

Essential Insights on Hereditary Cancer at the DC

Nordic Conference on Diagnostic Centers

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Agenda

- Hereditary cancer – basic concepts
- Cancer predisposition syndromes (CPS)
- Characteristics
- Insights

Case report

Male 60 years

Referred to diagnostic centre by the GP

Tired. Healthy lifestyle, normally physically active both at work and at home

- Hb 113, (reticulocytes, thrombocytes, white blood cell differential, kalium, albumin, ferritin and MCV all normal)
- Serum protein electrophoresis "slight inflammation", normal immunoglobulins, no M-component.
 CRP 5.2 and SR 41
- Benign prostatic hyperplasia, PSA 4.6. Regular check-ups by urologist

Case report

Male 60 years

Family history of cancer:

- Sister breast cancer at the age of 40 and 58. Stomach cancer at the age of 55, both breasts removed and the stomach as well.
- Father urological cancer.
- Sister has undergone genetic investigation, and her children should have an increased risk of cancer.

Contact with sister who informs that she has a *CDH1* mutation

Case report

Male 60 years

CT thorax and abdomen:

- Normal

Gastroscopy:

- Macroscopically normal
- Targeted multiple biopsies
- PAD: Diffuse gastric cancer/Signet ring cells carcinoma confirmed in 2 biopsies

Genetic test: Carrier of the familiar pathogenetic *CDH1* variant.

Genetics and heredity



Mapping of the human genome
1990-2006

<https://science.sciencemag.org/content/291/5507/1304>
<https://www.nature.com/nature/volumes/409/issues/6822>

Classifying pathogenetic variants

Benign	Likely benign	Uncertain significance	Likely pathogenic	Pathogenic
1	2	3	4	5

[Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology - ScienceDirect](#)

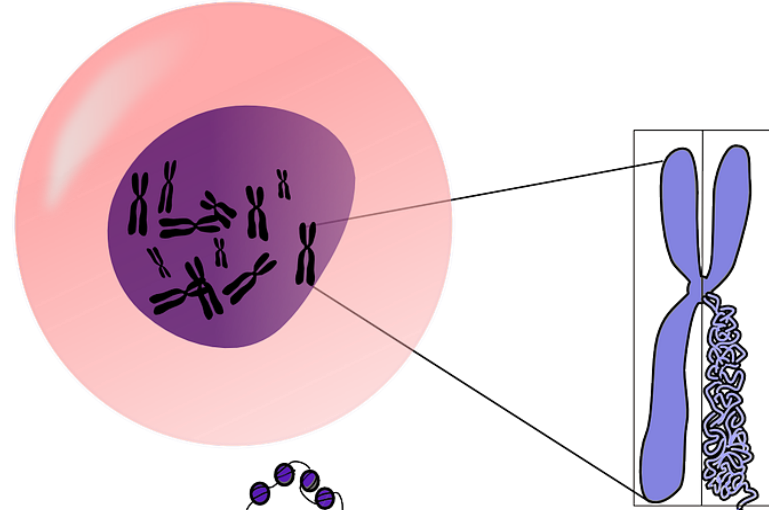
Congenital or acquired



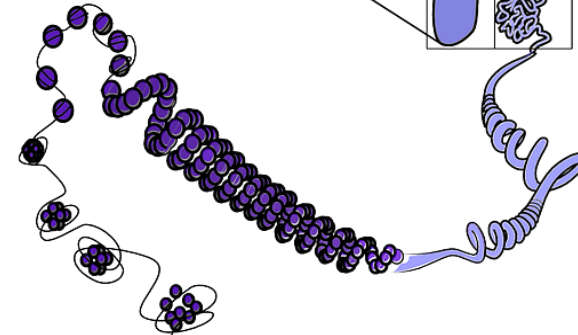
Congenital:
Constitutional – hereditary
(Found in all cells of the body)

Acquired:
Somatic – non-hereditary
(Genetic changes in tumour)

Cell nucleus



Chromosome



DNA helix

DNA with the four bases:
Guanine, adenine cytosine
and thymine

Cancer predisposing syndromes

Rare

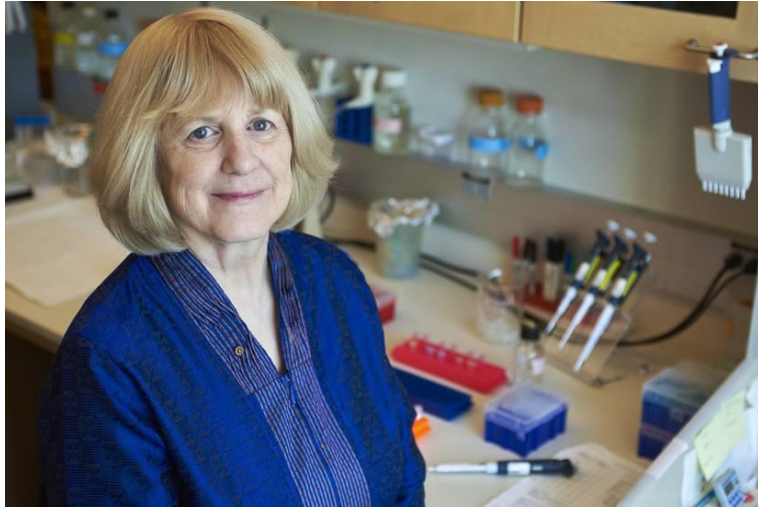
- Benign and malignant tumours
- Often multiple organs at risk
- Other disabilities

Common – not rare

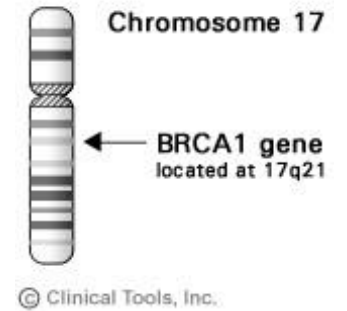
- Hereditary breast - ovarian cancer syndrom
 - Hereditary colon- and endometrial-cancer (Lynch syndrome)
-
- Hereditary predisposition syndromes – known for a long time
 - 1990s knowledge of genetic causes

Characteristic of cancer predisposition syndromes

- Young onset (compared to the general population)
- Several primary cancers
- Several associated cancers in the family
- Rare cancer types



