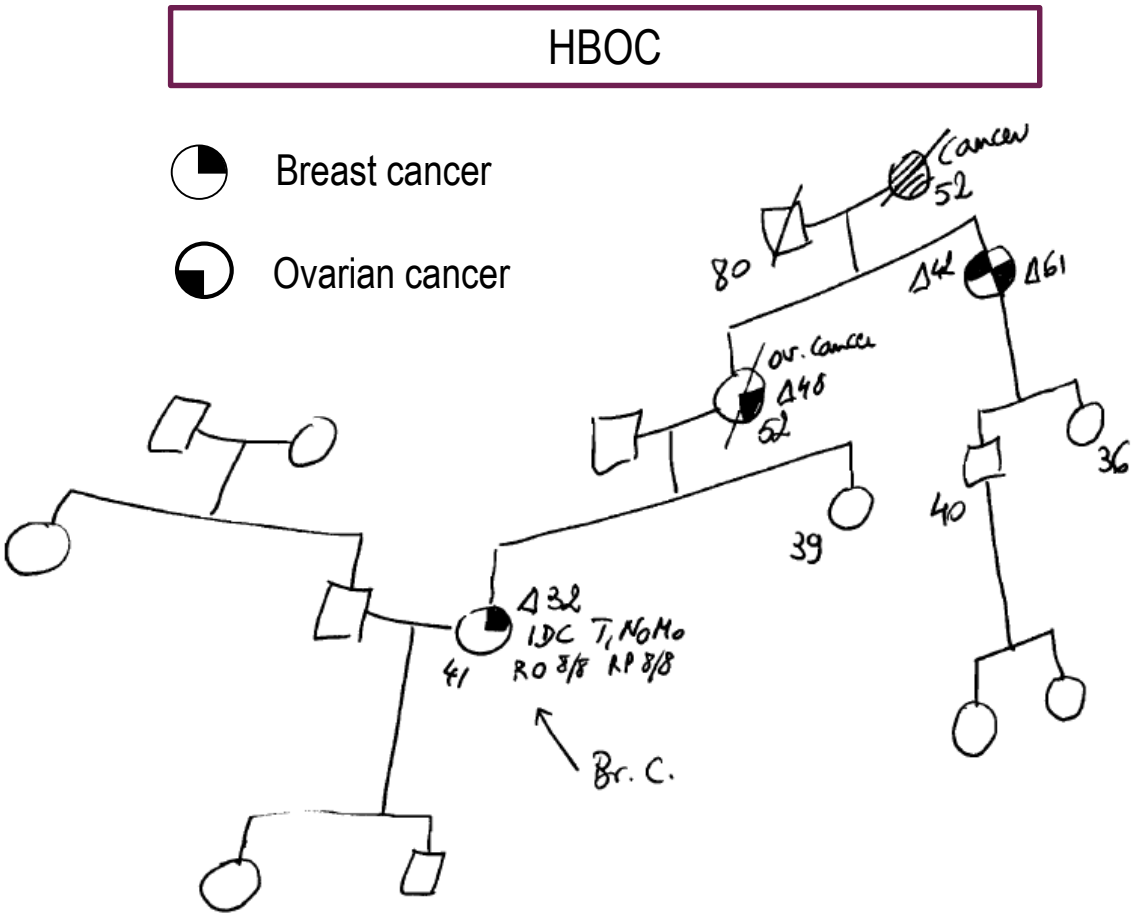
Cartoons by Prof Marc Abramowicz.

PEDIGREE: SYMBOLS USED



Cartoon from some old paperback edition of The Metabolic and Molecular Bases of Inherited Disease + addition by Prof Marc Abramowicz.

CLINICAL PEDIGREE



Cartoon by Prof Marc Abramowicz.

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME (HBOC)

HBOC is a hereditary cancer predisposition syndrome

- With high relative risks of breast cancer and/or ovarian cancer
- And/or some other cancer types, including melanoma, pancreatic cancer, and prostate cancer[1]

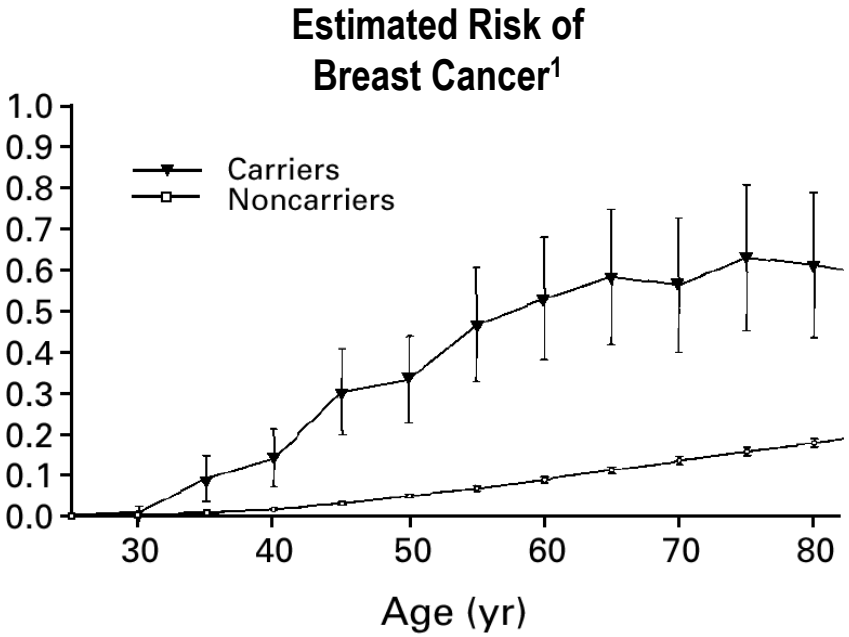
Most families with HBOC are linked to either the BRCA1 or the BRCA2 gene[2]

Penetrance is age- and gender-related

- Penetrance = proportion of mutation carriers who develop disease

1. Paluch-Shimon S, *et al.* Ann Oncol 2016; Lecarpentier J, *et al.* J Clin Oncol 2017; Shindo K, *et al.* J Clin Oncol 2017.
2. Ford D, *et al.* Am.J. Hum. Genet.1998; Couch FJ, *et al.* Science 2014.

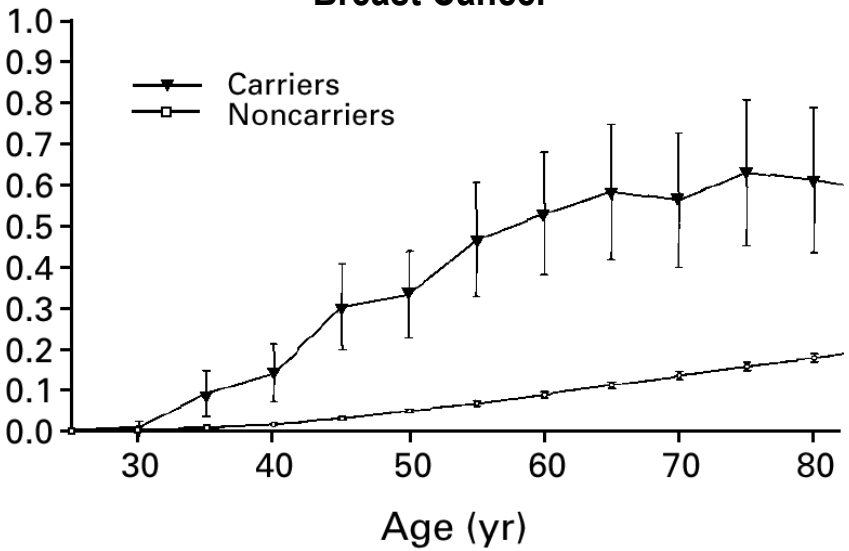
PENETRANCE OF THE BRCA GENE DEFECT



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..

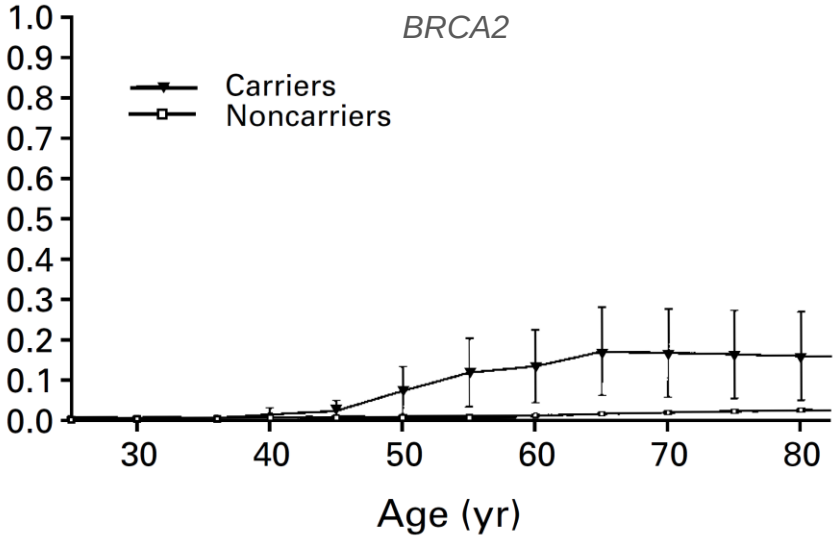
PENETRANCE OF THE BRCA GENE DEFECT

Estimated Risk of Breast Cancer[1]



Estimated Risk of Ovarian Cancer[1]

BRCA2



Breast cancer in BRCA1 carrier:

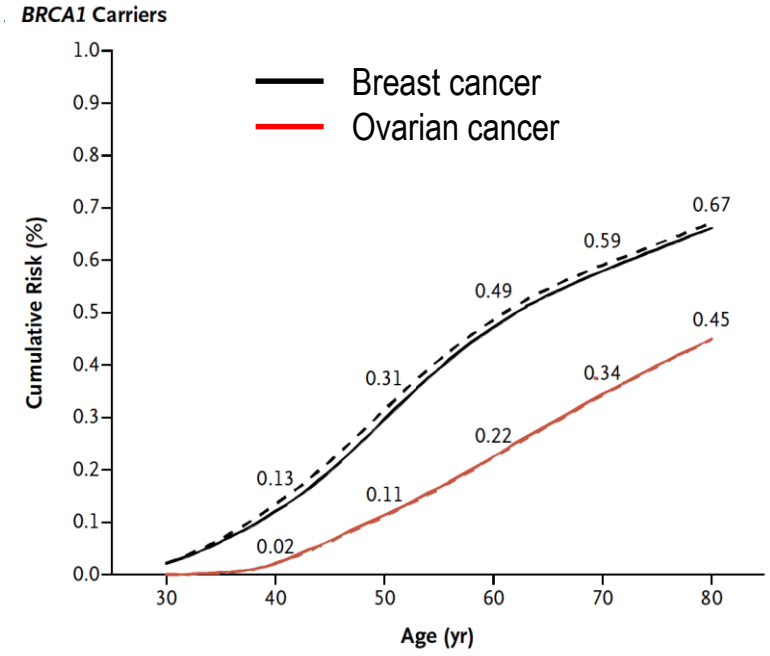
- ✓Typically triple negative (TNBC)[2]
- ✓2-3 recurrence /100 women/year
- ✓Shorter interval if earlier onset[3]

