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Hereditary cancer syndromes

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Výstupy z učení

- Student se naučí rozpoznat akutní život ohrožující stavy u diabetiků.

- Student se naučí základní principy první pomoci u diabetiků.

Basic Dogmas of Oncology

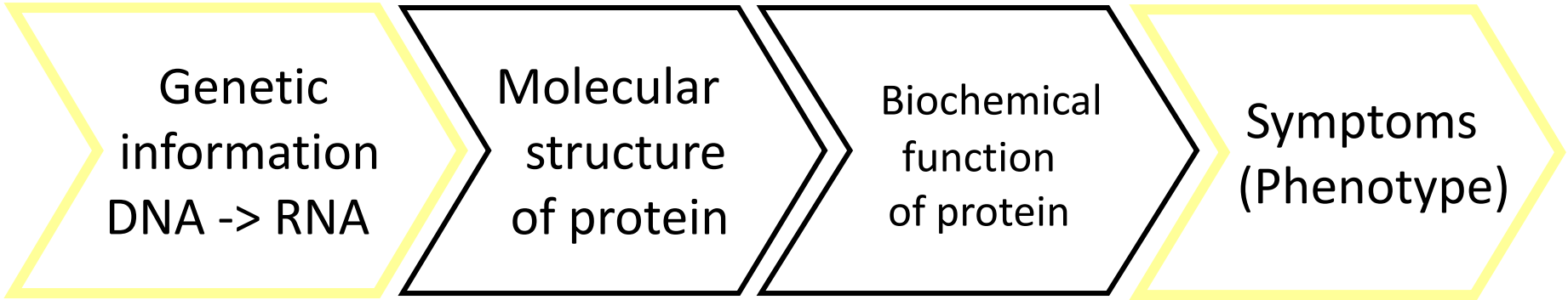
I) Cancer is a genetic disease

Aberrant gene expression is a key step in the initiation, promotion and progression of the tumor

II) Carcinogenesis is a multistep process

Carcinogenesis is a multistep process involving alterations in at least two distinct classes of genes

III) Biological correlates of gene expression are identifiable



Hereditary cancer syndromes

MOLECULAR BIOLOGY

- Cancer- Accumulation of series of mutations at various cancer-susceptibility genes
- Most solid adult Tx requires 5-10 rate limiting mutations to acquire malignant phenotype
- Uncontrolled cell growth, invasion and metastasis

GATE-KEEPER GENES

- Oncogenes-
  c-ras, k-ras
- Tumour Suppressor genes (Anti-oncogenes)
  p53, p21

CARE-TAKER GENES

- Stability genes/ DNA mismatch repair genes (DNA MMR)
  MLH1, MSH2, MSH6

Hereditary cancer syndromes

MOLECULAR BIOLOGY

- Everyone has two copies of each gene, one from each parent.
- Most people are born with two normal copies of each gene.
- In hereditary cancers a person is born with changes or mutations in one copy of a cancer-susceptibility gene
- In the majority of these cases, the changes were inherited from the mother or father.
- Knudson's "two-hit" hypothesis- two hits/ mutations within a genome are necessary for a malignant phenotype to develop'

➢ Hereditary cancer- One hit is already present in every cell (from birth)- only one additional hit is necessary

Additional hit-

1.Gain in function- Proto-oncogene→ Oncogene

2.Loss of function- Inactivates Tx Suppressor gene

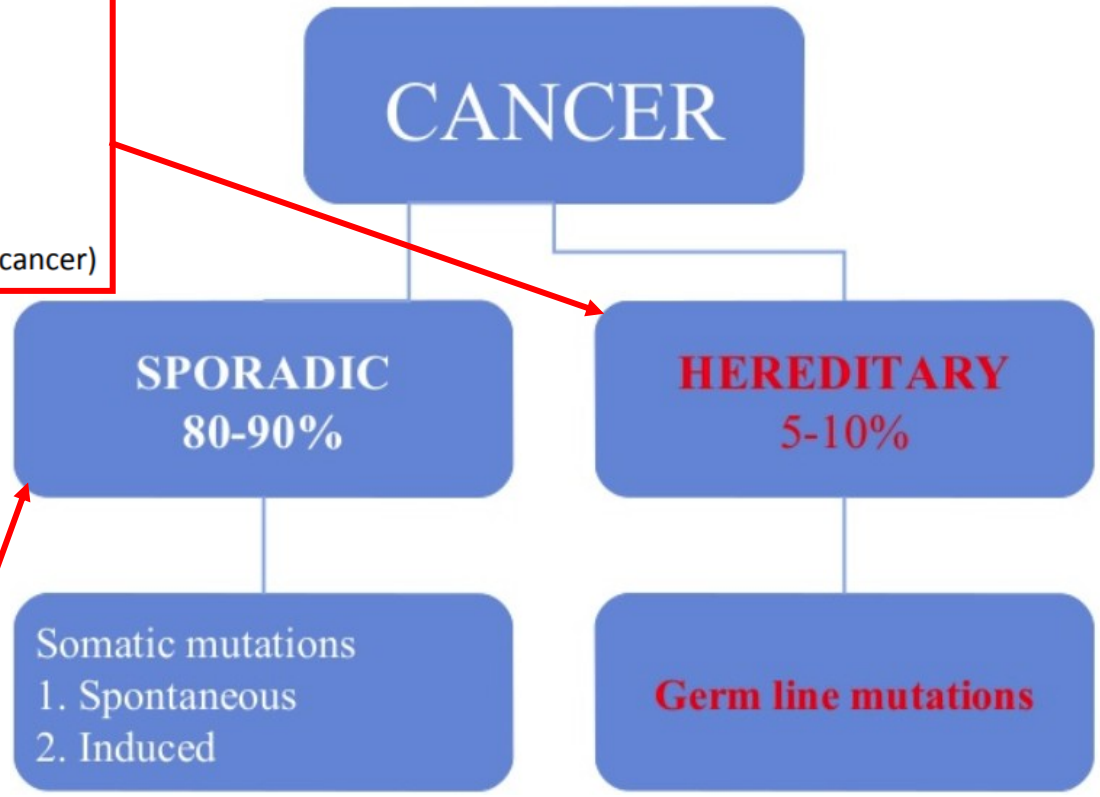
➢ Sporadic cancer- Both hit occurs within a single somatic cell (after birth)

'Carl O. Nordling in 1953, Alfred G. Knudson in 1971

Hereditary cancer syndromes

Hereditary cancer ~5-10%
- Early diagnosis
- Bilateral cancers
- Multiple primaries in an individual
- Multiple affected family members
- Spanning a number of generations
- Rare cancers (ovarian cancer, male breast cancer)

Familial cancer ~ 15-20%
- More cases of a specific type(s) of cancer within a family than expected, but no specific pattern of inheritance
- Age of onset variable
- May result from chance clustering of sporadic cases
- May result from common genetic background (low penetrance gene), similar environment and/or lifestyle factors



Cancer is a common disease, so some families will have some members who having the same cancer but that does not mean the cancer in that family is hereditary.

Hereditary cancer syndromes

GENETIC SUSCEPTIBILITY

- To describe the high risk for cancer in people with an inherited mutation
- People with an inherited gene change have a 50% chance of passing the mutation to each of their children
- Do ***not*** increase the risk for every type of cancer
- ***Not everyone*** who is born with a gene change will develop cancer

WHY?