Mary Claire King
1946-



Research Articles

Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21

JEFF M. HALL, MING K. LEE, BETH NEWMAN, JAN E. MORROW,
LEE A. ANDERSON, BING HUEY, MARY-CLAIRE KING

Science, New Series, Vol. 250, No. 4988 (Dec. 21, 1990), pp. 1684-1689

<https://biology.indiana.edu/news-events/named-lectures/muller-award-past.html>



BRCA1

Breast cancer

Ovarian and fallopian tube cancers

BRCA2

Breast cancer

Ovarian and fallopian tube cancers

Prostate cancer

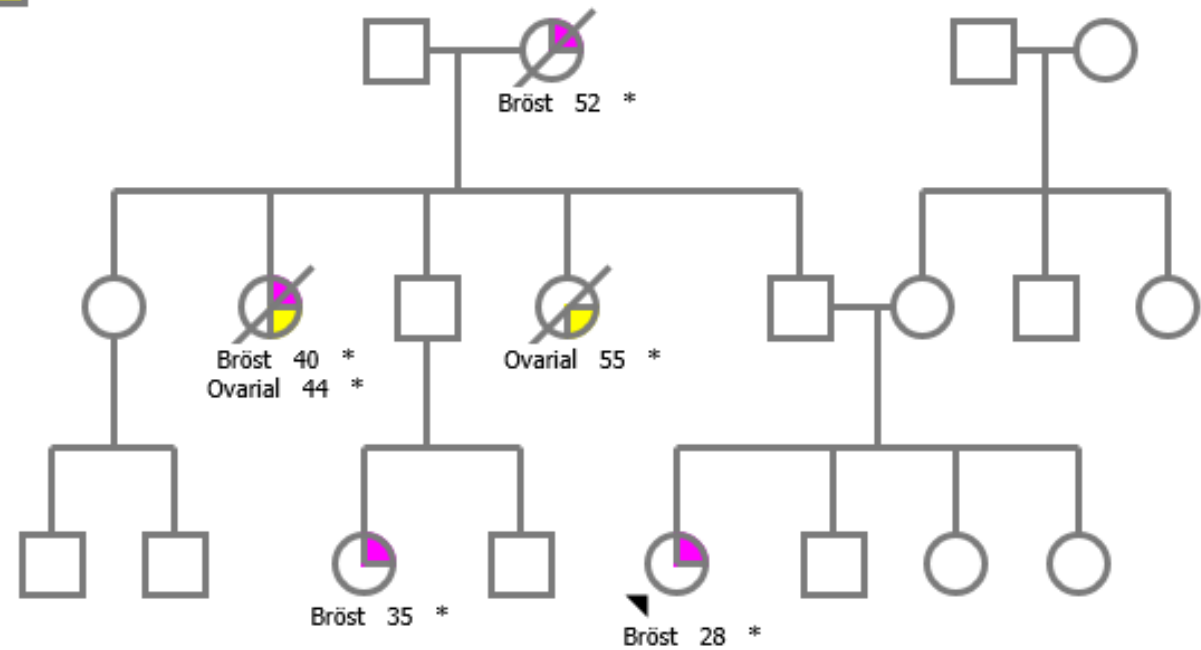
Male breast cancer



Bröst



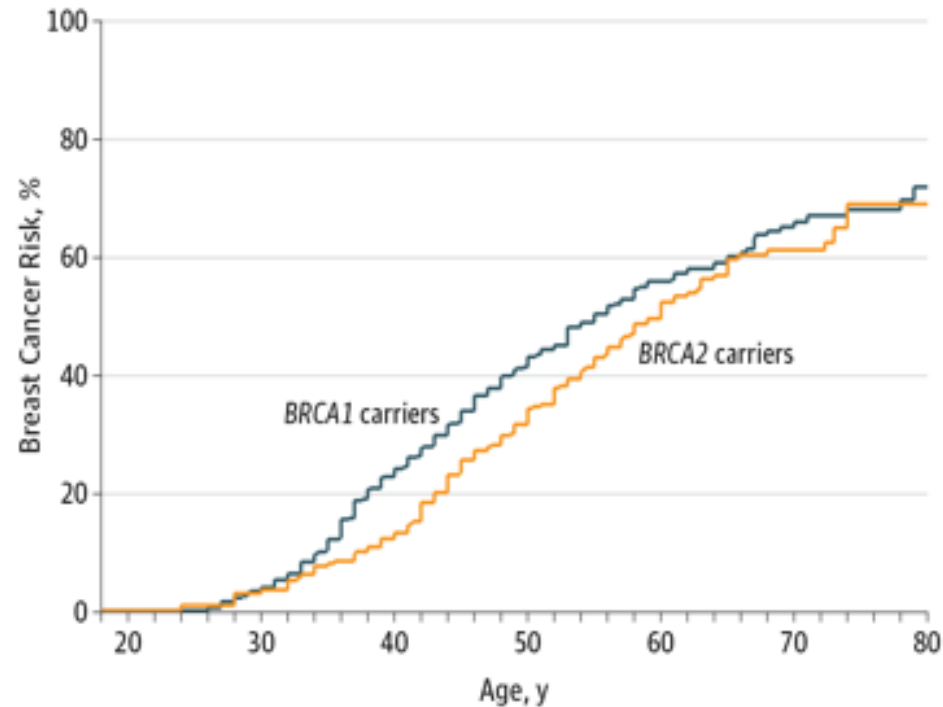
Ovarial/Tubar



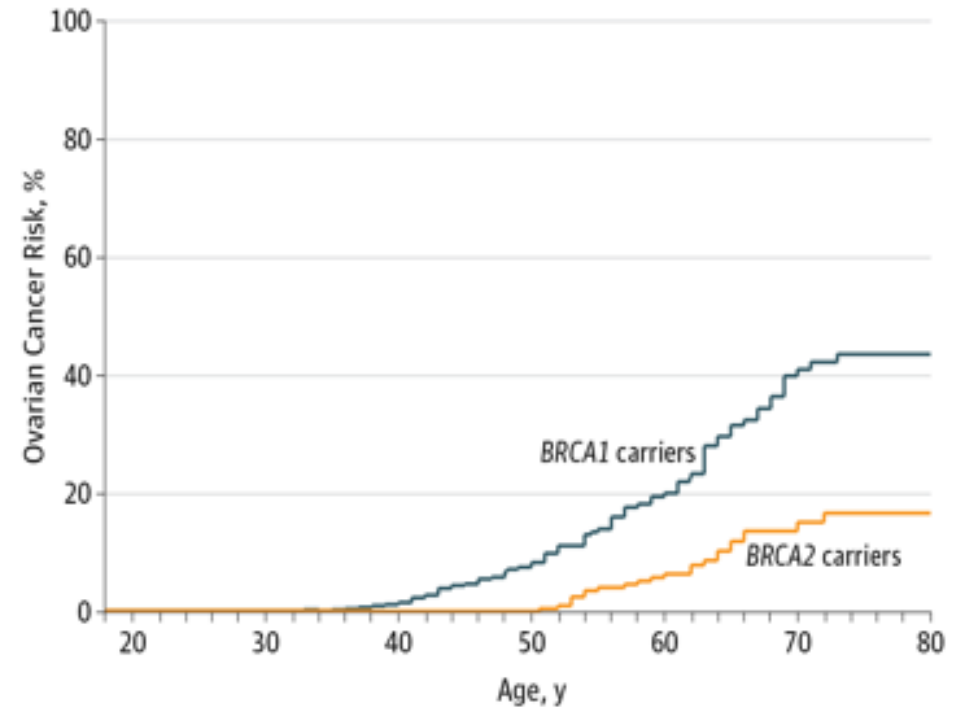
Fictional pedigree

Risks of breast and ovarian cancer for *BRCA1* and *BRCA2* Variant Carriers

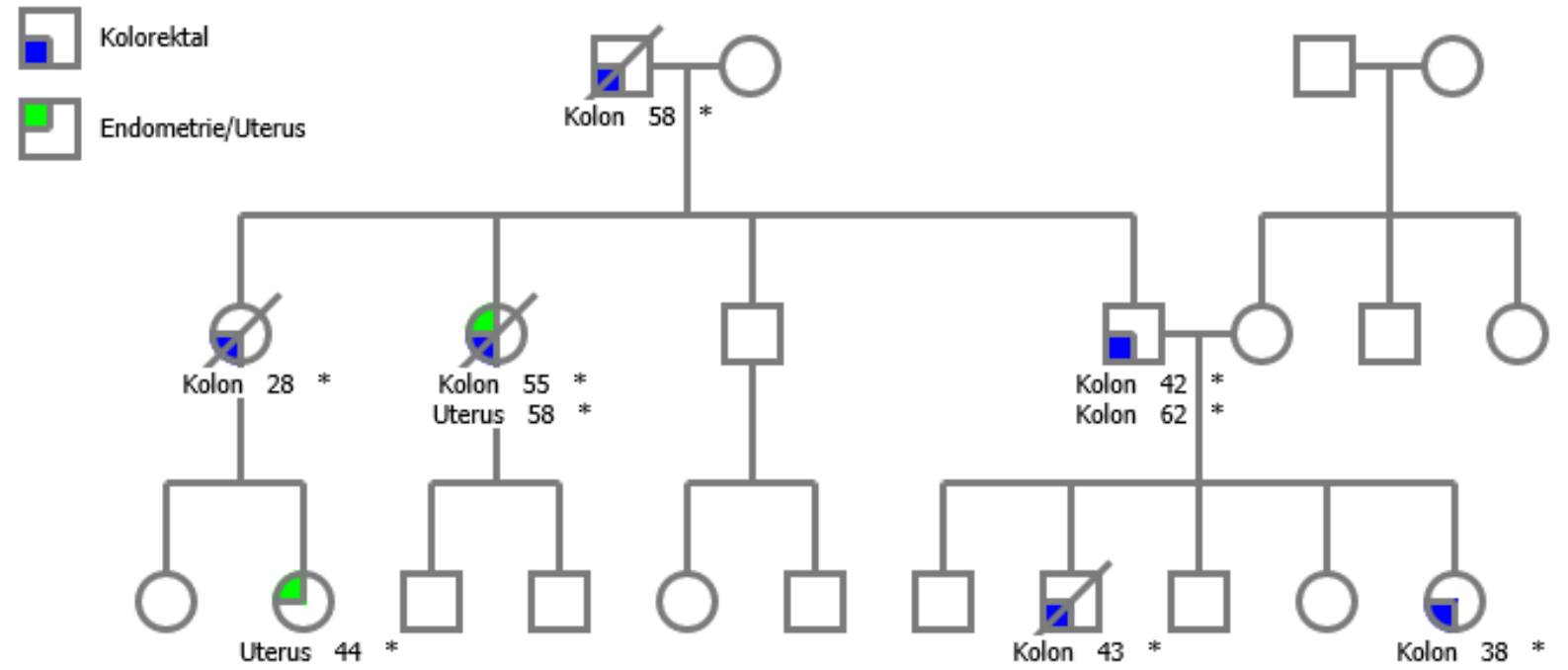
A Cumulative risk of first breast cancer among *BRCA1* and *BRCA2* mutation carriers