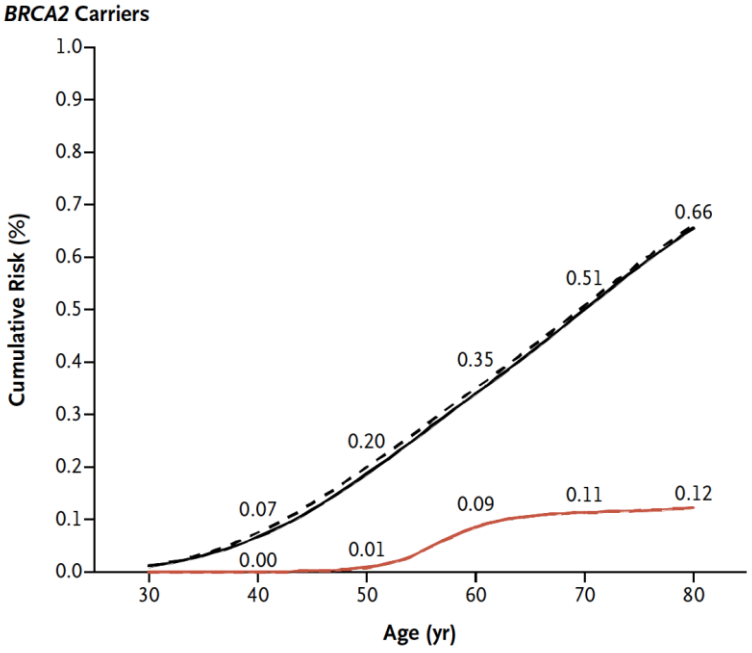
Ovarian cancer in BRCA1/2 carrier:

- ✓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.

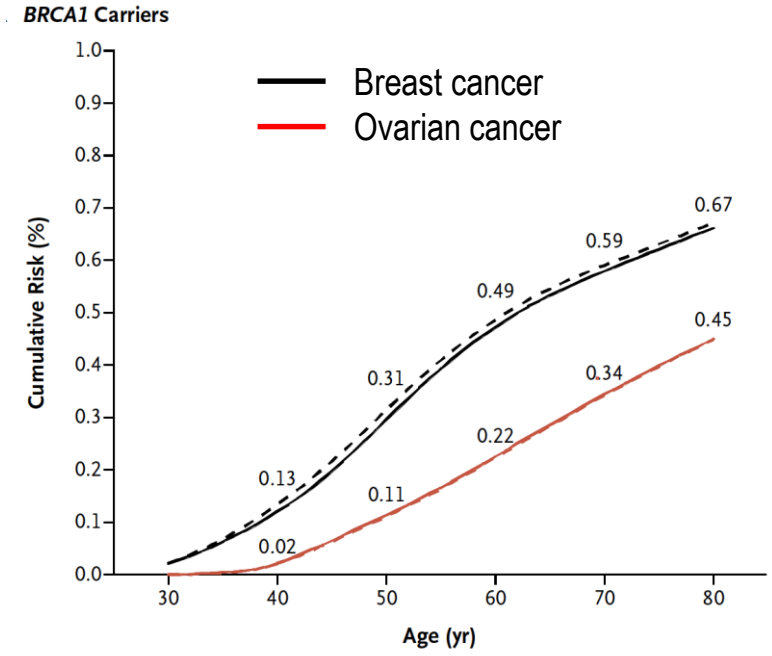
HBOC CUMULATIVE RISKS

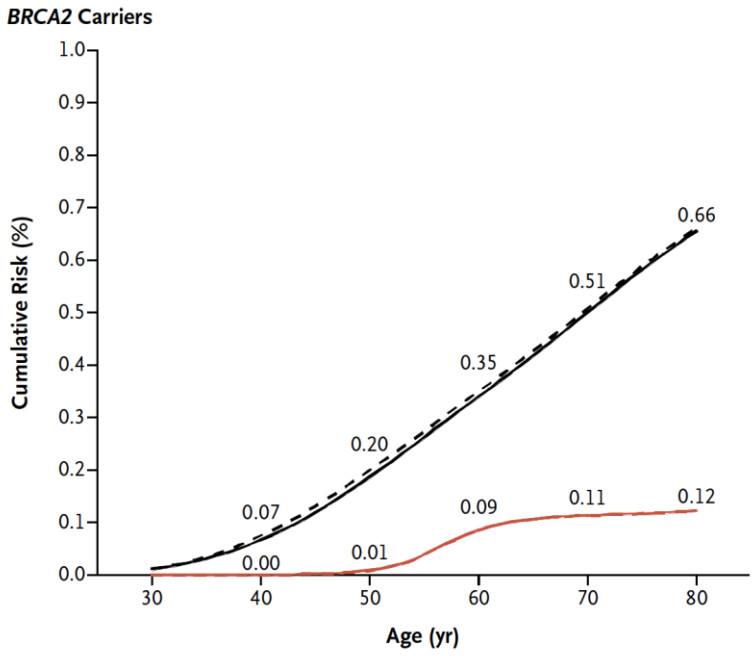




From N Engl J Med, Hartmann LC, Lindor NM, The Role of Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer, 374, 454-68.

HBOC RESIDUAL RISKS





Risk at age 2 if asymptomatic at age 1

- R (2) – R (1)
- 1 – R (1)

Ex: residual ovarian risk in BRCA1 if asymptomatic at age 60:

= (0.45-0.22)/(1-0.22) = 0.295

From N Engl J Med, Hartmann LC, Lindor NM, The Role of Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer, 374, 454-68.

LYNCH SYNDROME (HEREDITARY NON-POLYPOSIS CRC, HNPCC)

Lynch syndrome is a hereditary cancer predisposition syndrome

- With high relative risks of colon cancer and/or endometrium cancer and/or ovarian cancer
- And/or some other cancer types, including small bowel, biliary tree, ureter and renal pelvis, and brain[1]

Lynch syndrome = Hereditary Non Polyposis Colorectal Cancer (HNPCC)

Most families with Lynch syndrome are linked to one of the genes encoding the protein subunits of the DNA mismatch repair (MMR) complex, MLH1, MSH2, MSH6 and PMS2, or to the EPCAM gene[2]

Tumours tend to present microsatellite instability (MSI)

Penetrance is age- and gender-related

- Penetrance = proportion of mutation carriers who develop disease

1. Lynch H & de la Chapelle A, J Med Genet 1999; Balmaña J, *et al.* Ann Oncol 2013;
2. Palomaki GE, *et al.* Genet Med 2009; Balmaña J, *et al.* Ann Oncol 2013; Yulderun *et al.* J Clin Oncol 2015.

LYNCH SYNDROME: INCOMPLETE PENETRANCE…

…Of colorectal cancer[2]

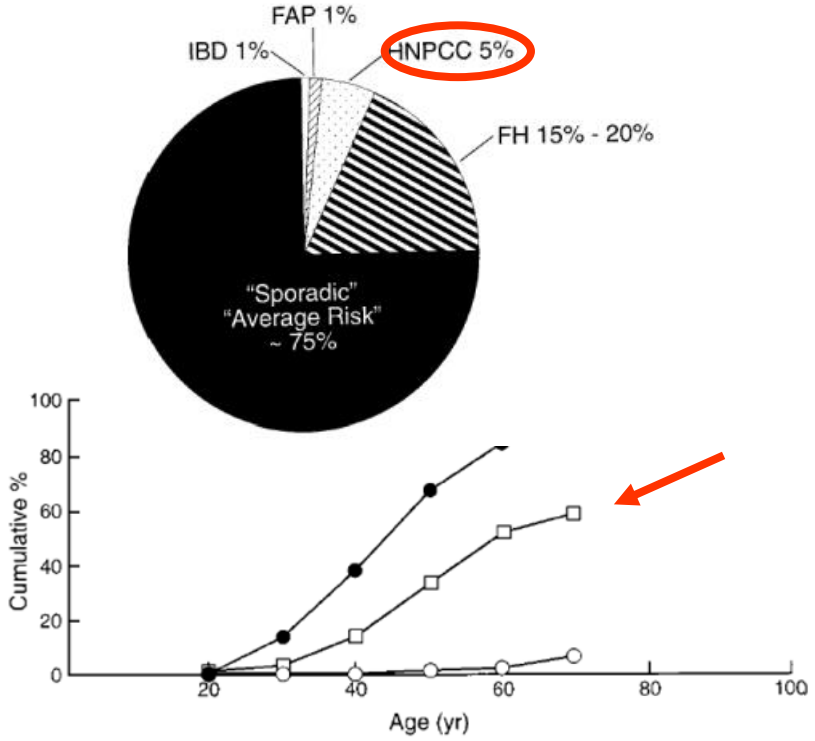
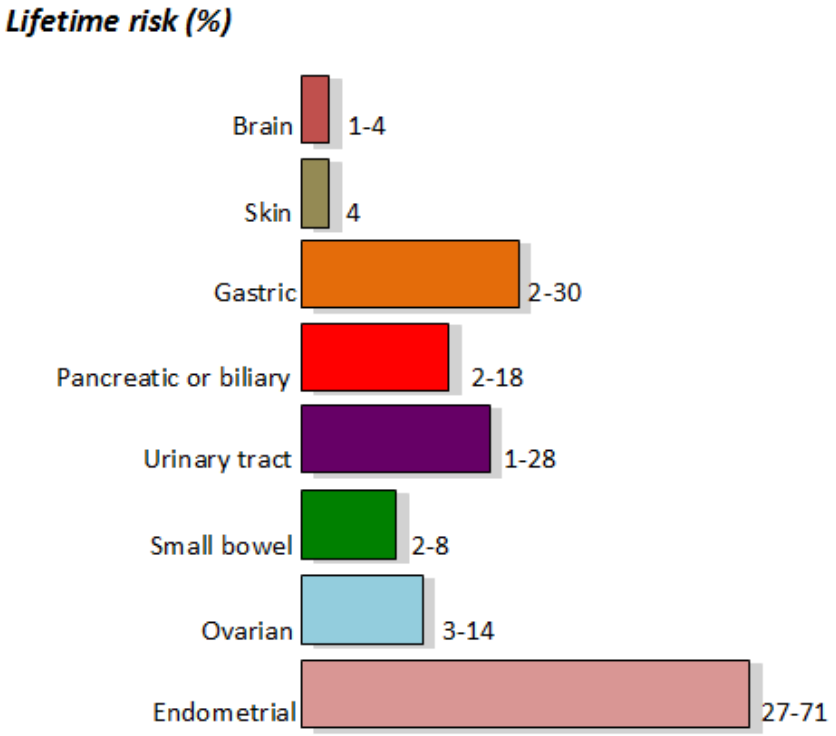


Figure 12. Cumulative incidence of CRC by age in subjects with genetic syndromes compared with the general population. ●, FAP; □, HNPCC; ○, general population.