- Second hit may not take place
- Incomplete penetrance- the AD gene is expressed at all or not
- Expressibility- Degree to which the phenotypes are expressed
- Co-dominance- alleles of a gene pair are different from each other but both are expressed

Hereditary cancer syndromes

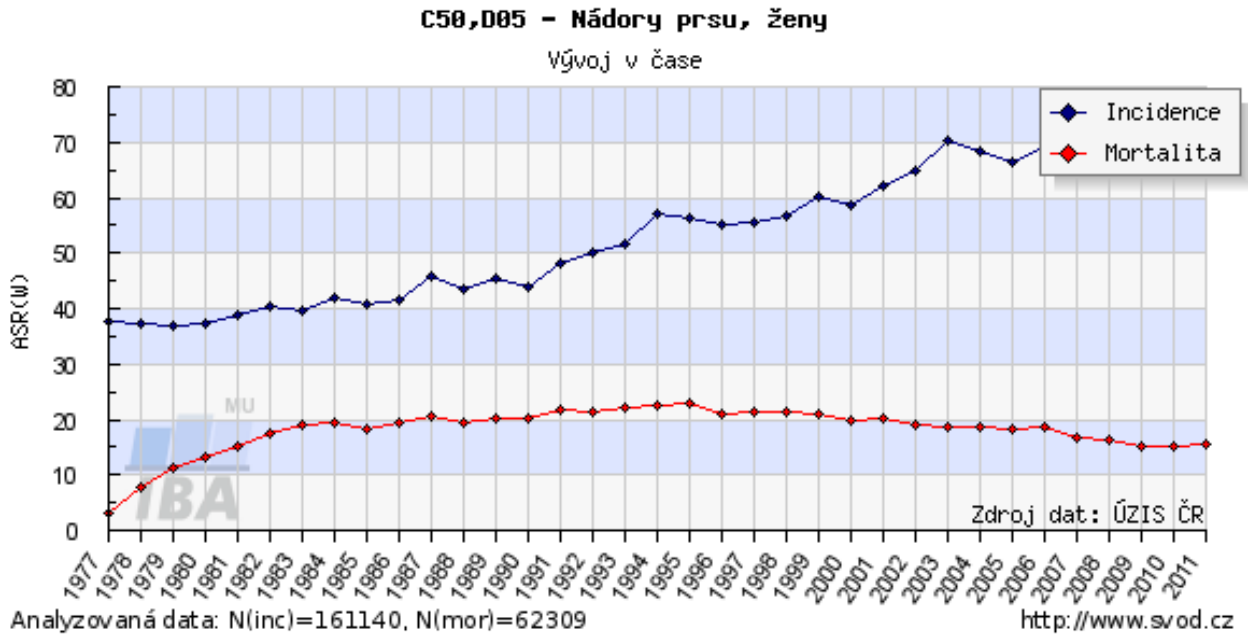
Hereditary Cancer Syndromes (most common)

- Hereditary Breast and Ovarian Cancer Syndrome (BRCA1 and BRCA2)
- HNPCC/Lynch Syndrome (MMR genes – MLH1, MSH2, MSH6, PMS2) and EPCAM gene
- FAP, AFAP and MAP (APC and MYH)
- Malignant melanoma (p16 , CDK4)
- Hereditary Diffuse Gastric Cancer (CDH1)
- Paraganglioma Syndromes (SDHB,C,D)
- Von Hippel Lindau (VHL)
- Cowden Syndrome (PTEN)
- Neurofibromatosis type 1 and type 2 (NF1 and NF2)
- Juvenile Polyposis (BMPR1A, SMAD4, LKB1)
- Li-Fraumeni Syndrome (p53)

Hereditary breast and ovarian cancer: HBOC

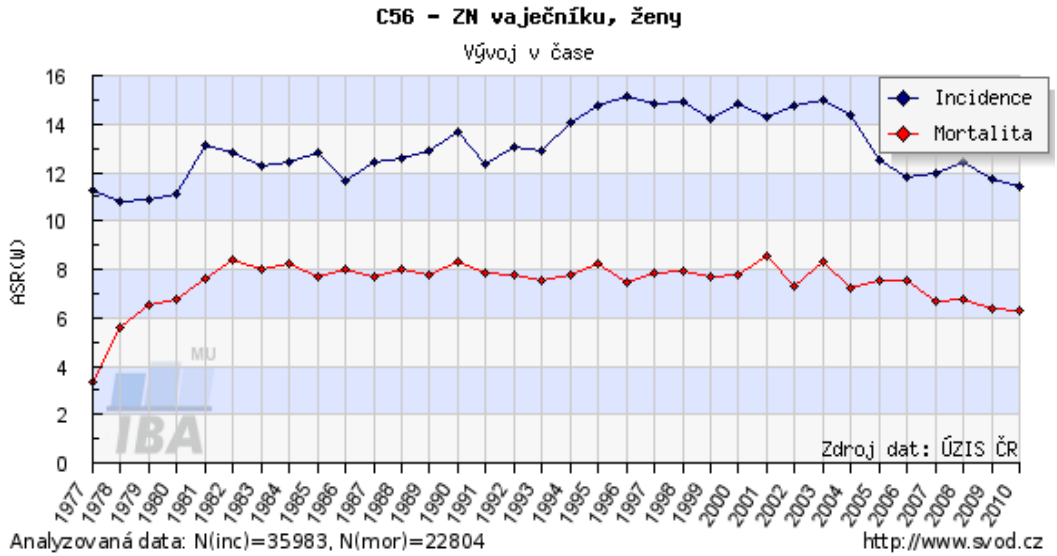
Breast cancer

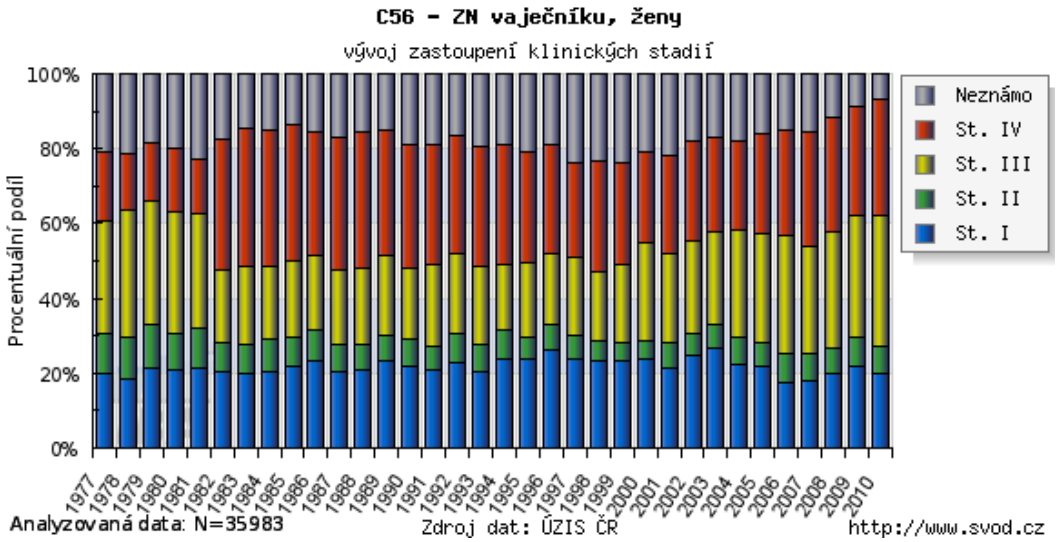
- the most frequent malignant cancer
  in female patients from Czech Republic
- rising incidence, declining mortality
- **5-10% of all breast carcinomas are hereditary**



Ovarian cancer

- ovarian, fallopian and primary peritoneal tumors make up to 15% of all malignant cancers in women
- Czech Republic is on the čth palce in Europe in incidence
- mortality is relatively high !!!
- early tumors have good prognosis, however most cancers are diagnosed **in stage III or IV**