B Cumulative risk of ovarian cancer among *BRCA1* and *BRCA2* mutation carriers



MLH1,
MSH2,
MSH6,
PMS
EPCAM



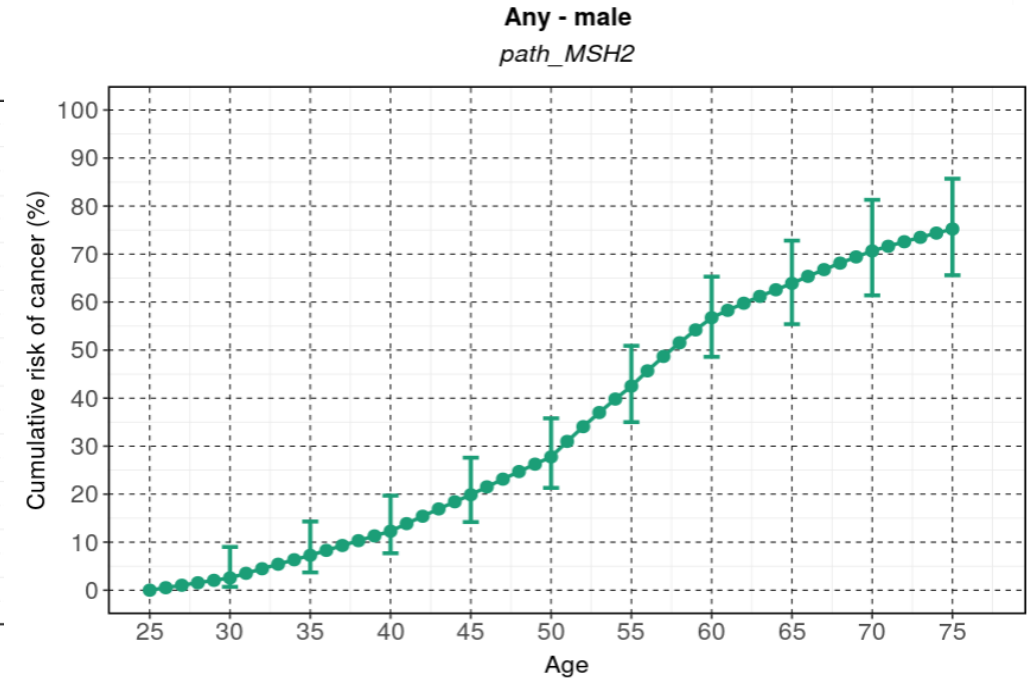
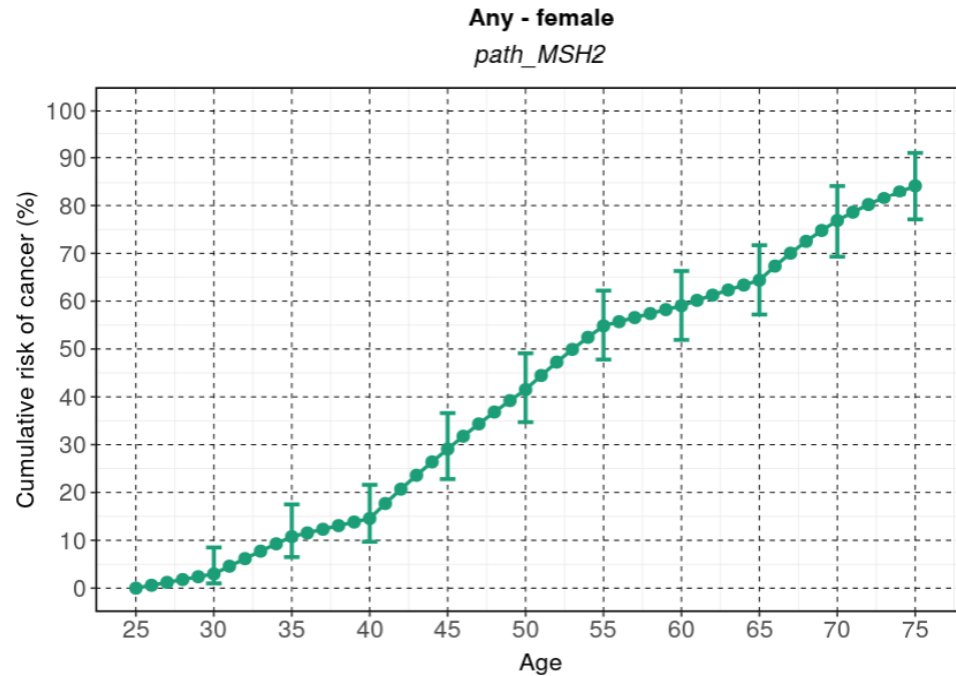
Fictional pedigree

Cumulative risks for cancer

Organs at risk:

Colorectum
Endometrium
Ovary
Stomach
Urinary tract (MSH2)
Prostate (MSH2)