…Of extra-colonic cancers[3]



1. Harkness EF, *et al.* 2015 J Med Genet and references therein; 2. Reprinted from Gastroenterology, 112(2), Winaver SJ, *et al.* , Colorectal Cancer Screening: Clinical Guidelines and Rationale, 594-642. Copyright 1997, with permission from Elsevier; 3. Durato F, *et al.,* 2013. Synergistic Effects of Low-Risk Variant Alleles in Cancer Predisposition, Carcinogenesis, Dr. Kathryn Tonissen (Ed.), InTech, DOI: 10.5772/55417. Available from: http://www.intechopen.com/books/carcinogenesis/synergistic-effects-of-low-risk-variant-alleles-in-cancer-predisposition. Available under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0),

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)

GENETIC HETEROGENEITY

Heterogeneity of loci

- BRCA1, BRCA2, CDH1, TP53, or other genes in HBOC
- MLH1, MSH2, MSH6, PMS2, or other genes in HNPCC

Heterogeneity of alleles

- 2 families with BRCA1- linked HBOC usually have 2 different mutations of BRCA1
- Same for BRCA2
- Same for every gene in Lynch
- …

Therefore, every new family needs full analysis of appropriate genes at least once, in proband

Caveat: all alleles do not have same penetrance*

*Easton DF, *et al.* NEJM 2015.

MULTIPLE GENES: 2 MODELS

Genetic heterogeneity

Various genes cause the same phenotype independently in various family

- BRCA1 or BRCA2 cause HBOC
- MLH1, MSH2, MSH6… cause HNPCC

Phenotype is **monogenic** (Mendelian inheritance) in each family

Multigenic inheritance

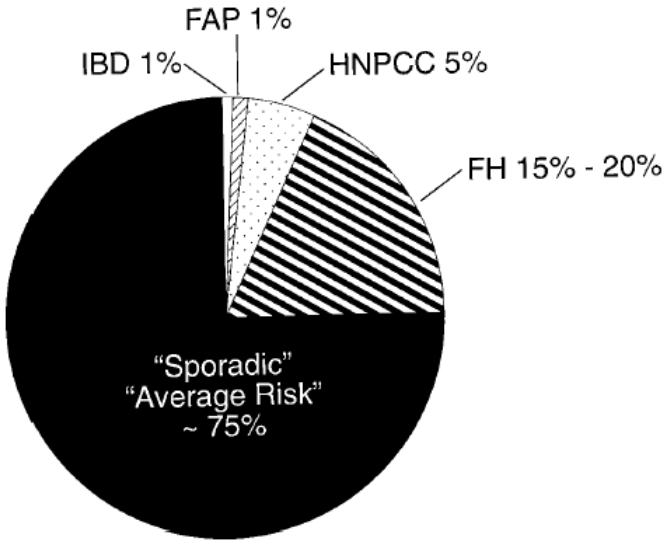
Several genes together cause one phenotype is a single patient

- Many genes in type 2 diabetes
- Many genes in mild familial predisposition to cancer

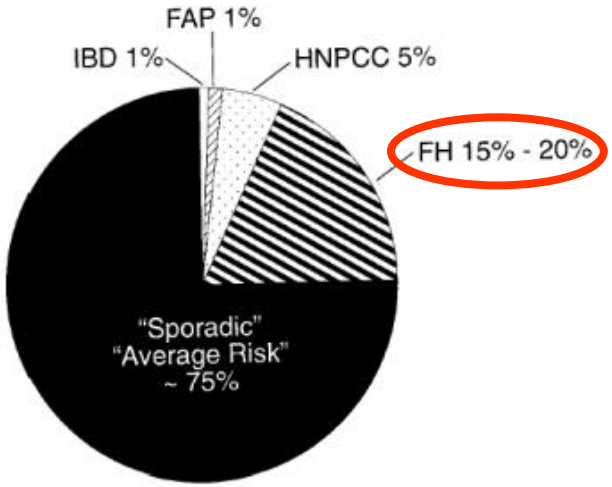
Phenotype has complex inheritance, **not monogenic**

GERMLINE SUSCEPTIBILITY

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



FAMILIAL COLORECTAL CANCER



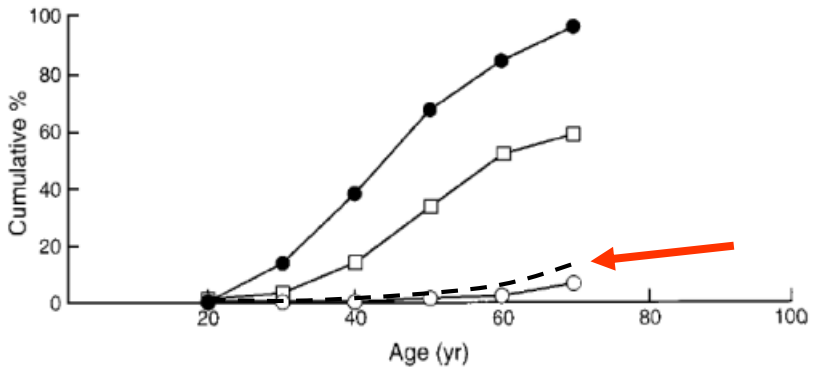


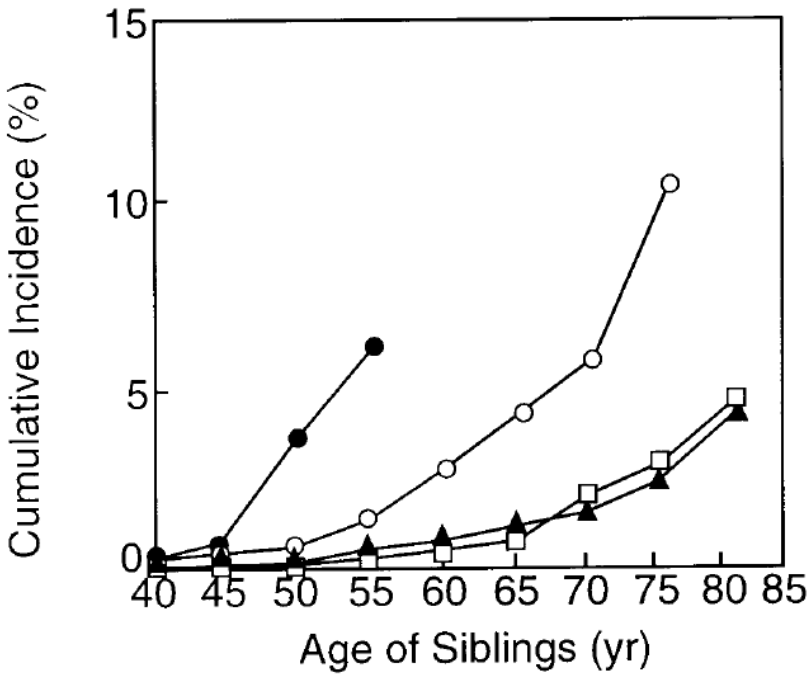
Figure 12. Cumulative incidence of CRC by age in subjects with genetic syndromes compared with the general population. ●, FAP; □, HNPCC; ○, general population.

Familial but not hereditary:

- ✓No polyposis
- ✓Amsterdam negative
- ✓Bethesda negative
- ✓No other hint for hereditary syndrome

FAMILIAL, NON HEREDITARY, COLORECTAL CANCER

Cumulative incidence of CRC in siblings of patients with adenomas



Several genes / polymorphisms

Low penetrance, each currently known only partially

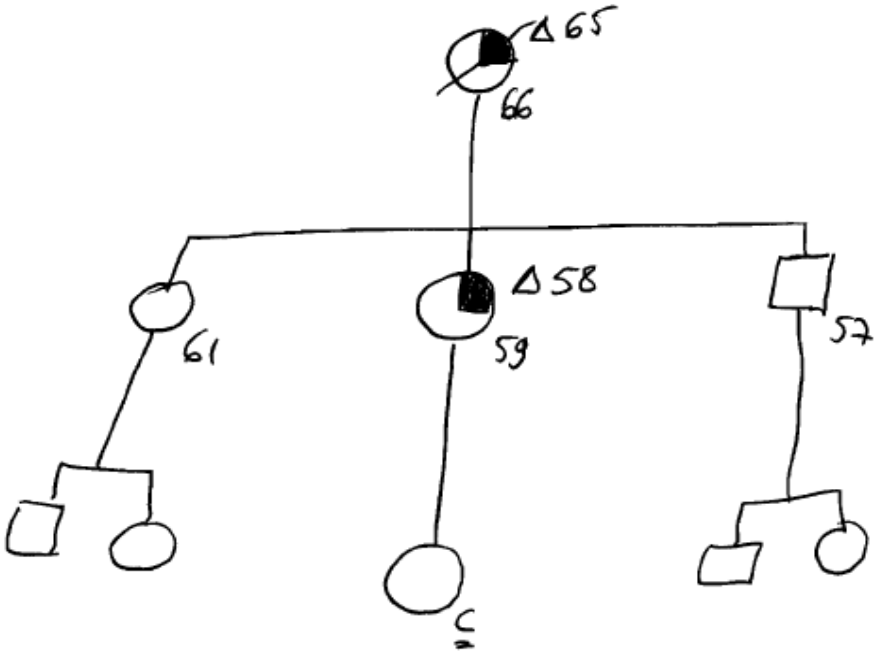
1. St John DJ, *et al.* Ann Intern Med. 1993; 2. Reprinted from Gastroenterology, 112(2), Winaver SJ, *et al.* , Colorectal Cancer Screening: Clinical Guidelines and Rationale, 594-642. Copyright 1997, with permission from Elsevier.