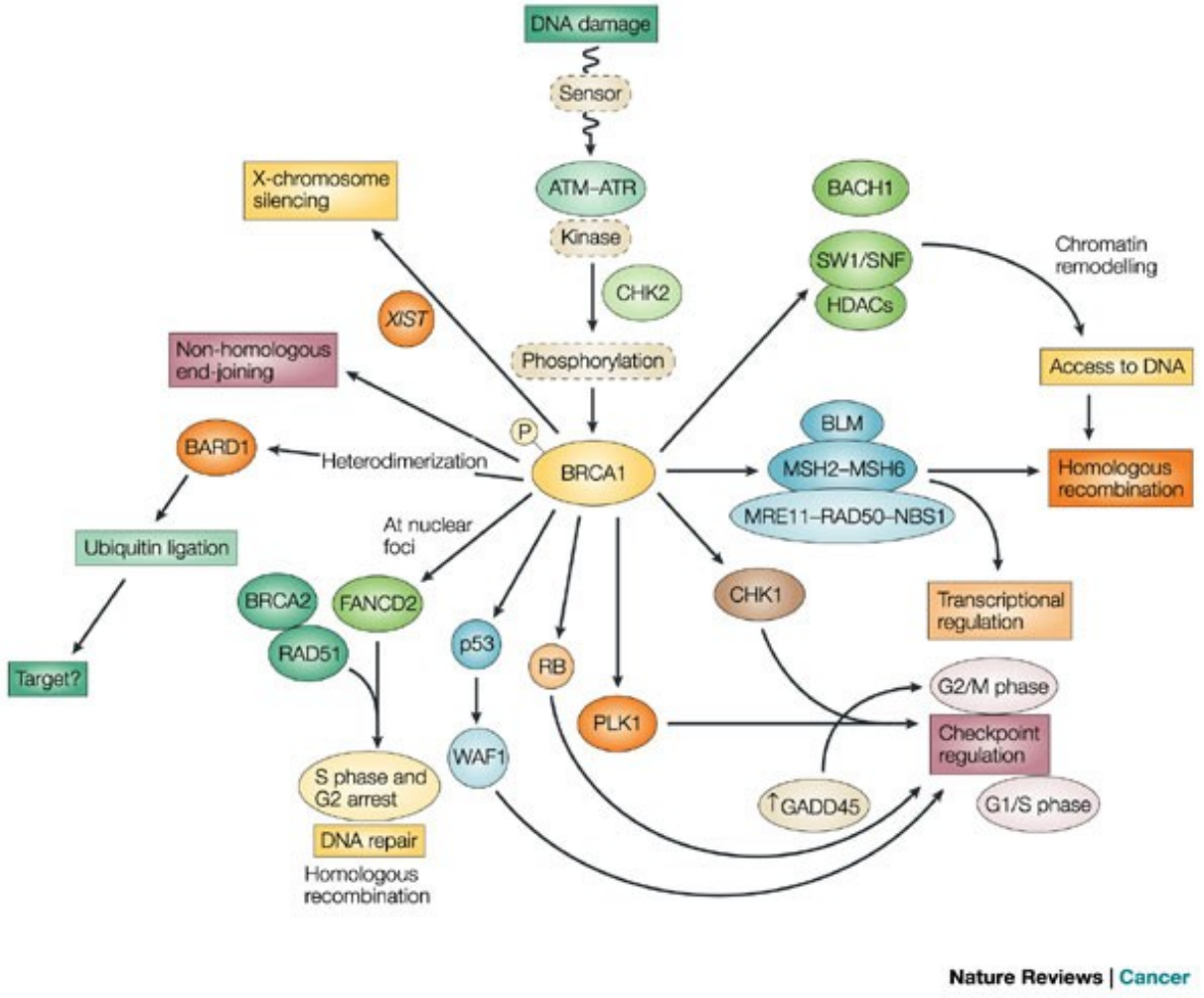




BRCA1 / BRCA2

- germline *BRCA1/2* mutations cause increased risk of malignancy
- **lifelong risk of breast cancer is 40-87% / 18-88%**
- breast cancer risk until 40 years is19% for *BRCA1* mutation carriers, 12% for *BRCA2* mutation carriers
- **lifelong risk of ovarian cancer is 22-65% / 10-35%**
- increased risk of other malignancies (endometrial cancer, cervix cancer, colorectal carcinoma, prostate and stomach cancer)

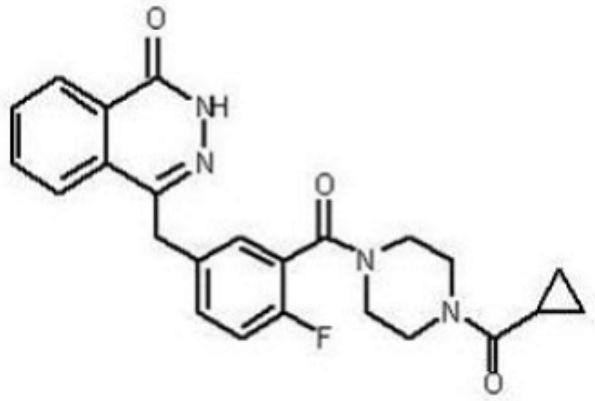
BRCA1/2 DNA cell pathways



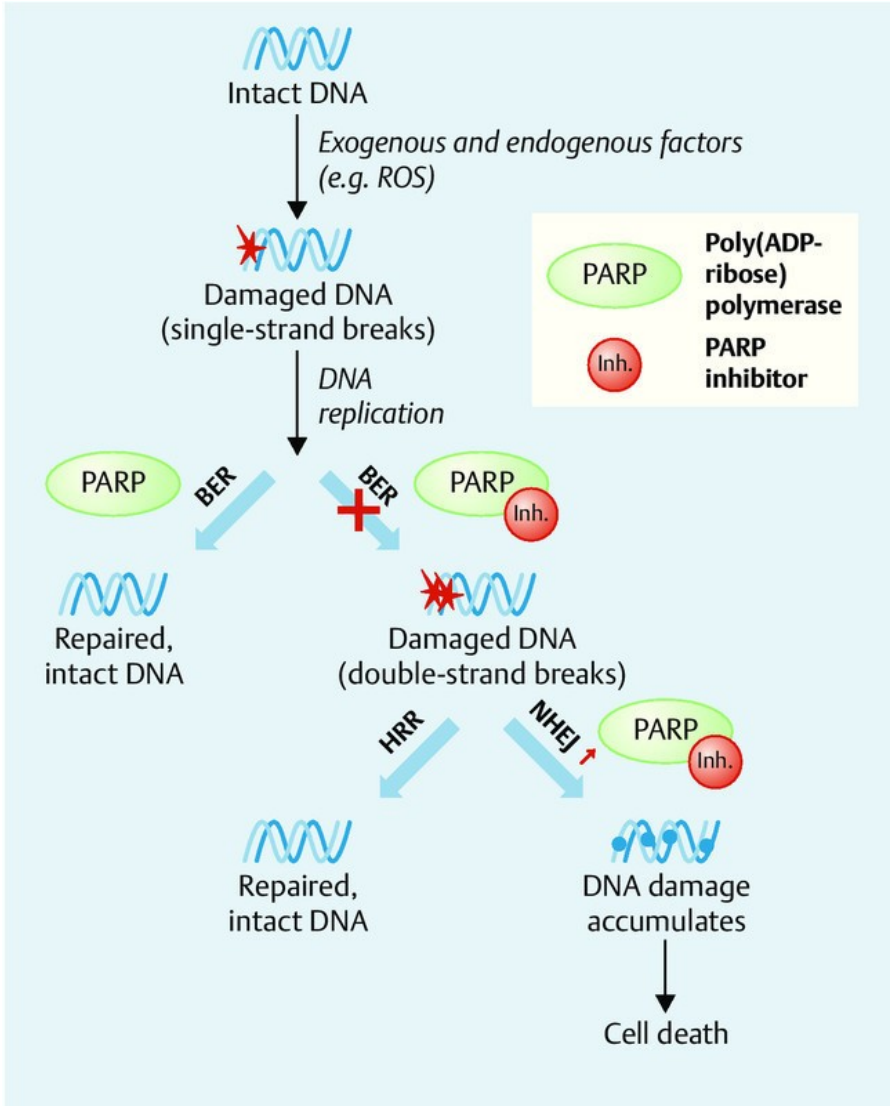
Level of

- **DNA repair**
- **cell cycle**
- **apoptosis**

PARP inhibitors



Olaparib
(Lynparza)



Other candidate genes

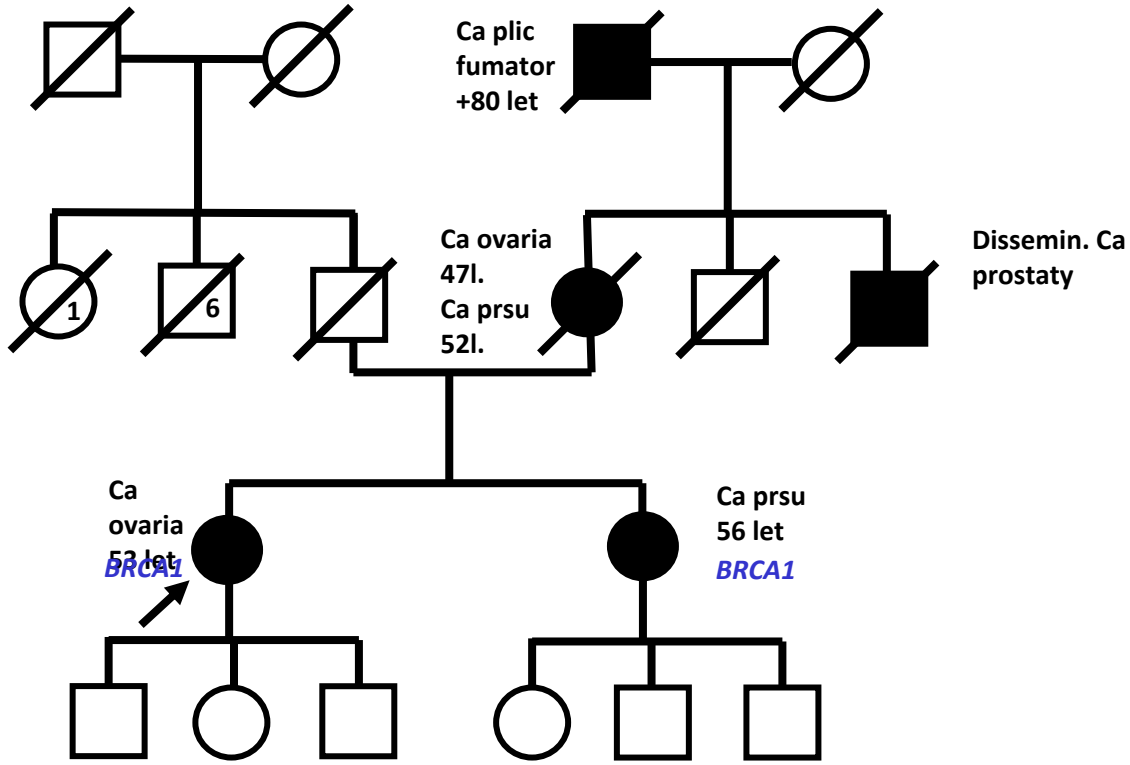
- There are further candidate genes increasing risko of hereditary breast and ovarian cancer
- ***ATM***, *APC, BARD1, BRIP1, CDH1,* ***CHEK2***, *EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN,* ***PALB2***, *PMS2, PTEN, RAD50, RAD51C, RAD51D, STK11,* ***TP53***
- **Gene panels:**
  CZECANCA: CZEch CAncer paNel for Clinical Application
  BRONCO- Brno ONCOlogical panel
- more than 300 genes associated with cancer susceptibility