Pancreas
Brain
Skin
Small bowel
Biliary tract



Hereditary gastric and breast cancer syndrom

CDH1

Diffuse gastric cancer

Lobular breast cancer

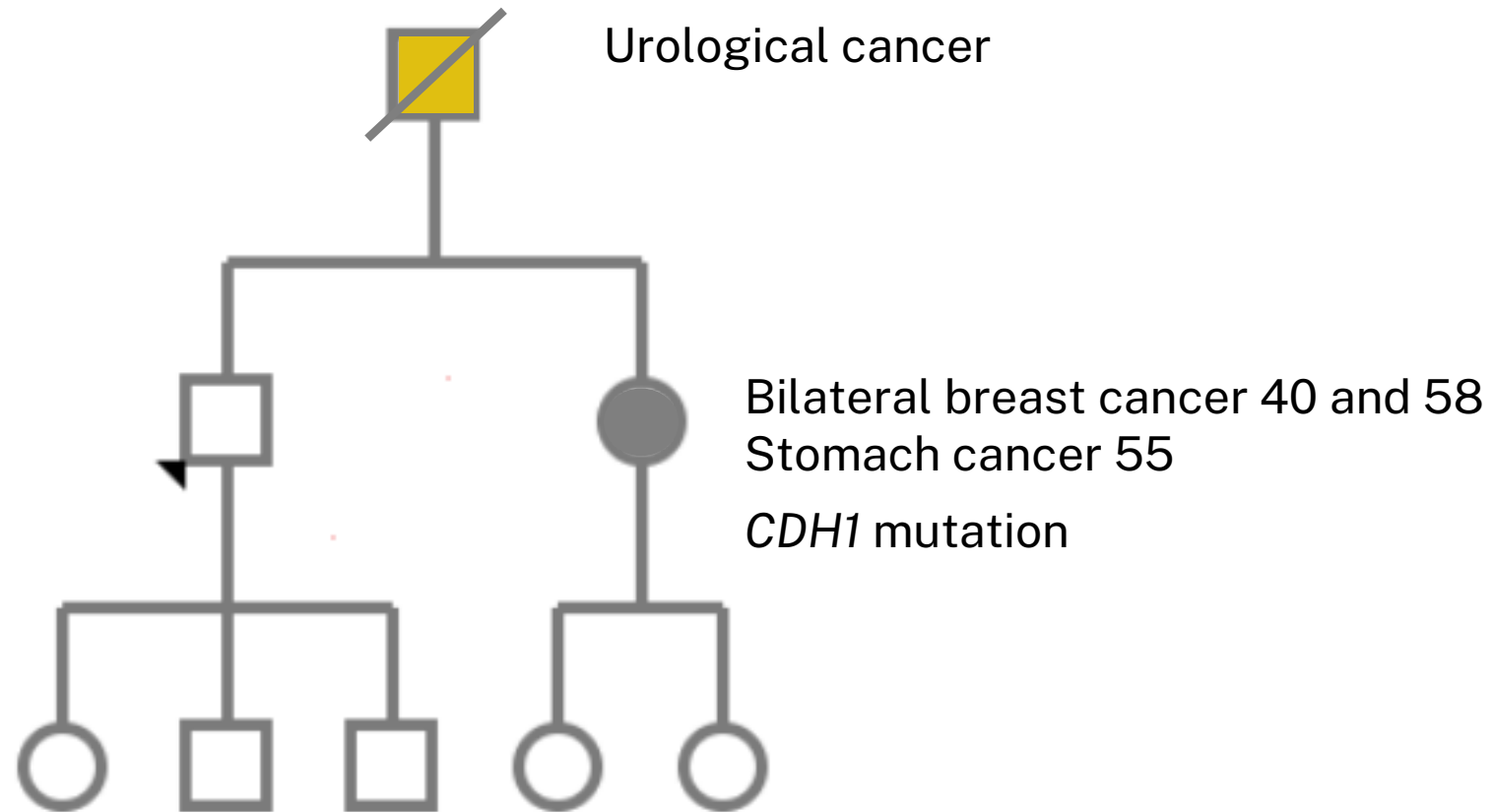
Criteria

One person with DGC and one of the following:

- One 1:st- or 2nd degree relative with DGC or in situ signet ring tumour
- DGC before age 40
- One 1:st – or 2:nd degree relative with lobular breast cancer before age 50
- A personal history of lobular breast cancer regardless of age and family history
- A personal history or a 1:st degree relative with cleft lip/cleft palate

Case report

Male 60 years



Fictional pedigree

Genetic analysis

- Blood sample
EDTA tube



- Tissue sample for
example skin biopsy)

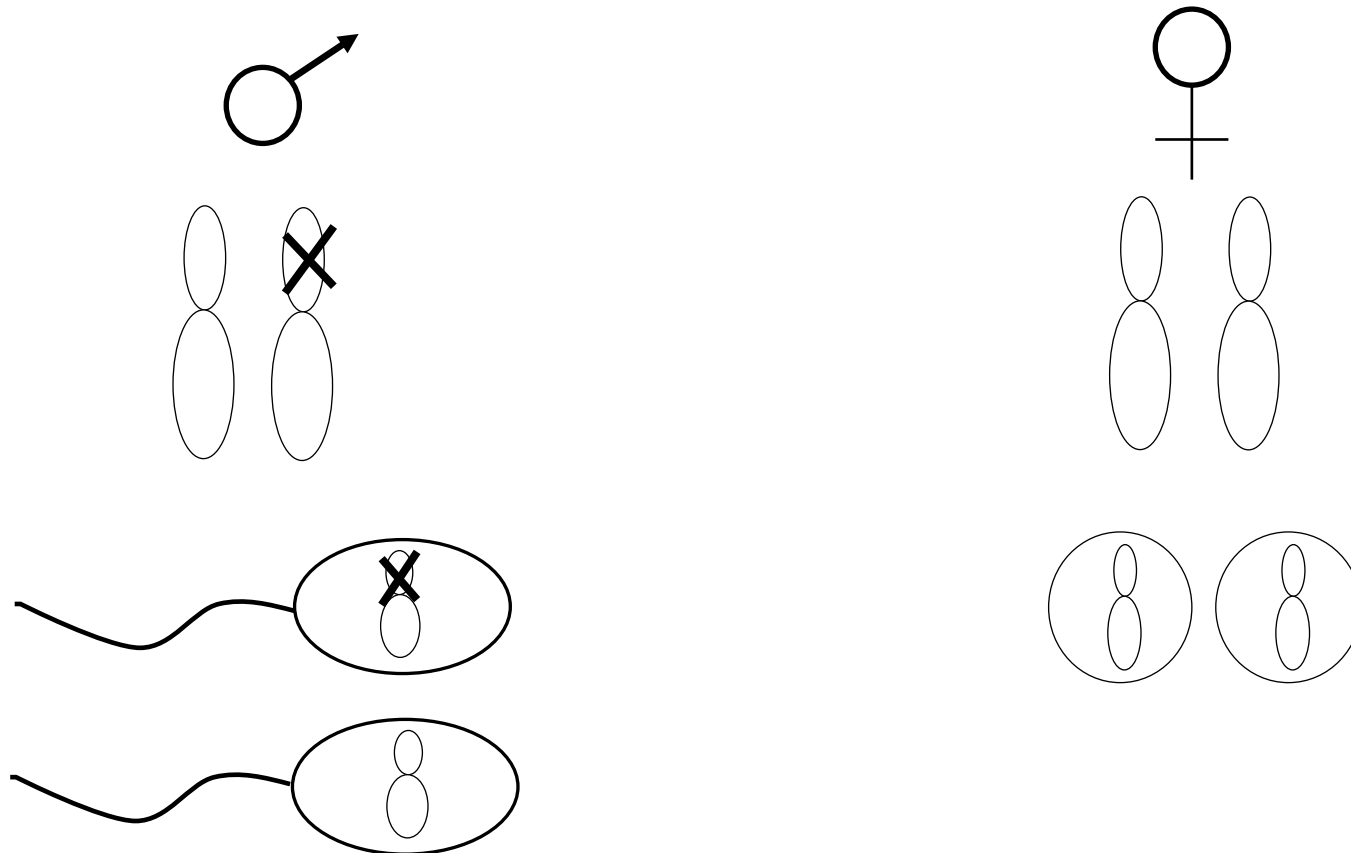


Purpose of diagnosing hereditary cancer

- To diagnose
- Identifying organs at risk
- Prevention
- If symptomatic, targeted investigation
- Treatment management
 - Surgery
 - Oncological treatment
- Inform at-risk relative
 - Carrier testing
 - Exclude hereditary cancer predisposition