FAMILIAL, NON HEREDITARY, BREAST CANCER

Either chance coincidence

or modest multigenic risk

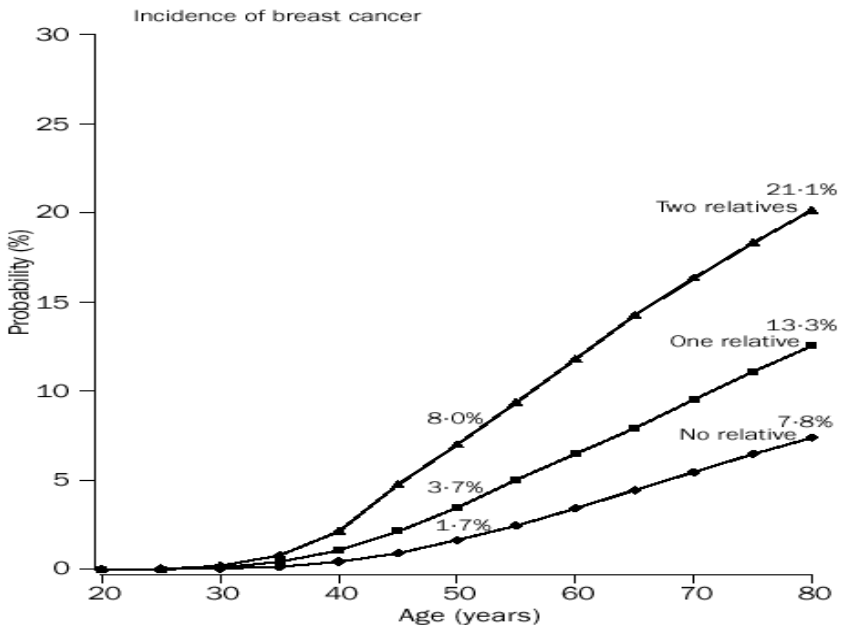
- Many low-penetrance alleles
- **No comprehensive, validated, useful DNA test available**

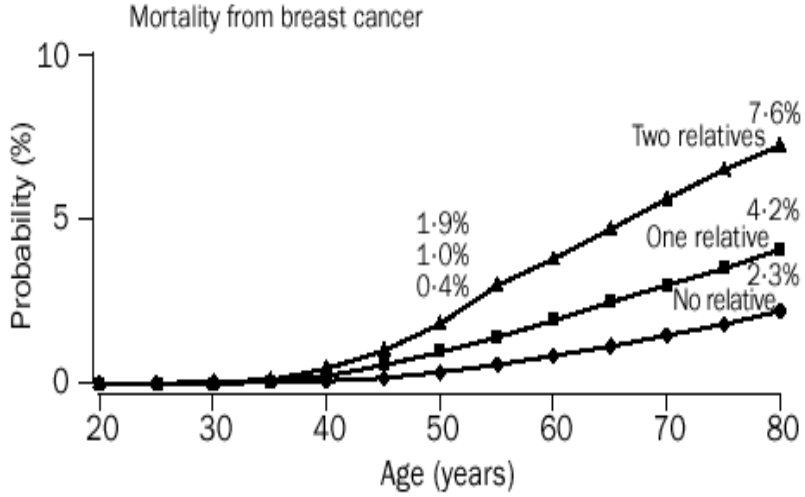


Cartoon by Prof Marc Abramowicz.

FAMILIAL BREAST CANCER

- Most women with breast cancer have no affected relative; most women with affected relatives will not develop BC
- If cancer, not at young age. Age of relative at diagnosis has little effect. 58,209 cases + 101,986 controls





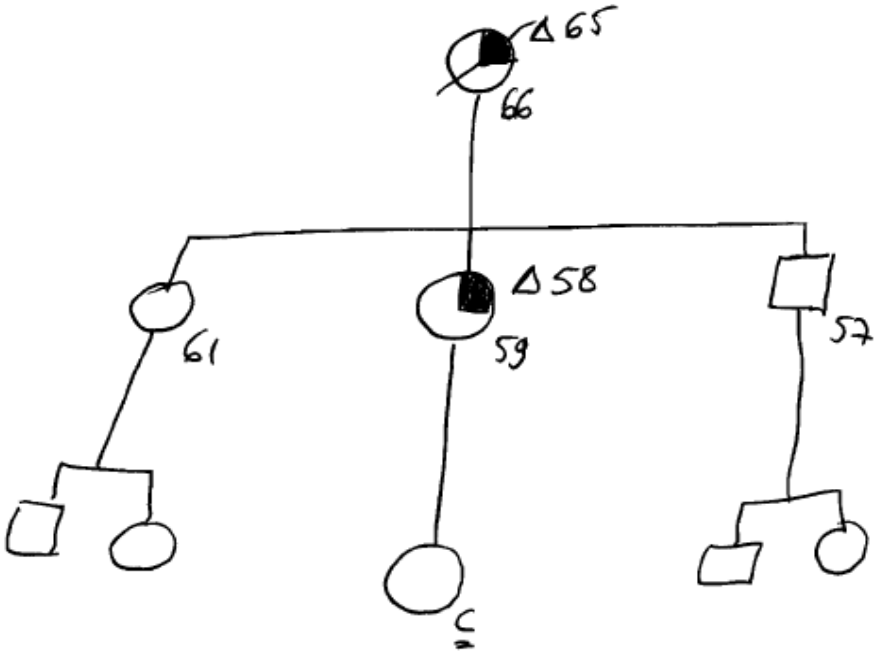
FAMILIAL, NON HEREDITARY, BREAST CANCER

Either chance coincidence

or modest multigenic risk

- Many low-penetrance alleles
- **No comprehensive, validated, useful DNA test available**

Empirical risk in consultant (20% lifelong for breast cancer)



GENETIC TESTING

For monogenic (Mendelian) inheritance of cancer risk

- Includes autosomal dominant with reduced penetrance
  = near-Mendelian
- Excludes multigenic, non-Mendelian inheritance

In affected cancer patients with suspected Mendelian risk

- Panel testing of multiple cancer genes (Next Generation Sequencing)

In unaffected at-risk relative (presymptomatic genetic testing)

- Focused analysis of the mutation previously identified in affected relative

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

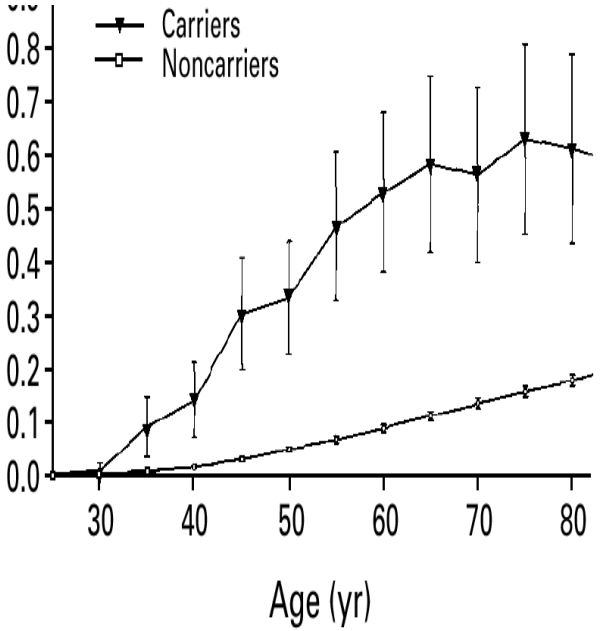
- Protein-truncating mutation, and/or
- Already reported in other patients
  - In-house data
  - Publically available databases, e.g. ClinVar-NCBI (https://www.ncbi.nlm.nih.gov/clinvar/)

Periodically re-assess VUS for reclassification as benign (most) or disease-causing (few) in large databases

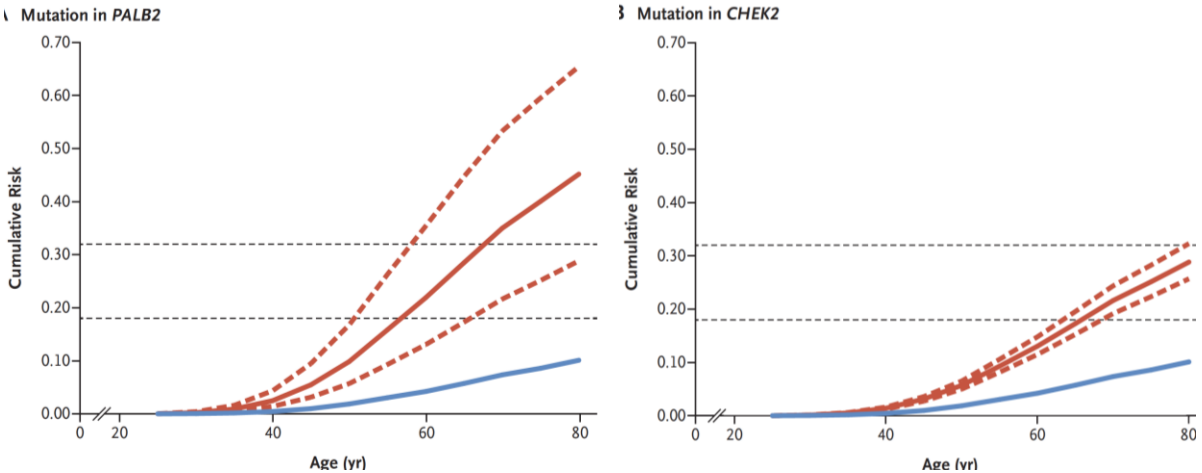
- And recall patients to the clinic for update if disease-causing

CLINICAL UTILITY DEPENDS ON ALLELE PENETRANCE

BRCA2 [1]



Risk of BC for a Carrier of a Deleterious Mutation in *PALB2* and for a Deleterious Mutation in *CHEK2* [2]



If mutation explains risk only partially, caveat:

- Undue alarm in mutation carrier
- False reassurance in non-carrier

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. From N Engl J Med, Easton DF, *et al.,* Gene-Panel Sequencing and the Prediction of Breast-Cancer Risk 372, 2243–57. Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

WHAT IS SPECIAL ABOUT GENETIC TESTS ?