BRCA1/2 mutation screening

- **NGS** – next generation sequencing
- **MLPA** analysis of large mutations or deletions
- comparison of detected mutations in databases, in silico prediction

Example pedigree

- **AD mode of inheritance**
- ccurence of breast / ovarian cancer in **younger pts**.
- occurence of neoplasms in every generation
- Occurence of other malignancies
- asymptomatic carriers! **(incomplete penetrance**)



Empiric assessment of cancer risk - Claus model

TABLE III
LIFE TIME RISK OF BREAST CANCER BASED ON FAMILY HISTORY OF BREAST CANCER
CLAUS MODEL

		Age of Cancer Onset in Relative					
		20-29	30-39	40-49	50-59	60-69	70-79
(1)	One affected first-degree relative	.211	.165	.132	.110	.096	.088
(2)	One affected second-degree relative	.142	.120	.104	.094	.094	.083
(3)	Two affected first-degree relatives						
	Age of onset in first affected relative	Age of onset in second affected relative					
	20-29	.484	.460	.434	.397	.354	.308
	30-39	.460	.437	.399	.353	.302	.252
	40-49	.434	.399	.354	.300	.246	.200
	50-59	.397	.353	.300	.245	.195	.158
	60-69	.354	.302	.246	.195	.156	.128
	70-79	.308	.252	.200	.158	.128	.109
(4)	Two affected second-degree relatives						
	Age of onset in first affected relative	Age of onset in second affected relative					
	20-29	.262	.256	.245	.231	.211	.189
	30-39	.256	.245	.230	.200	.186	.162
	40-49	.245	.230	.209	.184	.159	.137
	50-59	.231	.200	.184	.158	.135	.117
	60-69	.211	.186	.159	.135	.116	.103
	70-79	.189	.162	.137	.117	.103	.094
(5)	One affected first- and second-degree relative						
	Age of onset in first-degree relative	Age of onset in second-degree relative					
	20-29	.450	.433	.407	.369	.320	.264
	30-39	.437	.414	.377	.329	.274	.219
	40-49	.417	.383	.338	.281	.225	.177
	50-59	.388	.343	.289	.233	.182	.143
	60-69	.349	.296	.239	.188	.148	.120
	70-79	.305	.248	.196	.154	.124	.105

Adapted from Claus et al [59]. Srivastava A, McKinnon W, **Wood ME**: Assessing Risk of Breast and Ovarian Cancer in Women with Strong Family Histories. Oncology (Huntingt) 15(7):899-902, 2001.

Individual risk

- assessment based on family history, age of onset in relative and character of found mutation
- molecular genetic investigation is indicated by **clinical geneticist**
- ossibility of preimplantation genetic diagnostics

Useful links:
http://www.omim.org
http://arup.utah.edu/database/BRCA/
http://cancer.sanger.ac.uk/cosmic

criteria for genetic testing

- sporadic form

According to NCCN, NICE, ESMO, SLGG

- **fallopian / ovarian / primary peritoneal cancer in any age**
- **triple negative breast cancer** (ER, PR, HER2 neg.) <60 years, medullary carcinoma almost always consistent with TNBC
- unilateral breast cancer <45 years
  (<50 if no family history known)
- **two primary breast cancers**, first <50 years or both <60 years
- **breast and pancreas cancer duplicity** in any age
- **male breast cancer** in any age

criteria for genetic testing
– familial form

According to NCCN, NICE, ESMO, SLGG

3 relatives

- At least 3 direct relatives (including the proband) with breast cancer in any age

2 relatives

- 2 direct relatives (including the proband) with breast cancer, at least one diagnosed <50 years, or both <60 years
- Proband with breast cancer of any age and a direct relative with ovarian cancer, triple-negative breast cancer or medullar breast cancer, male breast cancer, pancreatic cancer or high/grade primary metastatic prostate cancer

Predictive testing of a known familial mutation above 18 yrs

Recommended screening of mutation carriers

- breast self-investigation since 18 years
- clinical breast investigation by a specialist twice a year since 25 years or 10 years earlier than the first occurence of breast/ovarian cancer in relatives
- 25-29 let: **MRI** and ultrasound, twice a years
- 30-65 let: **MRI** a mammography, twice a year
- gynecological investigation twice a year including transvaginal ultrasound
- further investigations (onkomarkers, screening for other malignancies, eg. gastroscopy, colonoscopy)

Prophylactic surgery

- **bilateral prophylactic adnexectomy**, at best in the age of 35-40 years in mutation carriers or immediately in elderly patients, possibility of hysterectomy is always considered (especially in *BRCA1* mutation carriers)

- **bilateral prophylactic mastectomy** at any time the patients asks, after consultation with oncologist and complex preventive investigations

Further considerations

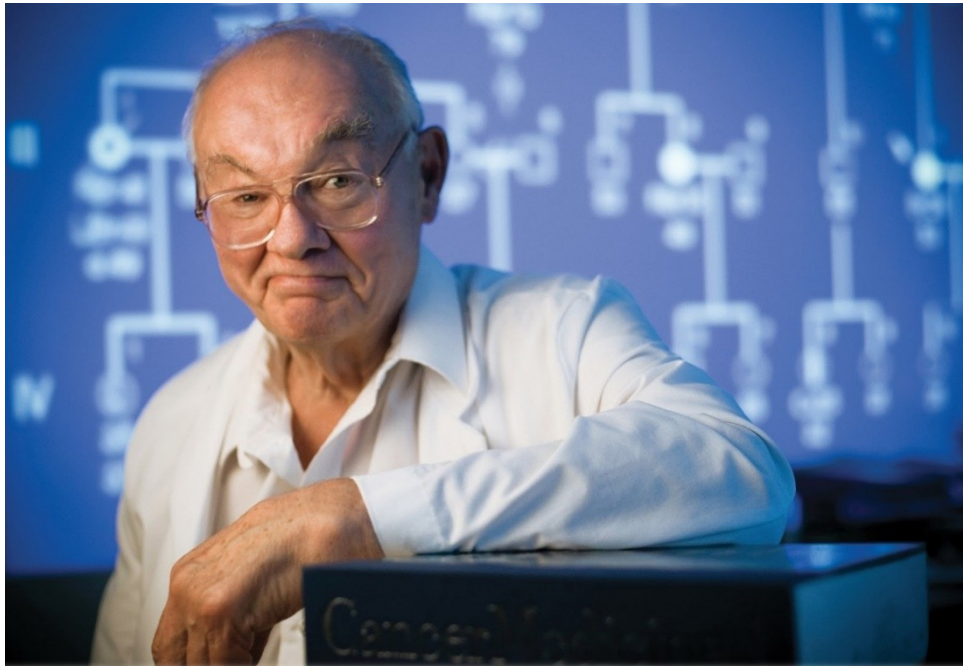
- **chemoprevention** – Tamoxifen
  Tamoxifen use can protect i *BRCA2* mutation carriers, but not in *BRCA1* carriers: *King et al., 2001*
- Tamoxifen increases survival by 1.8 years and quality adjusted survival by 2,7 years: *Grann et al., 2002*

- role of oral contraceptives? Low dose COC possibly protects against ovarian cancer in BRCA1/2 carriers but its role in breast cancer is uncertain (probably no increased risk)

- **reprodukční rozhodnutí**

The best protection is an early detection!