Autosomal dominant inheritance

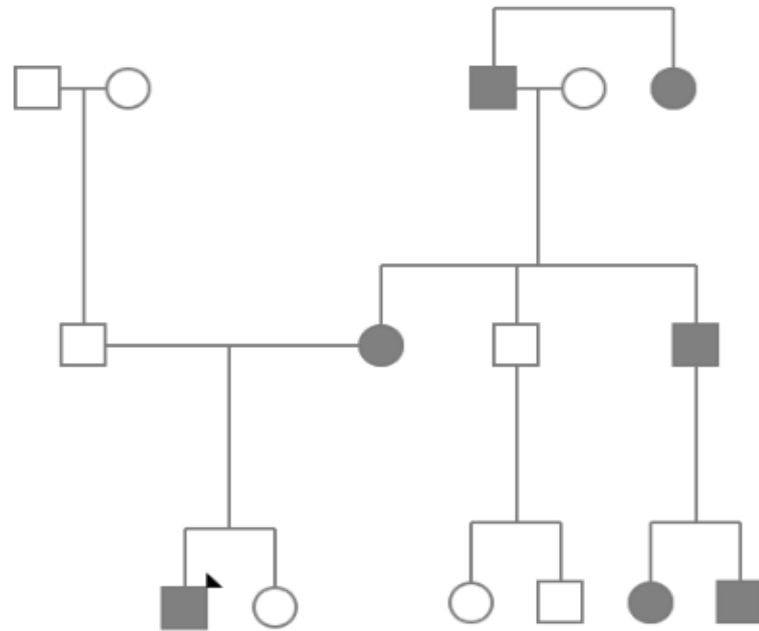
- Inherited equally regardless of sex
- 50 % recurrence risk



Autosomal dominant inheritance

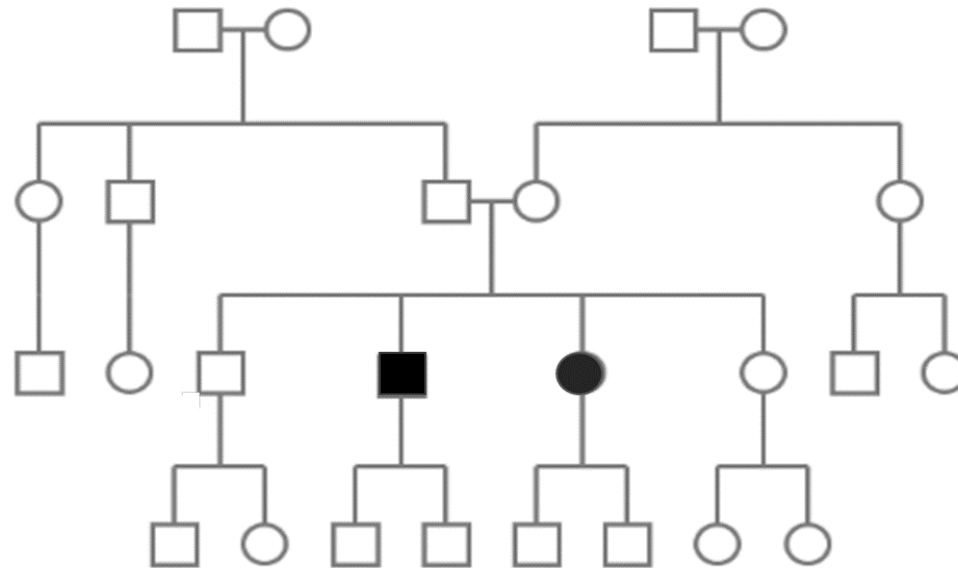
- More than one generation
- Both sexes
- Inheritance also through men

■ sjuk



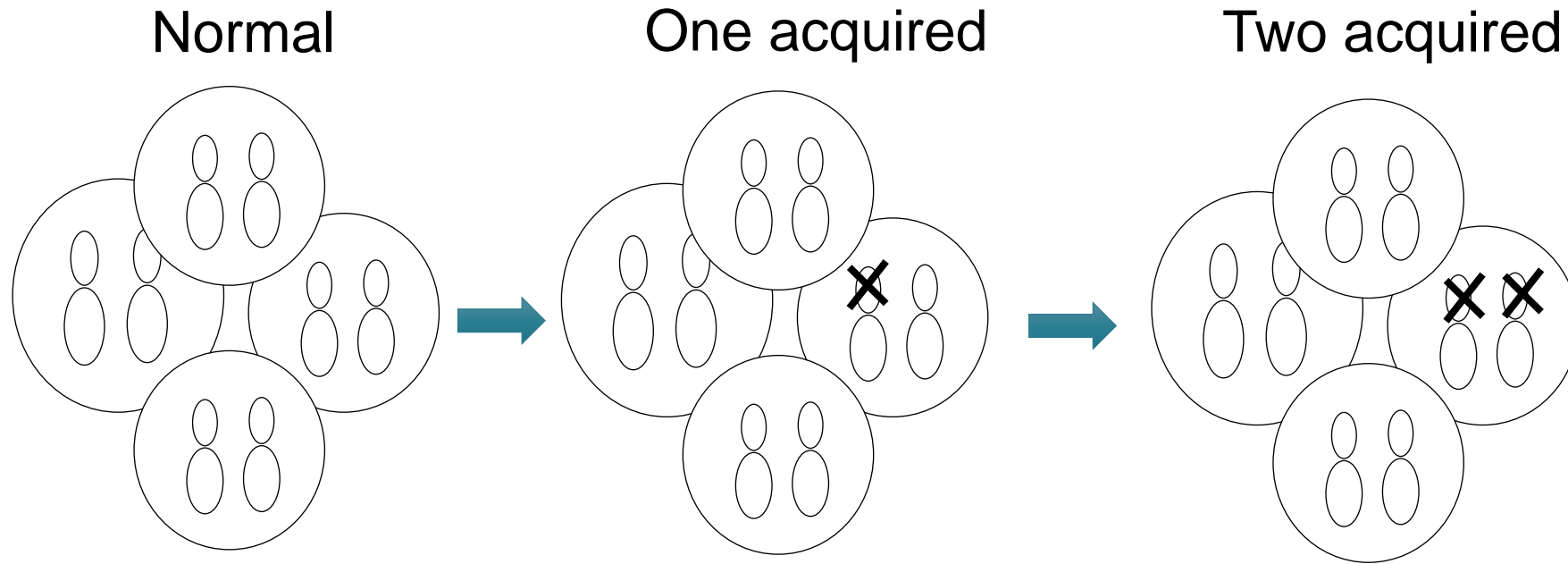
Autosomal recessiv inheritance

- Usually only one generation
- Both sexes
- Parents of sick child healthy
- Children of sick person healthy
- Increased incidence of consanguinity