Unchanged, throughout life. Before birth.

Abnormality is present before symptoms start

Mutations are familial; can be traced in relatives

DNA is very stable. Can be analysed on stored material, pre-or post-mortem

=> Not performed in every patient with breast or ovarian cancer

=> Perform only in the frame of genetic counselling*

*ASCO 2010; NCCN 2018.

INDICATIONS FOR GENETIC TESTING

In symptomatic cancer patients

Do not test all patients with cancer (ASCO 2010; NCCN 2018)

- Or should we ?
- Prepare for incidental detection of germline, familial mutations in tumour DNA (somatic mutations)

Test patients with some increased likelihood of inherited mutation

- Plausibility of mutation threshold considered for testing has decreased over years: 10% >5 % >?
- National Comprehensive Cancer Network (NCCN) guidelines, 2018
  - http://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf.
- American College of Medical Genetics and Genomics and the National Society of Genetic Counsellors: Hampel H, *et al.* Genet Med 2015.

RISK ASSESSMENT MODELS

Computerised algorithms

Breast Cancer Risk Assessment Tool (BCRAT) (Gail model)

BRCAPRO

IBIS

BOADICEA

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

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

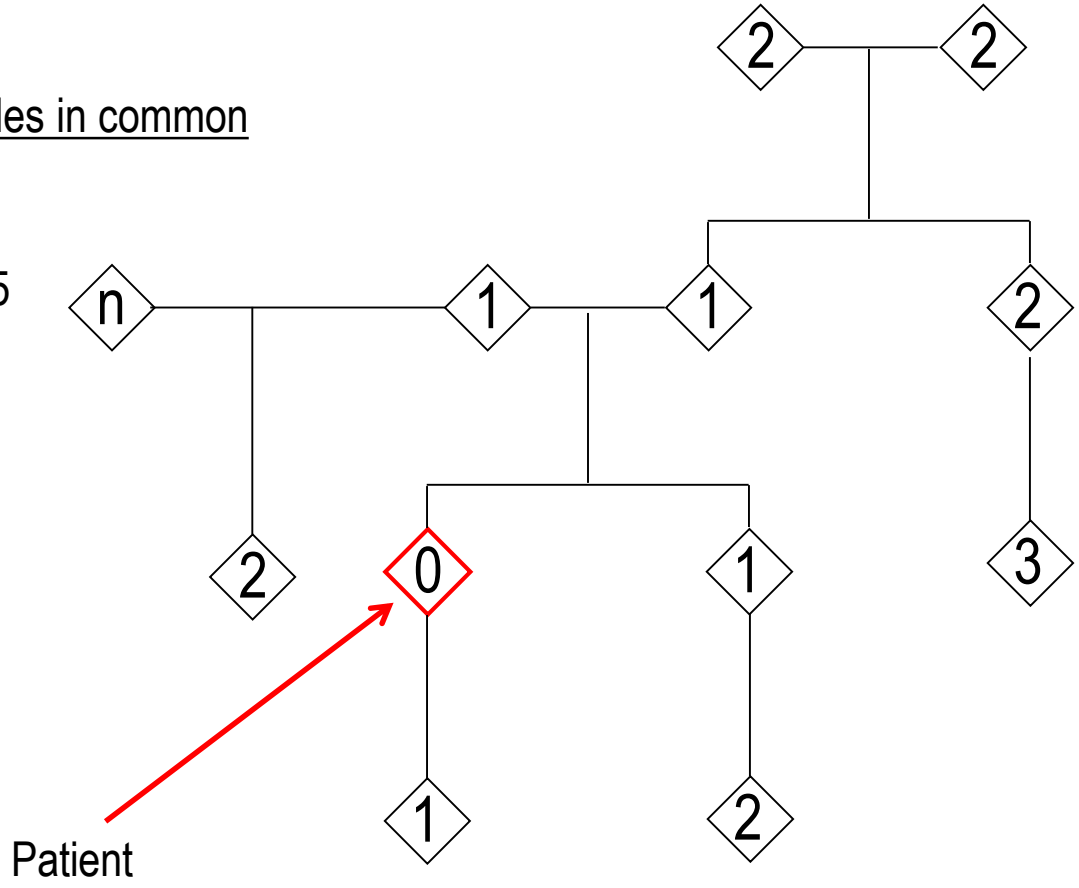
Other, more inclusive criteria

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

ESMO

DEGREES OF RELATIONSHIP

d° of relationship	alleles in common
1 = first degree r.	.50
2 = second degree r.	.25
3 = third degree r.	.125



CANCER PATIENT TRAJECTORY WITH GENETIC COUNSELLING (GC)

Suspected hered c.	**Pre-test GC**	Genetic Test	**Post-test GC**
Personal history	Family tree	Blood sample	Give results + interpretation
Family history	Inform patient about outcomes of genetic test	DNA analysis	Family issues
	Consent signed		Psychological support

Cartoon found free of rights, on Google images.

GENETIC COUNSELLING: WHAT IS IT?

Genetic counselling is a **communication process** which deals with the human problems associated with the **occurrence or risk of occurrence** of a genetic disorder in a family.

This process involves an attempt by one or more appropriately **trained person** to help the individual or family to: (1) **comprehend the medical facts** including the diagnosis, probable course of the disorder, and the available management, (2) appreciate the **way heredity contributes to the disorder and the risk of recurrence** in specified relatives, (3) understand the alternatives for dealing with the risk of recurrence, (4) **choose a course of action** which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision, and (5) to make the **best possible adjustment** to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

American Society of Human Genetics, 1975.

PRE-TEST GENETIC COUNSELLING IN SYMPTOMATIC PATIENT

Inform and empower the patient who already has cancer about the following:

Estimate genetic risk (likelihood that mutation is present)

Options for genetic testing, and implications of testing :

If test shows mutation, what difference does it make regarding my condition?

- Risk of new primary tumour, e.g. ovarian
- Preventive options, e.g. risk-reducing salpingo-oophorectomy
- Therapeutic perspectives, e.g., PARP1 inhibitor drugs

If test shows mutation, what difference does it make regarding my family?

- Risk of inheriting mutation (50% in FDRs, both sexes (!))
- Penetrance of various aspects of the syndrome, if mutation present.

YOUNG NULLIPAROUS WOMEN WITH BREAST CANCER

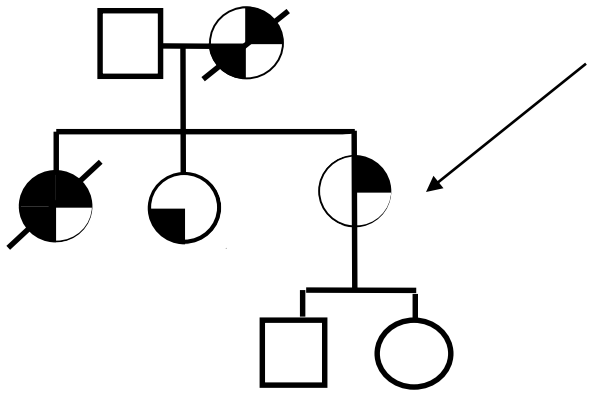
32 y/o G0P0, invasive ductal carcinoma, ER 8/8 PR 8/8 Neu –

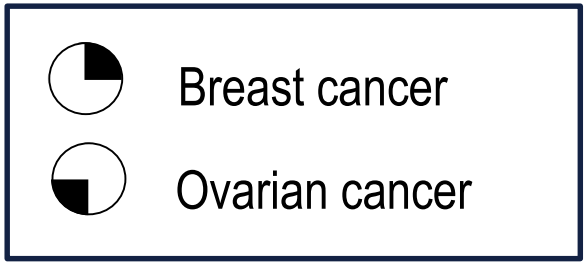
- => If BRCA mutation carrier:
  - Increased risk of 2nd primary tumour
  - Increased risk of ovarian cancer
- => Chances for pregnancy are further reduced

32 y/o G0P0, invasive ductal carcinoma, TNBC

- => If BRCA1 mutation carrier:
- Increased risk of 2nd primary tumour
  - 2nd TNBC with short interval (Graeser MK, *et al.* JCO 2009)
- Increased risk of ovarian cancer
- => Chances for pregnancy are further reduced

MUTATION NOT FOUND, HIGH A PRIORI PLAUSIBILITY OF HBOC





Expected mutation, not found

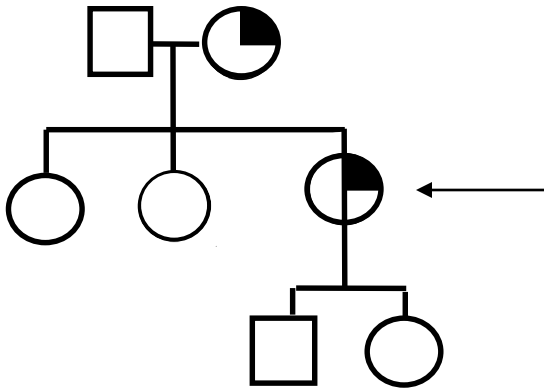
- False negative result of BRCA analysis?
- Phenocopy?
  Phenocopy = phenotype caused by environment, that mimics the genetic condition.
  Sporadic breast cancer, expected by chance in 10% women in general population

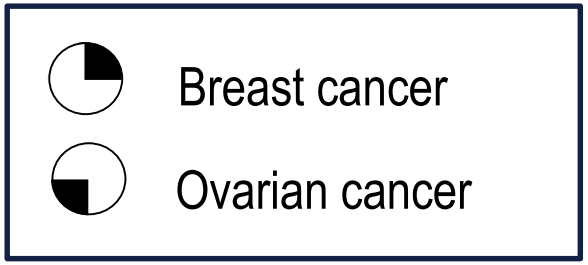
Phenocopy much less likely in ovarian cancer

Sporadic ovarian cancer expected by chance in 1% women in general population

Cartoon by Prof Marc Abramowicz.