Hereditary nonpolypous colorectal carcinoma (NPCC)
Lynch syndrome



*Prof. Henry T. Lynch, MD. *1928 -*

'Hereditary factors in cancer: study of two large midwestern kindreds', Arch. Intern. Med., 1966

Research of several families with colorectal and other cancers in US states Michigan and Nebraska

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Lynch syndrome

- the most frequent congenital predisposition to colorectal cancer
- high penetrance, AD mode of inheritance
- approximately 2-5% of all colorectal cancers
- 28-75% risk of colorectal cancer in men,
  24-52% risk of colorectal cancer in women
- Risk of other tumors: endometrial cancer, ovarian cancer in women, gastric cancer, urinary tract cancers, hepatobilary cancers, cancer of small intestine, brain tumors

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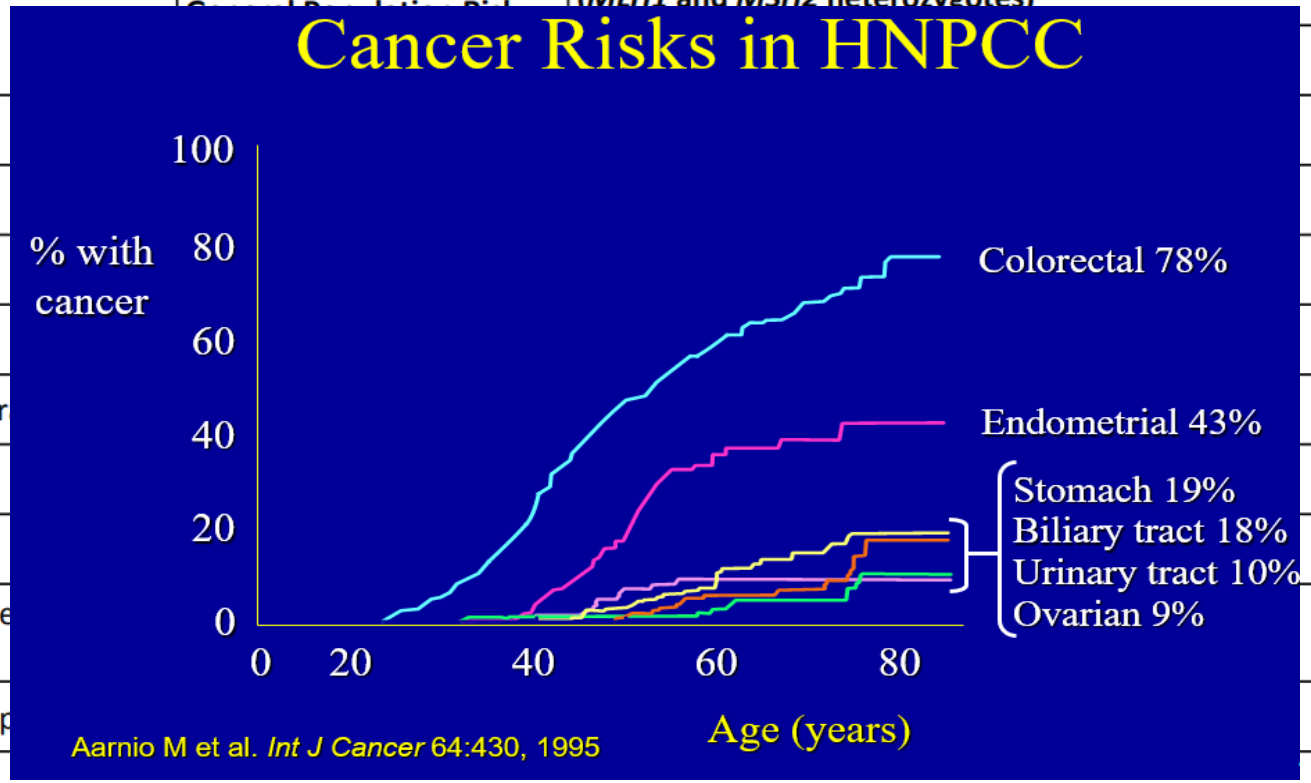
Lynch syndrome

Cancer Type		Lynch Syndrome (*MLH1* and *MSH2* heterozygotes)
Colon		
Endometrium		
Stomach		
Ovary		
Hepatobiliary tr		
Urinary tract		
Small bowel		
Brain/central ne system		
Sebaceous neop		