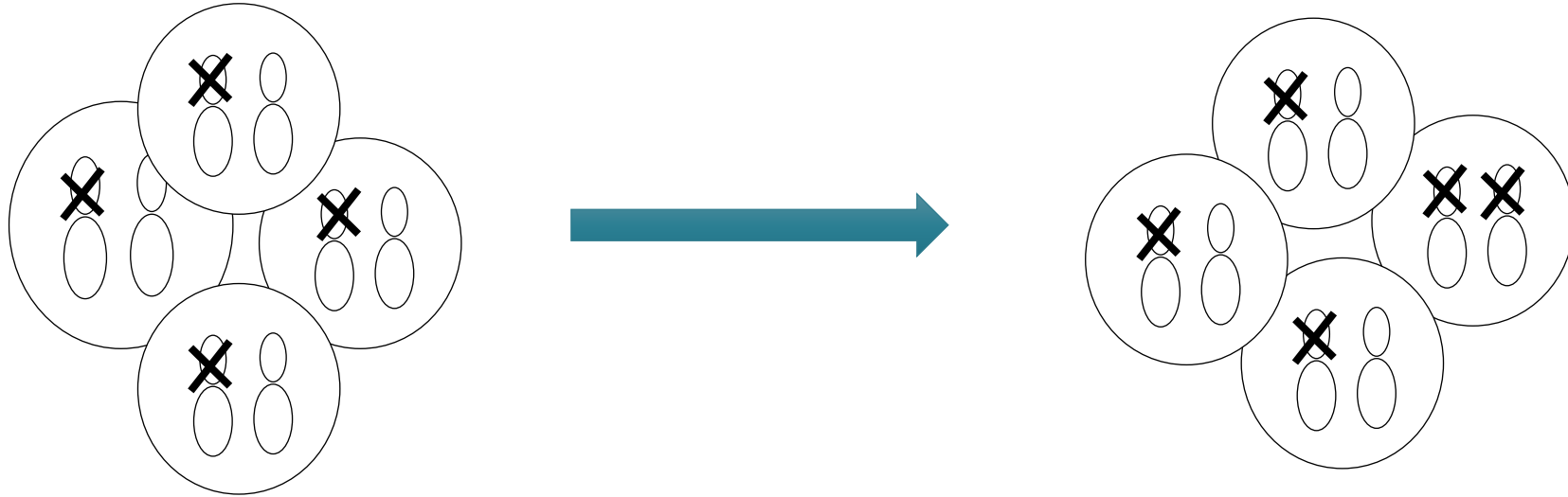
Two-hit hypothesis



- Cancer at a later age
- Reduced risk of new primary cancer
- Reduced risk of multifocal cancer

Congenital mutation

One congenital + one acquired



- Cancer at an earlier age
- Increased risk of a new primary cancer
- Increased risk of multifocal cancer

Genetic counselling

Hereditary disease has an impact on:

- How one's life will be
- Children
- Family planning

Need to manage the effects:

- Medical
- Psychological



Sheldon Reed (1910-2003)

[https://www.cell.com/ajhg/pdf/S0002-9297\(07\)63889-0.pdf](https://www.cell.com/ajhg/pdf/S0002-9297(07)63889-0.pdf)



Frank Clarke Fraser
1920-2014

<http://ceo.medword.net/?lectures=genetic-counseling>

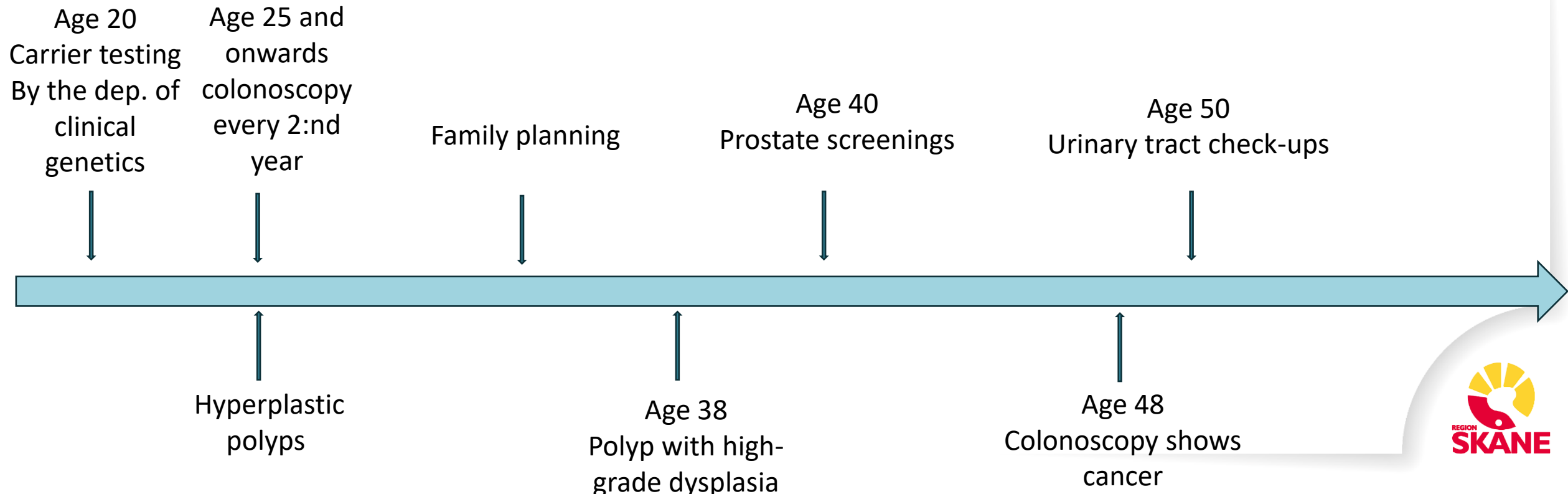
- Guilt – having transmitted a genetic disorder
- Threat – breach of confidentiality, personal integrity
- Family formation, parental role
- Actual problems with illness, often rare
- Survival guilt
- Depression/grief

Male age 25

Family history: Father at age 65 disseminated colon-cancer.

Grandmother endometrial cancer deceased at age 52 and cousin diagnosed with advanced cancer of colon at age 36.

Lynch syndrome (*MSH2*)



At the Diagnostic Centre

When a patient is referred with symptoms that could be pathogenetic

- Ask about family history
- Cancer diagnosis? Age of diagnosis ? Alive? Deceased?
- Ongoing/previous genetic investigation?

- Anyone with a genetic mutation?
 If so – Consult or refer to Clinical Genetics department

- If a family history of cancer or patient is diagnosed with cancer and fulfills the criteria for genetic investigation
 –Consult or refer to the clinical geneticist

- If the patient is a carrier of a pathogenetic variant
 Always important to inform the recipient of different ongoing investigations.