MUTATION NOT FOUND, LOW A PRIORI PLAUSIBILITY OF HBOC



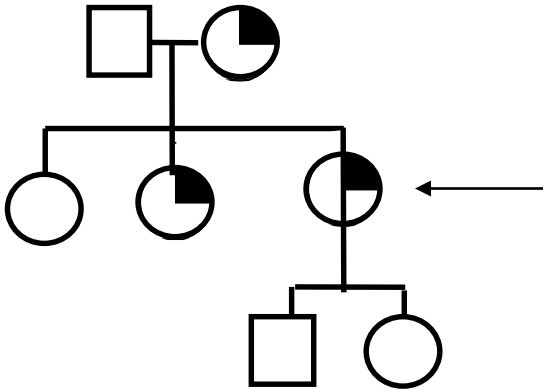


No mutation found

- Probably not HBOC (true negative result) – assume modest, multigenic risk
- False negative of BRCA analysis ?
- Phenocopy ?
  Sporadic breast cancer, expected by chance in 10% women in general population

If phenocopy, no indication for testing remains in this family => stop

MUTATION NOT FOUND, MODEST A PRIORI PLAUSIBILITY OF HBOC



Breast cancer

Ovarian cancer

No mutation found

- Probably not HBOC (true negative result)
- False negative of BRCA analysis ?
- Phenocopy ?
  Sporadic breast cancer, expected by chance in 10% women in general population

Even if proband negative, indication for testing remains in this family
=> test affected sister too

POST-TEST GENETIC COUNSELLING IN SYMPTOMATIC PATIENT – NORMAL RESULT

If gene panel analysis shows no mutation in cancer patient

- Sporadic cancer – somatic mutations only
- Familial predisposition, not hereditary – low penetrance alleles
- Hereditary cancer, highly penetrant mutation missed by test (false negative result)

Confront normal result with family history

- Assume false-negative if FHx highly suggestive of hereditary cancer
  - Ovarian cancers, TNBCs, early onsets,…
  - Right-sided colon cancer with MSI, and endometrial cancers…
- => assume high-risk in 1st degree relatives and reassess in 2 years

- Assume multigenic predisposition in other cases
  - ~Life-long risk x 2 in 1st degree relatives

INDICATIONS FOR GENETIC TESTING ASYMPTOMATIC

At-risk relatives

Presymptomatic genetic testing (PGT)

The best and most reliable approach =

- Find mutation in affected patient in the family
- Then test unaffected, at-risk relative

PRESYMPTOMATIC GENETIC TESTING (PGT)

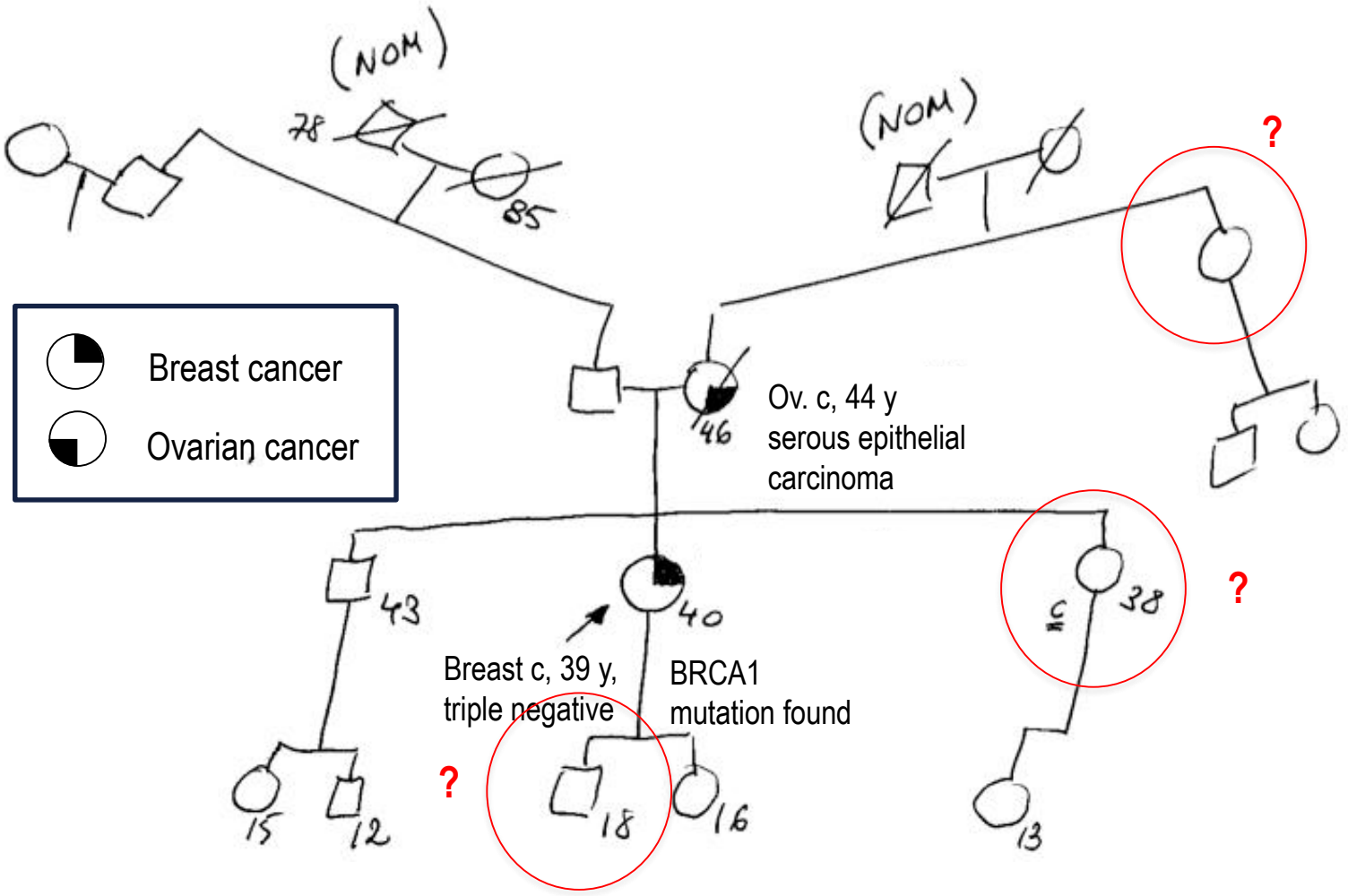
Identify germ-line mutation in affected relative

Test presence/absence of that mutation in unaffected relative = PGT

Cartoon found free of rights, on Google images.

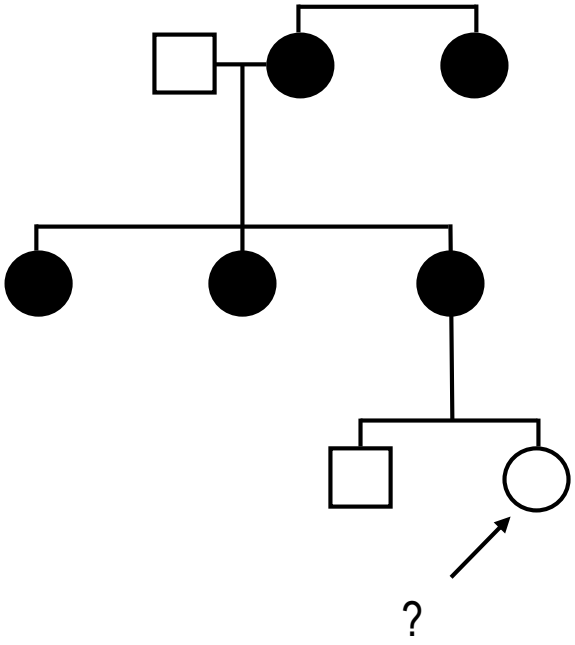
PRESYMPTOMATIC GENETIC TESTING (PGT)

In consultant (c) after age 18 y

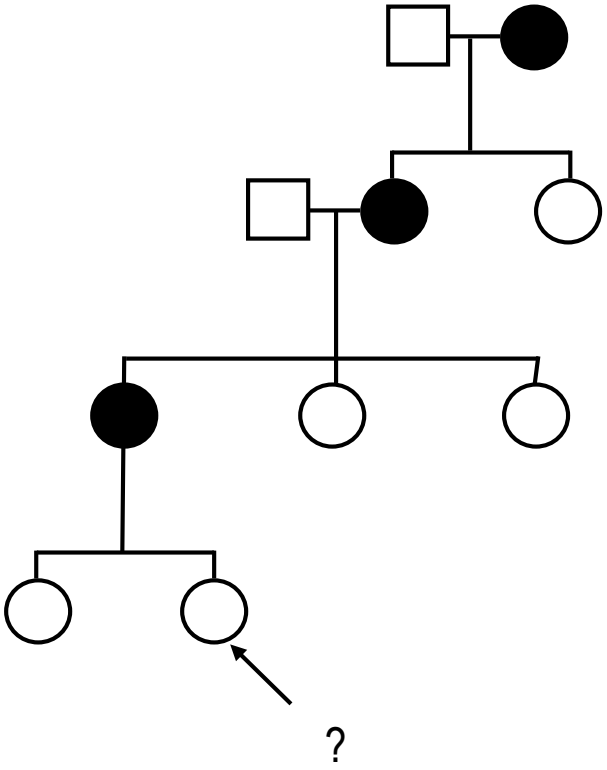


Cartoon by Prof Marc Abramowicz.

SUBJECTIVE RISK



Subj: « all women are affected in our family »



Subj: « only elders are affected in our family »

Cartoon by Prof Marc Abramowicz.