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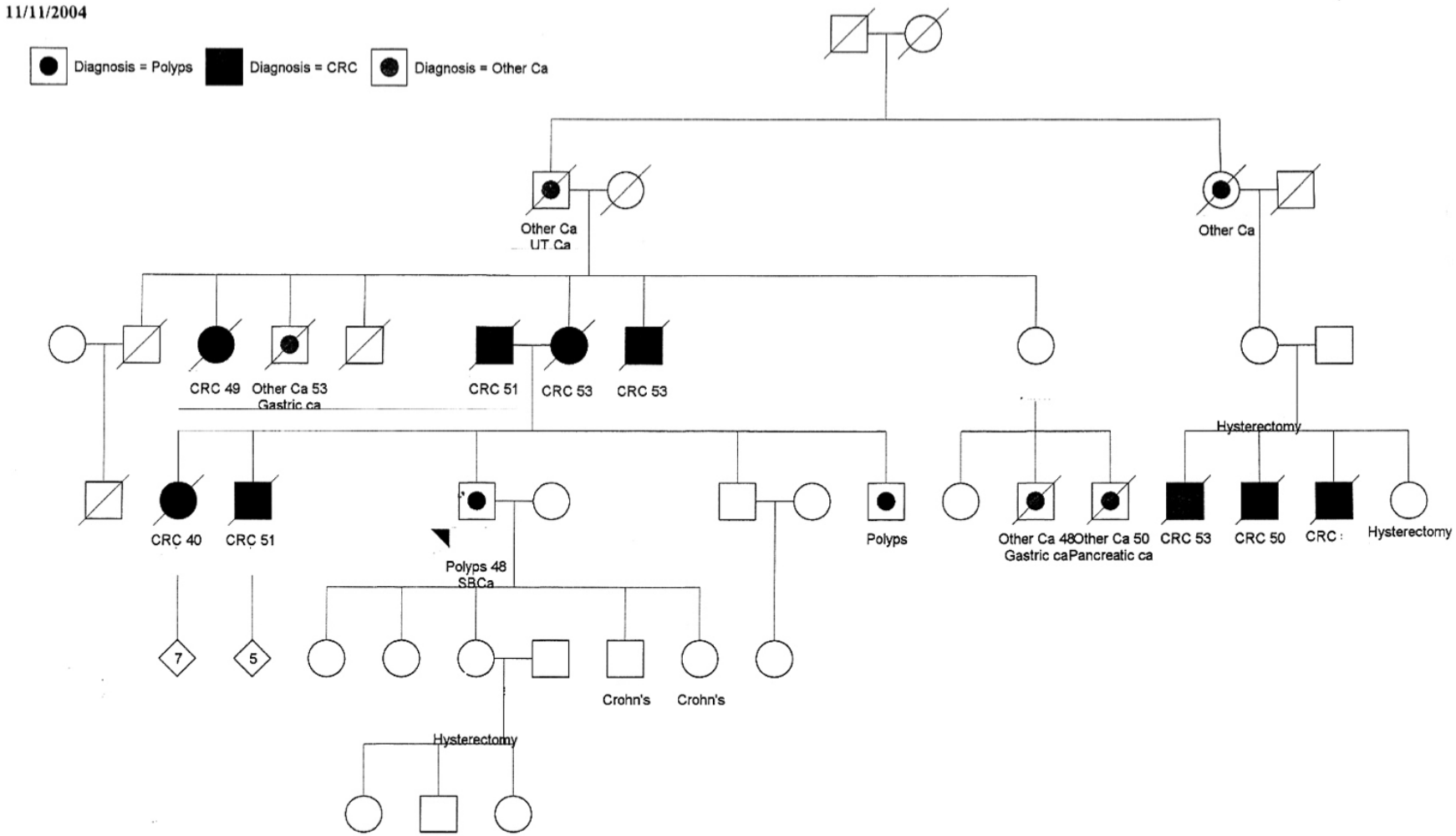
11/11/2004
Diagnosis = Polyps
Diagnosis = CRC
Diagnosis = Other Ca
Other Ca
UT Ca
Other Ca
CRC 49
Other Ca 53
Gastric ca
CRC 51
CRC 53
CRC 53
Hysterectomy
CRC 40
CRC 51
Polyps 48
SBCa
Polyps
Other Ca 48
Gastric ca
Other Ca 50
Pancreatic ca
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Hysterectomy
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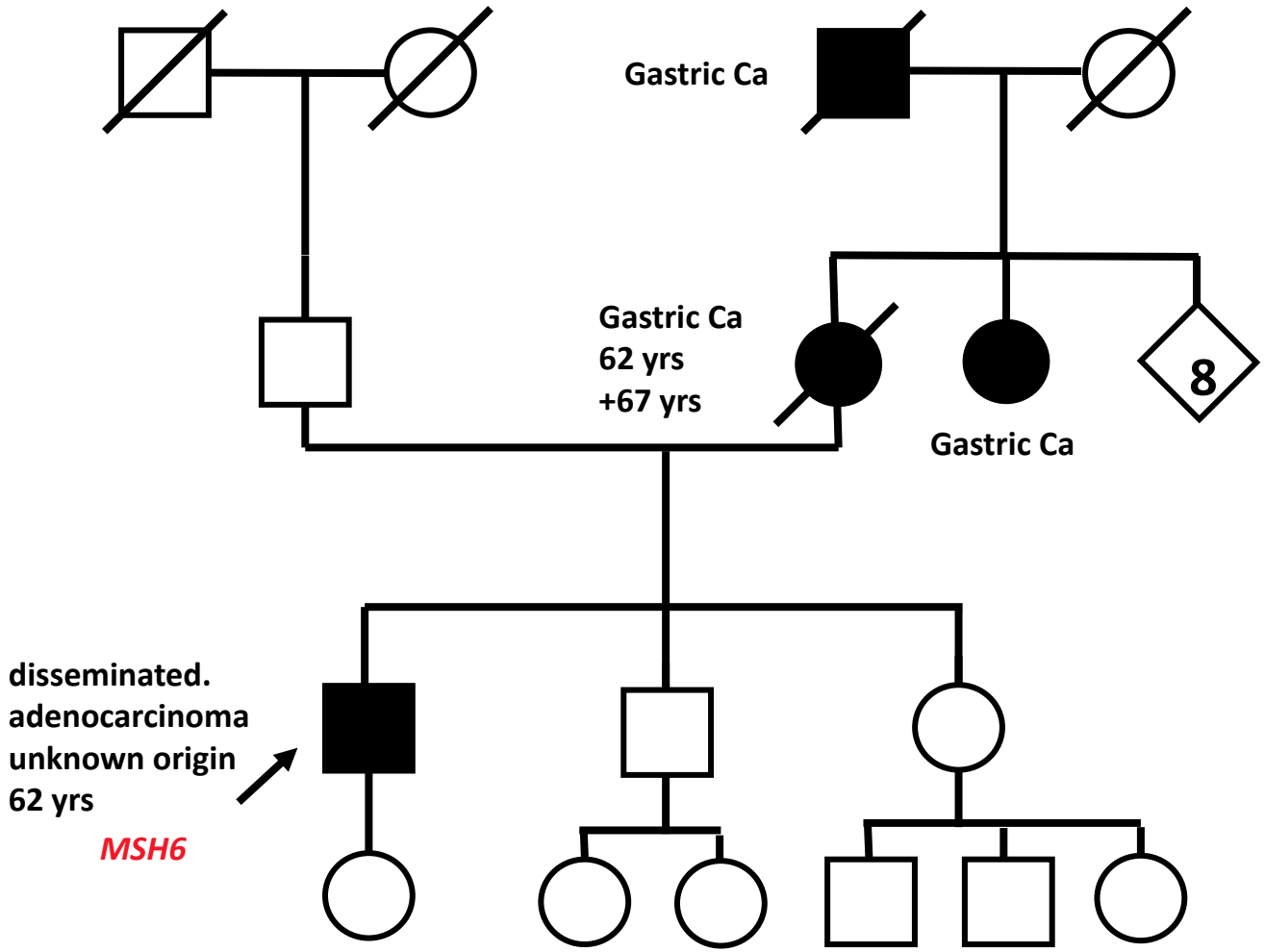
Crohn's
Crohn's
Hysterectomy

Example pedigree



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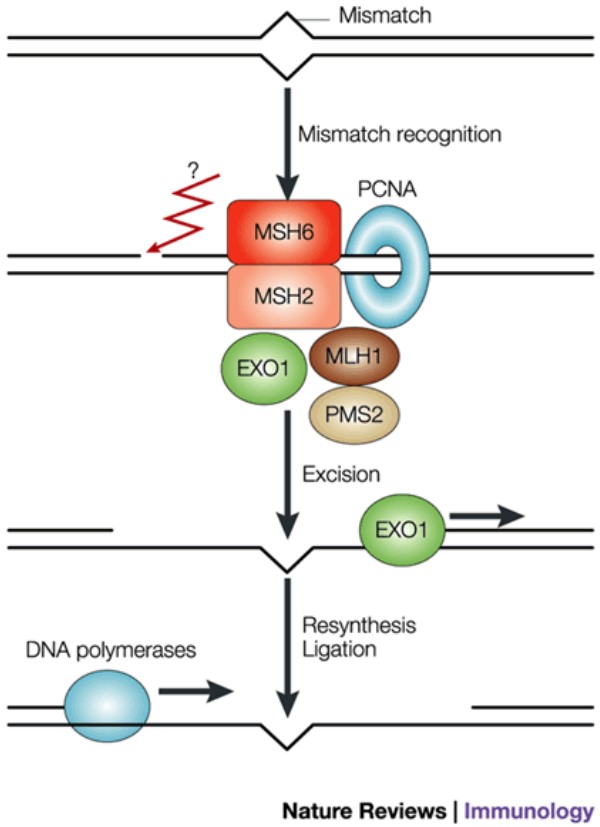
MLH1, MSH2, MSH6 and PMS2 genes

- **mismatch repair genes**
- system responsible for genetic stability in prokaryotes and eukaryotes
- recognition of mismatch nucleotides, excision and repair by DNA polymerases



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Indikation for mutation screening
MLH1, MSH2, MSH6, PMS2
Amsterdam criteria I/II

- at least three family members with colorectal carcinoma (or other tumor in HNPCC spectrum), one of thgem is a first degree relative to the other two
- at least two generations affected
- at least one patient younger than 50 years at the time of diagnosis
- the tumor has been verified by pathologist
- familiar adenomatous polyposis excluded

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Dispenzarization of asymptomatic mutation carriers

- total clinical examination by specialist once per year
- coloscopy once per 2 years, starting at 20 years, or 10 years earlier than onset of cancer in the youngest affected relative
- in women: gynaecological examination once per year, starting at 18 years, transvaginal USG + CA125 1/year starting at 20, 2/year starting at 35
- aspiration biopsy of endometrium 1/year starting at 30
- USG of the abdomen 1/year starting at 30
- urine stick and sediment examination 1/year starting at 30
- gastroscopy 1/3-4 years starting at 35
- further examinations according to the family history and considerations of the attending clinician