Genetic investigation

*The routine for genetic testing may differ depending on local operations.
Ask your clinical genetics department*

There could be “fast track”:

- For example, breast-, ovarian- colorectal-, endometrial cancer
- The clinician informs the patient about the test
- Take a blood sample and send it to the clinical genetics department
- Receive the test result
- Inform the patient of the result.
- If a constitutional mutation is found – the patient is referred to the clinical genetics department for genetic counselling.

If there is a genetic mutation that runs in the family:

- The patient is referred to the clinical genetics department for genetic counselling and carrier testing under patient request.

Case report

Male 58 years

Referred by the GP

Since 6 months diabetes. Insulin therapy.

Liver test

Cholestatic pattern

ALP 8. Bilirubin 38, otherwise normal liver function test

Fairly lean

Lost 8 kg in the last six months, now weighing 74 kg 1.82 m tall

Deteriorated general condition – tired, does not go on walks.

Non-smoker, moderate alcohol consumption

Case report

Male 58 years

Has recently been informed that his cousin is diagnosed with breast cancer and a *BRCA2* mutation.

Included in the cancer patient pathway AOS (Severe non-specific symptoms that could be due to cancer)

CT-thorax and abdomen – thorax normal but abdomen shows a suspected tumour mass located in corpus of the pancreas

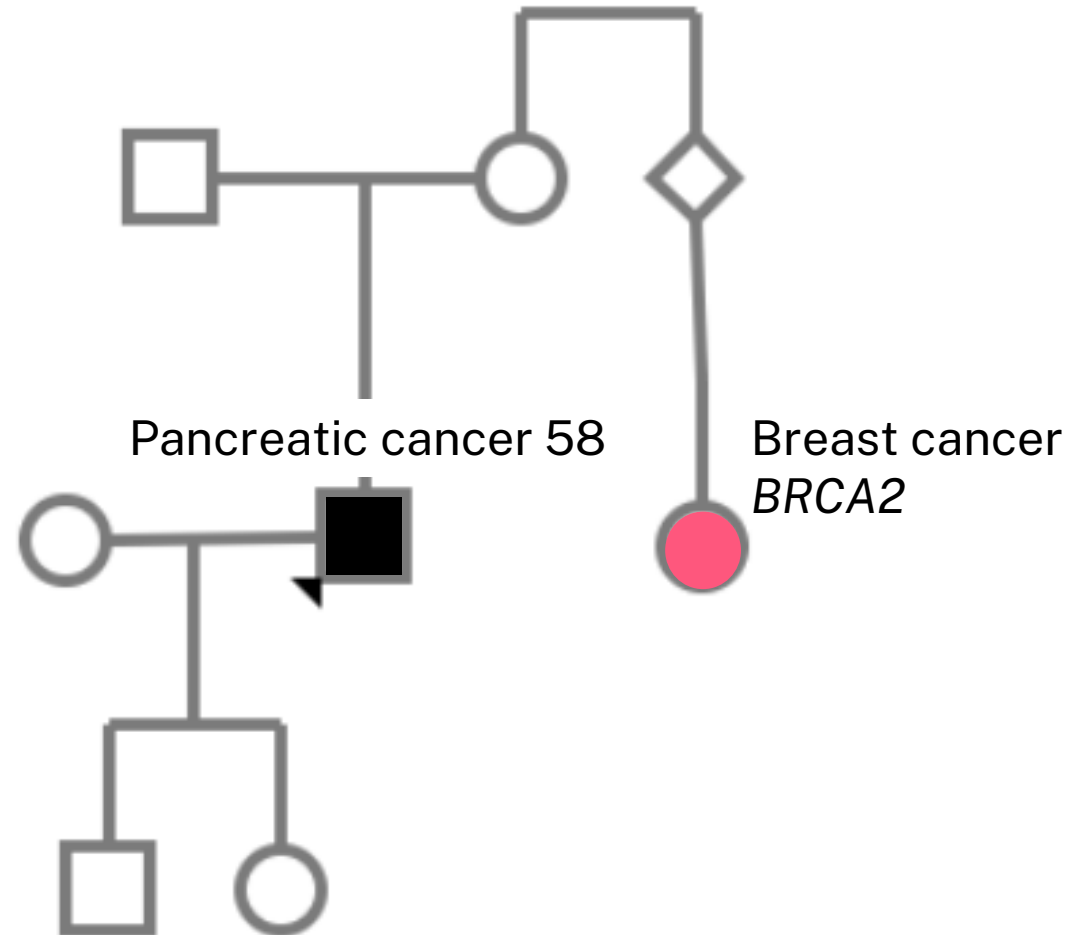
CA19-9 1050 CEA 5

MR Pancreas Tumour locally advanced

Case report

Male 58

Parents died at the age of 50 and 48 in a car accident.



Fictional pedigree

National clinical cancer guidelines

Hereditary tumour risk syndromes among children and adults

Ärftliga tumörrisksyndrom hos barn och vuxna



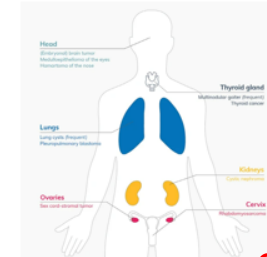
Nationellt vårdprogram

Ange datum.Version: 1.0

Filtera på: Gen Syndrom

Gen

- PTCH1
- SUFU
- DICER1
- FANCA
- BRCA2
- PALB2



Kliniskt omhändertagande

Hud – basalcancer (BCC)

Livstidsrisk

Uppföljning vuxen (ja/nej)
Råd om lämpliga söskyddsåtgärder
Hudkontroller hos hudläkare: årligen tills det första BCC, därefter var 3-6 månad

Ålder uppföljning
10 år
Tidigare om tidigare strålbehandling

Nationellt vårdprogram
[NVP Basalcancer](#)

Referens uppföljning
Verkouteren 2022 (GENTURIS) PMID: 34375441
Guerrini-Rousseau 2021 PMID: 33860896

Uppföljning, annat

Uppföljning barn (ja/nej)
Ja

- Odontogena keratocystor (OKC) +
- Medulloblastoma (mindre frekvent än vid SUFU) +
- Meningioma (mindre frekvent än vid SUFU) +
- Cardiac fibroma +

Under preparation

Thanks!

*"What we keep in memory
is ours forever"*