PRESYMPTOMATIC PATIENT TRAJECTORY WITH GENETIC COUNSELLING (GC)

hered c. known in family	**Pre-test GC**	Psychol	Genetic Test	**Post-test GC**
• Causal mutation found in affected relative • Consultant = unaffected adult at-risk relative	• Inform about the syndrome • Inform about outcomes of genetic test • Consent signed	• Coaching • Support	• Blood sample, x 2 • DNA analysis, x 2	• Give results + interpretation • Initiate prevention if possible • Psychology support • Family issues

PRE-TEST GENETIC COUNSELLING IN PRESYMPTOMATIC PATIENT

Inform and empower the adult at-risk relative about the following:

Genetic risk (likelihood that mutation is present) (usually 50%)

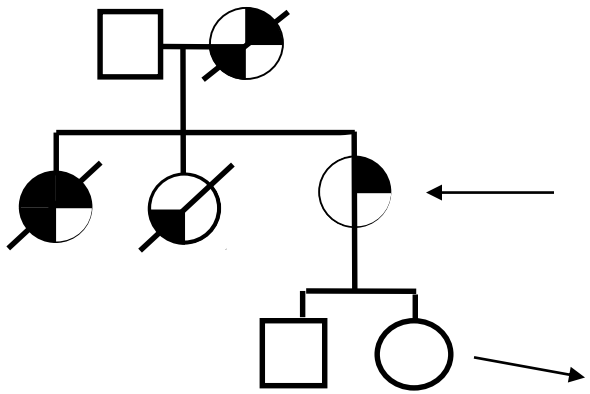
Testing procedure. Importance of psychological coaching

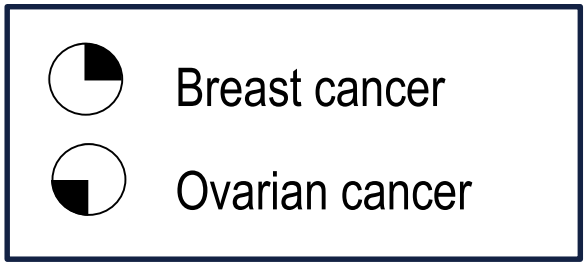
Medical attitude if mutation found to be present

- Penetrance of various aspects of the syndrome
  - Risk of primary tumour, e.g. ovarian; special cases (early onset TNBC)
- Preventive options, e.g. risk-reducing salpingo-oophorectomy (G0P0?)
  - Ovarian tissue preservation, hormonal replacement,…
- Therapeutic perspectives, e.g., PARP1 inhibitor drugs
- Risk in offspring, and primary prevention methods (pregestational, prenatal)

Residual risks if mutation found to be absent

PGT FOR HBOC



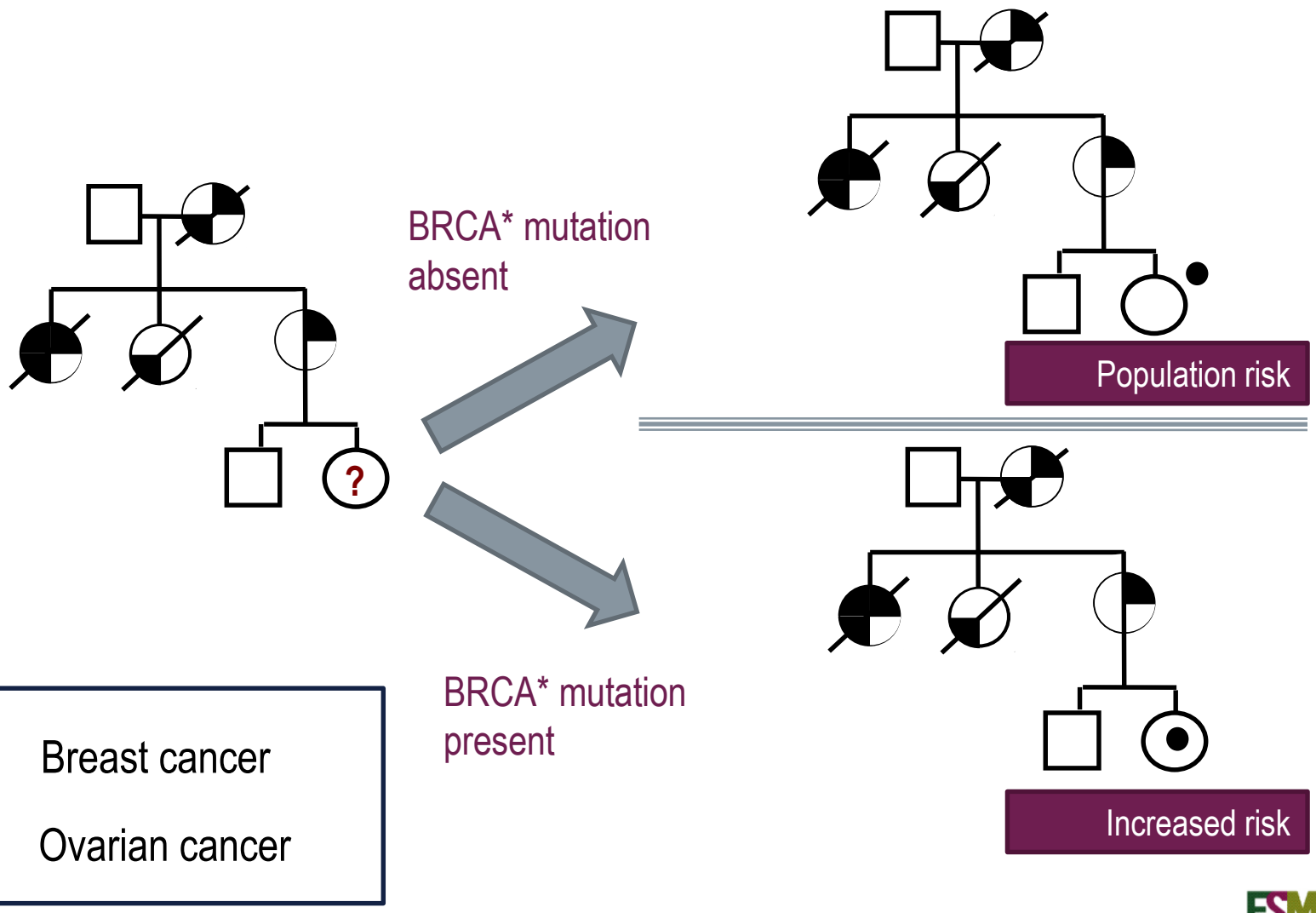


Blood DNA analysis => BRCA* mutation found

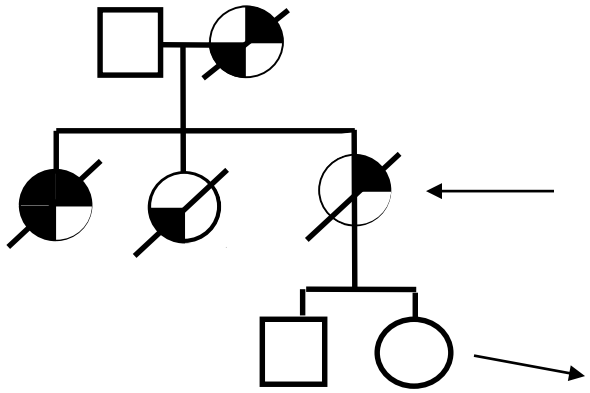
PGT: 5 steps procedure

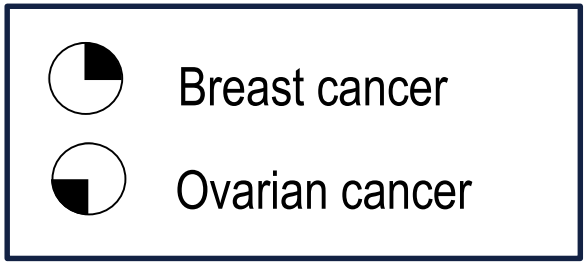
- Pre-test genetic counselling
- Psychological consult / coaching
- DNA analysis for presence/absence of BRCA* mutation
  - Duplicate blood samples
- Post-test genetic counselling:
  tell result, initiate medical attitude if carrier
- Psychological follow-up

OUTCOMES OF PGT FOR HIGHLY PENETRANT MUTATION



PGT WHEN NO TEST PERFORMED PREVIOUSLY IN AFFECTED RELATIVE



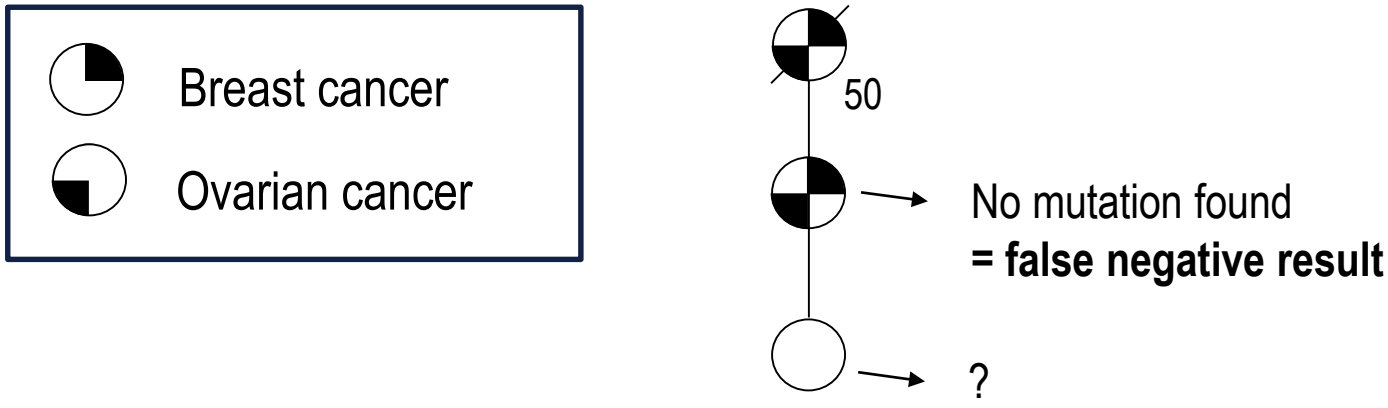


If all affected relatives died without DNA test:

PGT may be performed « blindly » asymptomatic at-risk relative, using full multiple gene panel

- If plausibility of mutation > 10% in her
- After pre-test genetic counselling, including chances for false negative results and VUS
- With psychological coaching/support

NO PGT IF MUTATION TESTED AND NOT IDENTIFIED IN AFFECTED RELATIVE(S)



Mother and grandmother had breast and (epithelial) ovarian cancer <50 years

- Germline mutation very likely present, but undetected by test

Consider daughter is at increased risk until proven otherwise

- Breast surveillance. Preventive mastectomy? Adnexectomy ?