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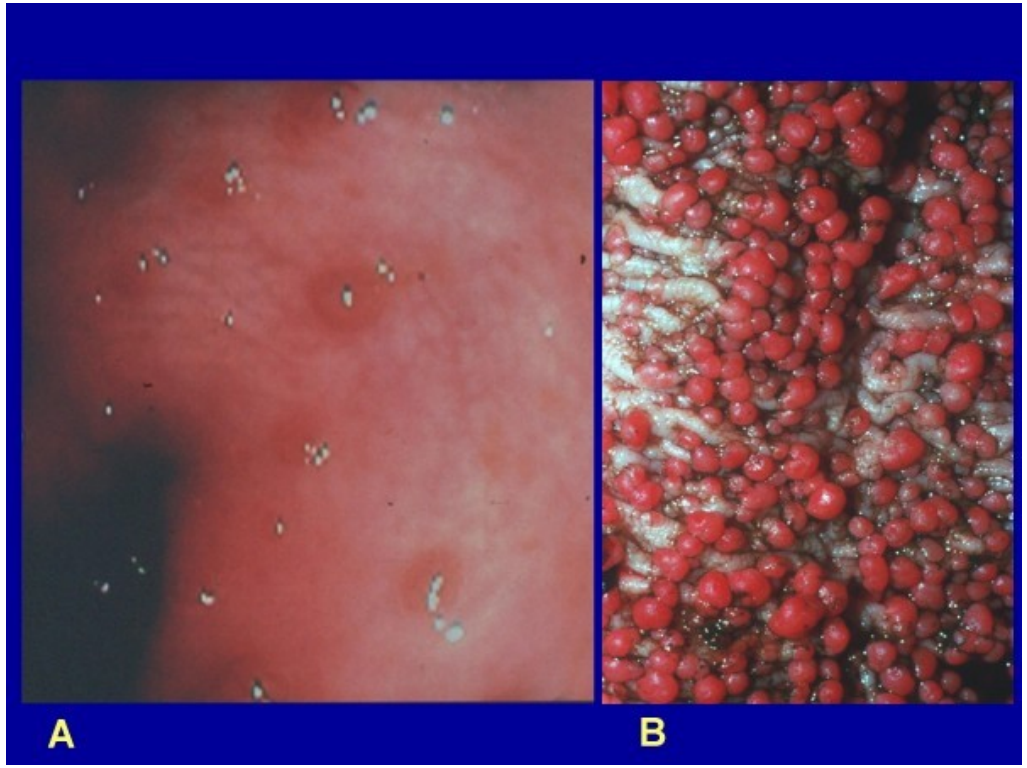
Familial adenomatous polyposis



Endoscopic findings in APC

Menzel, 1721: Multiple colorectal polypous lesions

Corvisart, 1824: Hypertrofic features in a sample of a 22-year old man with more than 20 „protrusions“ of colon ascendens

Lockhart-Mummery, Dukes, 1925, Lancet: „Cancer and heredity“

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Familial adenomatous polyposis

- occurence of more than 100 adenomatous polyps of large intestine (or less in younger age)
- onset of polyp formation around 15 years, at 35 years in 95% of patients
- high risk of colorectal carcinoma, often multiple carcinomas, at a very early age
- **penetrance of the disease near 100% until 50 years!!!**
- *APC* gene – classical/attenuated form (AD),
  MUTYH gene (MYH-asociated polyposis) (AR)
- other associated malignacies (desmoid tumors, hepatoblastoma)

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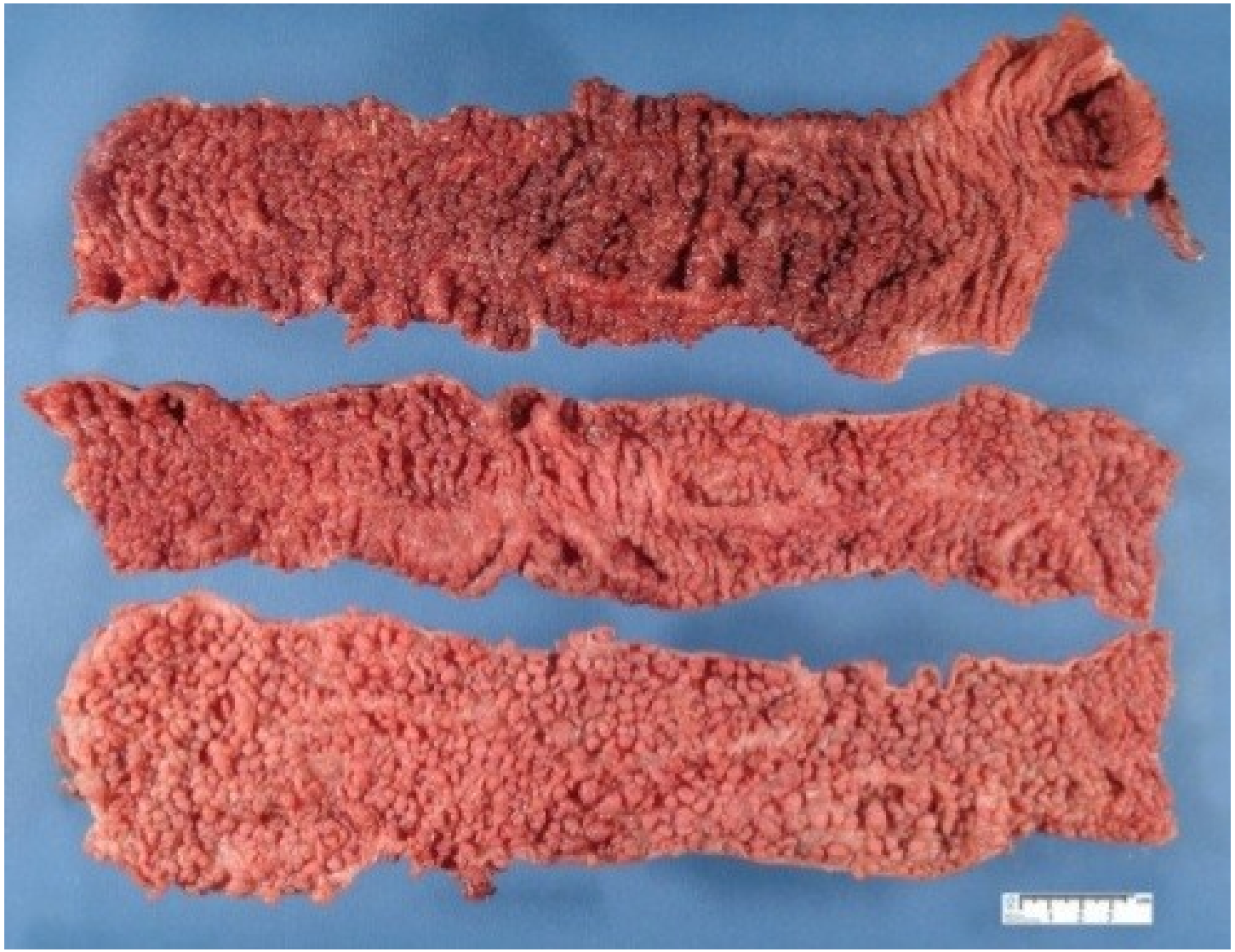

Macroscopic pathological sample of the large intestine affected by APC

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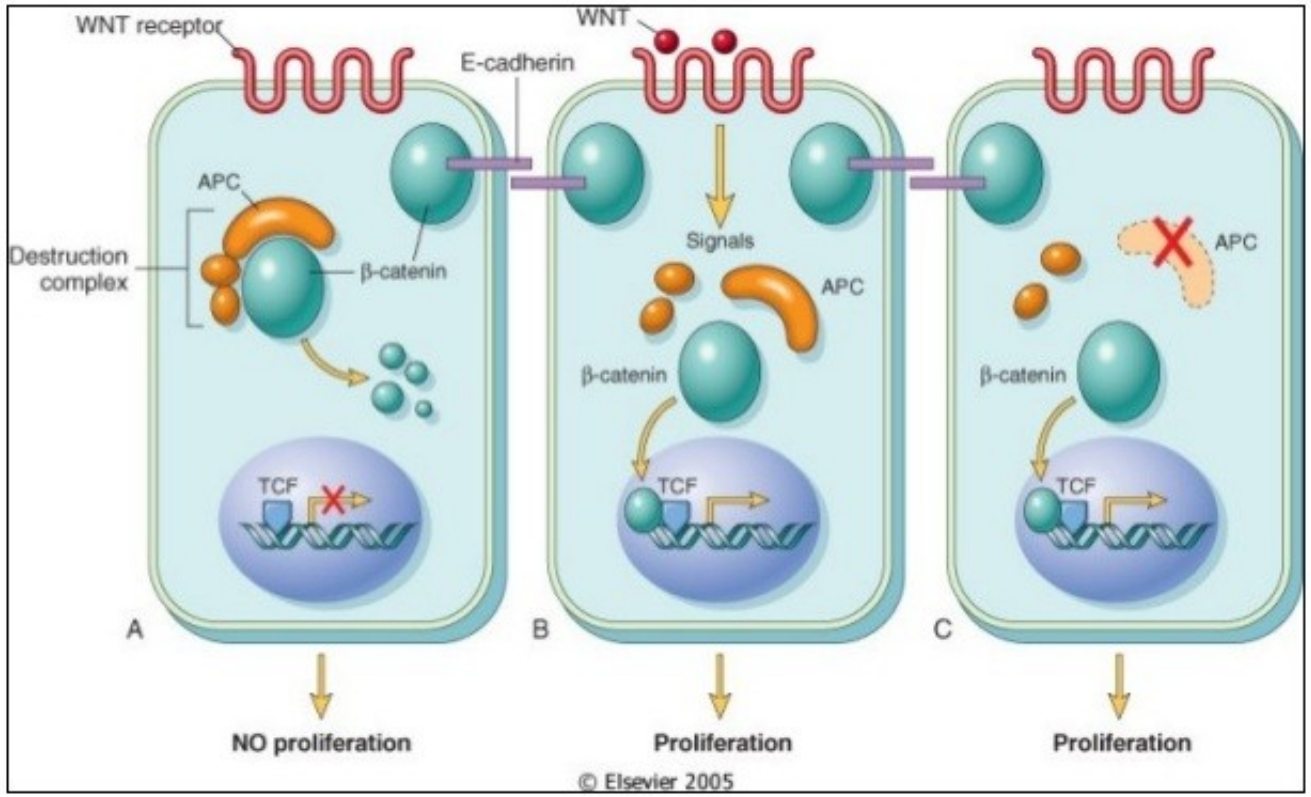
APC gene