Update genetic test in 2-3 years

PRESYMPTOMATIC PATIENT TRAJECTORY WITH GENETIC COUNSELLING (GC)

hered c. known in family	**Pre-test GC**	Psychol	Genetic Test	**Post-test GC**
• Causal mutation found in affected relative • Consultant = unaffected adult at-risk relative	• Inform about the syndrome • Inform about outcomes of genetic test • Consent signed	• Coaching • Support	• Blood sample, x 2 • DNA analysis, x 2	• Give results + interpretation • Initiate prevention if possible • Psychological support • Family issues

PGT POST-TEST GENETIC COUNSELLING – ABNORMAL RESULT

Convey test result to consultant

Review information with consultant about

- Risks (organ-specific penetrances)
- Prevention strategies
- Available therapies when cancer present
- Risks in offspring, and other relatives
- Provide counselling letter to consultant (and referring specialist)

Psychological support

PGT POST-TEST GENETIC COUNSELLING – NORMAL RESULT

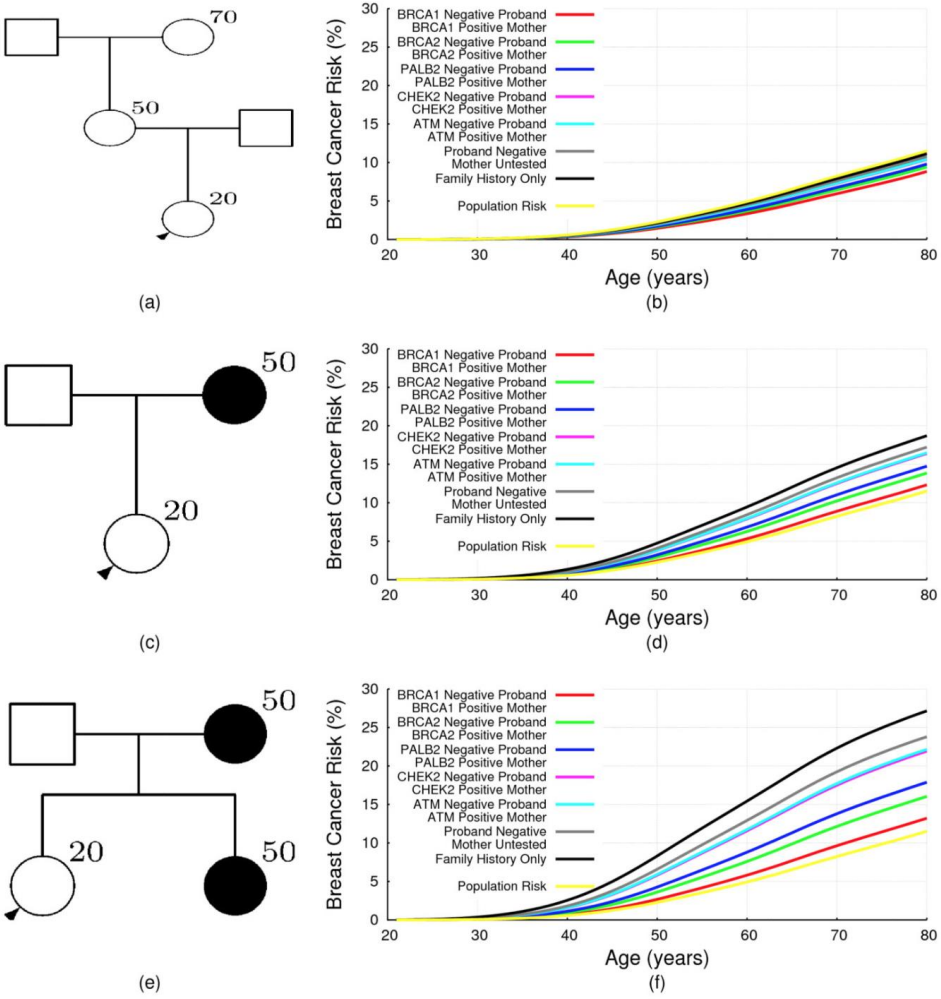
Good news, but…

Residual risk in mutation-negative patient depends on penetrance of the mutation

- Close to normal population risk in BRCA1 families
- Higher than population risk in CHEK2 families*

*Lee K, *et al.* Genet med.2016

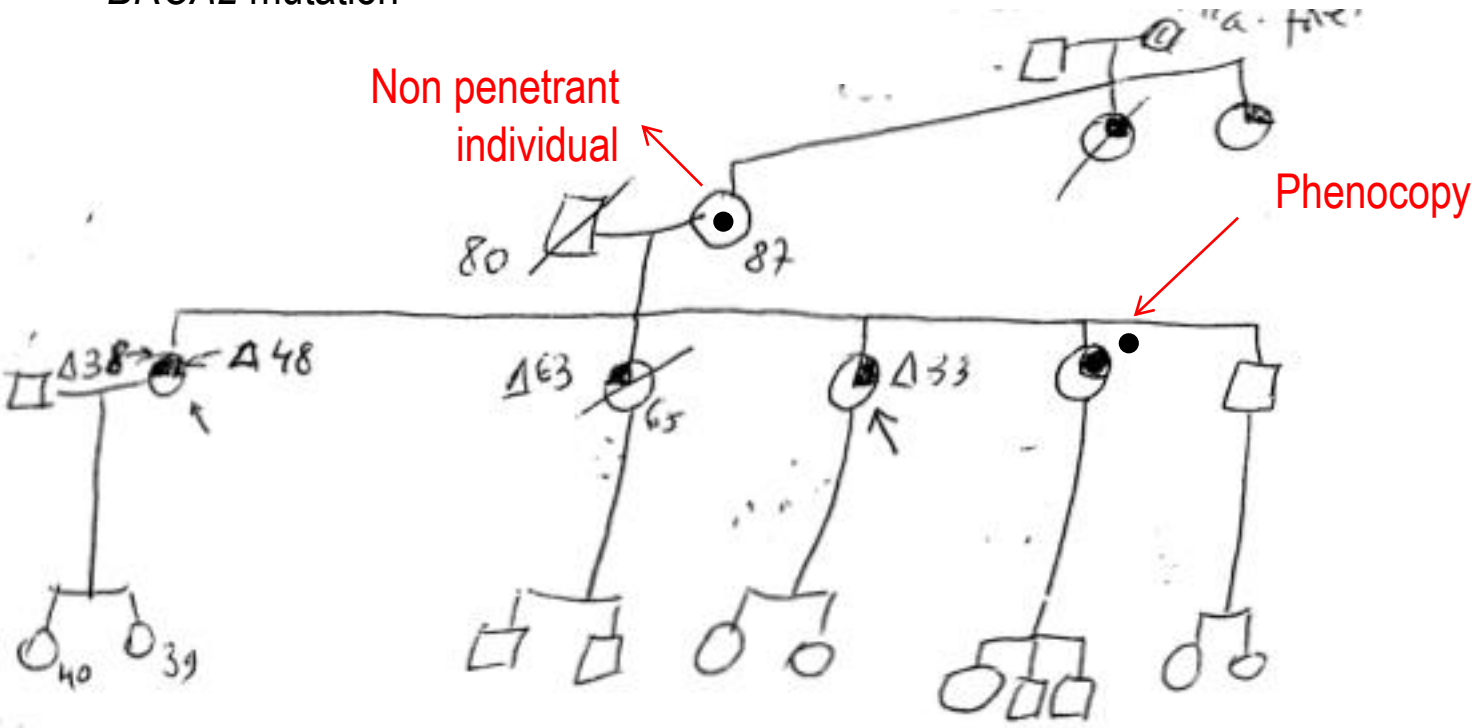
PENETRANCE REFLECTS RISK CAPTURED BY MUTATION



- If *BRCA1* is present in cancer patient, absence in relative removes most of the increased risk
- If *CHEK2* is present in cancer patient, absence in relative removes little of the increased risk

BRCA2: PENETRANCE SLIGHTLY < BRCA1

BRCA2 mutation

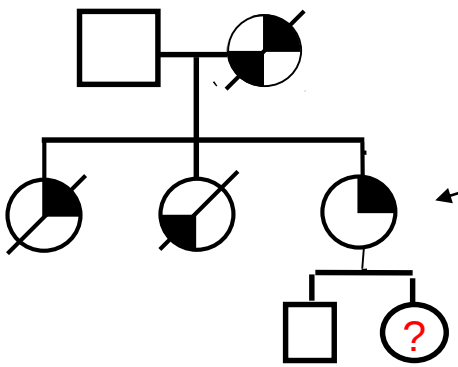


Cartoon by Prof Marc Abramowicz.

WHO DOES WHAT IN PATIENTS' TRAJECTORIES

- Genetic testing and (pre-test) counselling in symptomatic cancer patient: CANCER TEAM
  - Trained in genetic counselling pre- and post-test
  - Trained in interpreting family histories and DNA test results
    - VUS, phenocopies, …
    - Negative result in spite of high plausibility of mutation
- Presymptomatic testing and counselling: GENETICS

HEREDITARY BREAST/OVARIAN CANCER



INDEX CASE (PROBAND)

Symptomatic

DNA test to identify mutation

Oncologist
OBGYN
for pre-test counselling

At-risk relative, asymptomatic

Presymptomatic Genetic Testing (PGT) if mutation found in proband

Geneticist needed pre- and post-test

Breast cancer

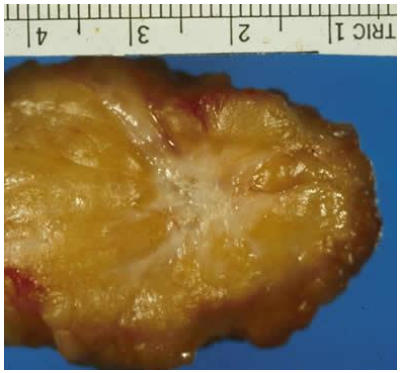
Ovarian cancer

TRENDS FOR THE FUTURE

Pathway-specific therapies

Pharmacogenetics

Liquid biopsies and biomarkers



Tumour DNA

Larger panel analyses

- Better known variants
- Better known penetrances

Germline variants found in tumours

Multigenic risk profiling (low penetrance alleles) in all women ?

With targeted prevention ?

Genome editing for inherited mutation?

Patient DNA

ESMO CLINICAL PRACTICE GUIDELINES

Prevention and Screening in BRCA Mutation Carriers and Other Breast/Ovarian Hereditary Cancer Syndromes: ESMO Clinical Practice Guidelines

Published in 2016 – Ann Oncol (2016) 27 (suppl 5): v103-v110
Authors: S. Paluch-Shimon, F. Cardoso, C. Sessa, J. Balmana, M. J. Cardoso, F. Gilbert and E. Senkus

These guidelines focus on cancer prevention and screening among individuals known to harbour a pathogenic BRCA1/2 mutation.

Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines

Published in 2013 – Ann Oncol 2013; 24 (Suppl 6): vi73-vi80.
Authors: J. Balmaña, F. Balaguer, A. Cervantes, D. Arnold

The guideline covers Lynch syndrome, familial colorectal cancer X syndrome, APC-associated familial adenomatous polyposis and MUTYH-associated polyposis

THANK YOU!