- **tumor-supressor gene**
- Wnt/ beta-katenin signal pathway inhibition

- plays a role in **cell adhesion, migration,** chromosome segregation, apoptosis and neural differentiation



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Indication for *APC* mutation screening

- all forms of diffuse intestinal adenomatous polyposis
- predictive testing can be performed at any age , even in children!
- If there is a clinical suspicion for APC, all first degree relatives should undergo colonoscopy during the investigation og clinical (parents, siblings, in children aged 10-15 years sigmoideoscopy)

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Dispensarisation of APC gene mutation carriers

- sigmoideoscopy every 1-2 years, starting at 10-12 years, colonoscopy after formation of first polyps
- If severe degree of polyposis is discovered, total colectomy or proctocolectomy is considered
- gastroduodenoscopy starting at 25 years, according to clinical degree
- USG investigation of abdomen 1/year in the first 10 years – heaptoblastoma screening
- further investigations depending on family history

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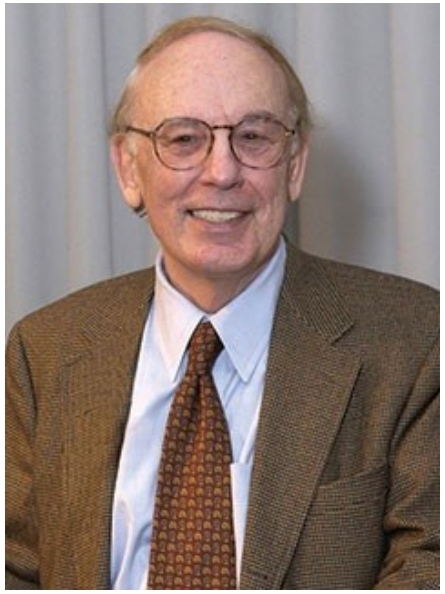
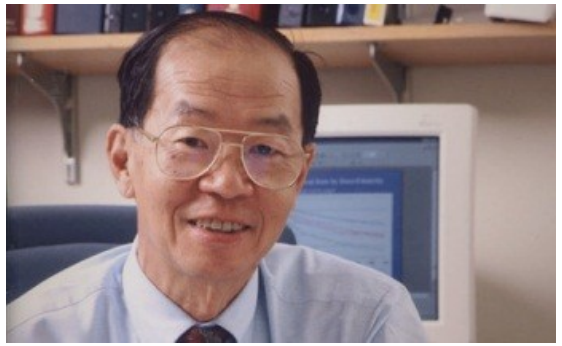
Li-Fraumeni syndrome

*Joseph F., Fraumeni, Jr., MD. *1933 -*





Frederick Pei Li, MD. 1940 - 2015

„Sarcomas of soft tissues, breast cancer and other neoplasms. A new familial syndrome?“ Ann Intern Med 1969

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Li-Fraumeni syndrome

- rare **autosomal dominant** cancer predisposition syndrome, 50% of individuals is affected by 40 years, up to 90% by 60 years of age
- 77% of malignancies belongs to these six types: breast cancer, sarkomas of soft tissues, osteosarcomas, brain tumors, adrenocortical carcinoma, and **leukemias**
- increased frequency of other malignancies
- classical LFS (*TP53* gene mutations)
  Li-Fraumeni-like syndrom (*CHEK2* gene mutations)

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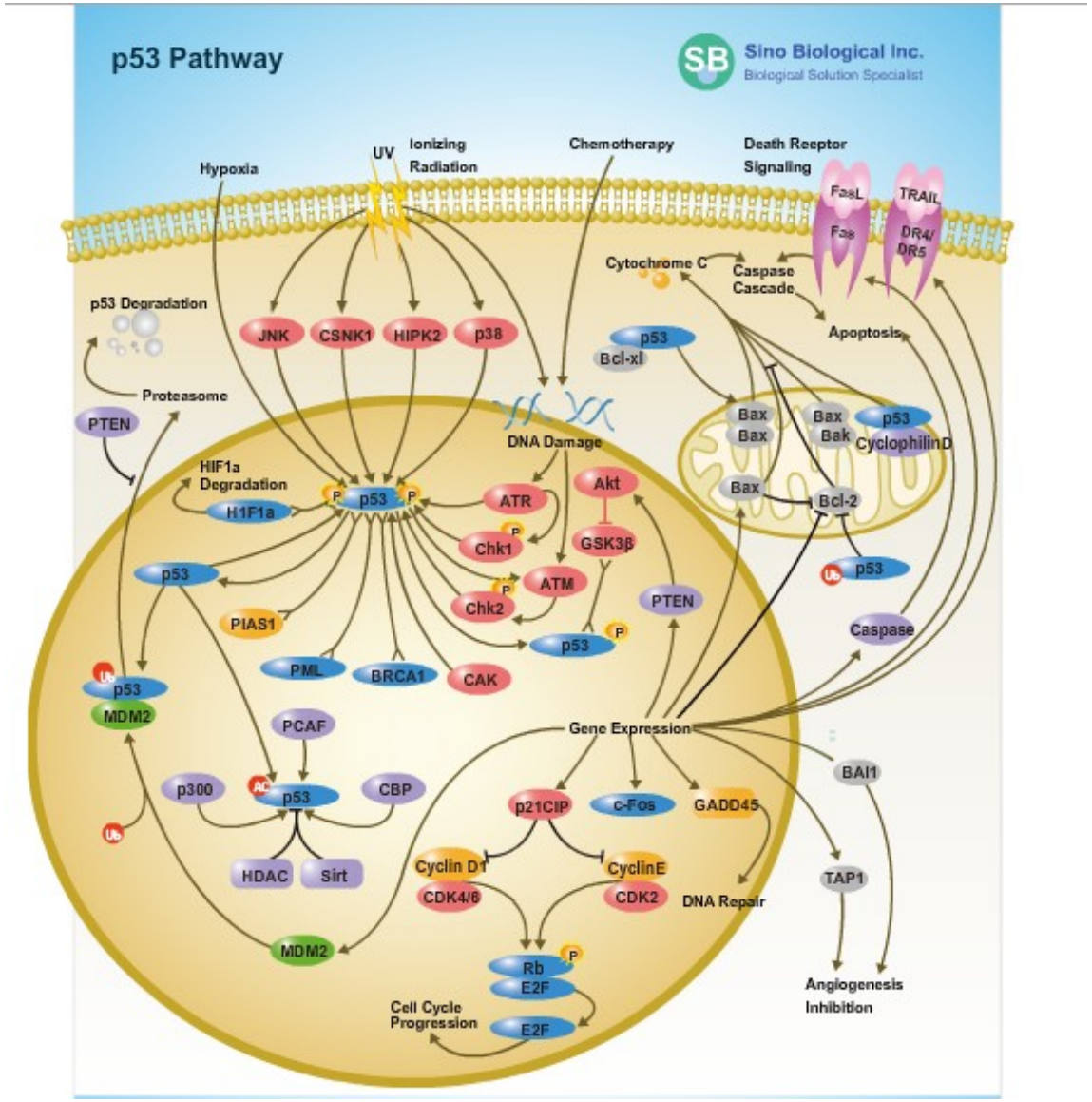
TP53 gene

- **„guardian of genome“**
- **transcription factor** responding to different forms of cellular stress
- regulates target genes, inducing **cell cycle arrest, apoptosis, DNA repair,,** cell senescence and changes in metabolism
- regulated by a list of **up- and downstream** genes



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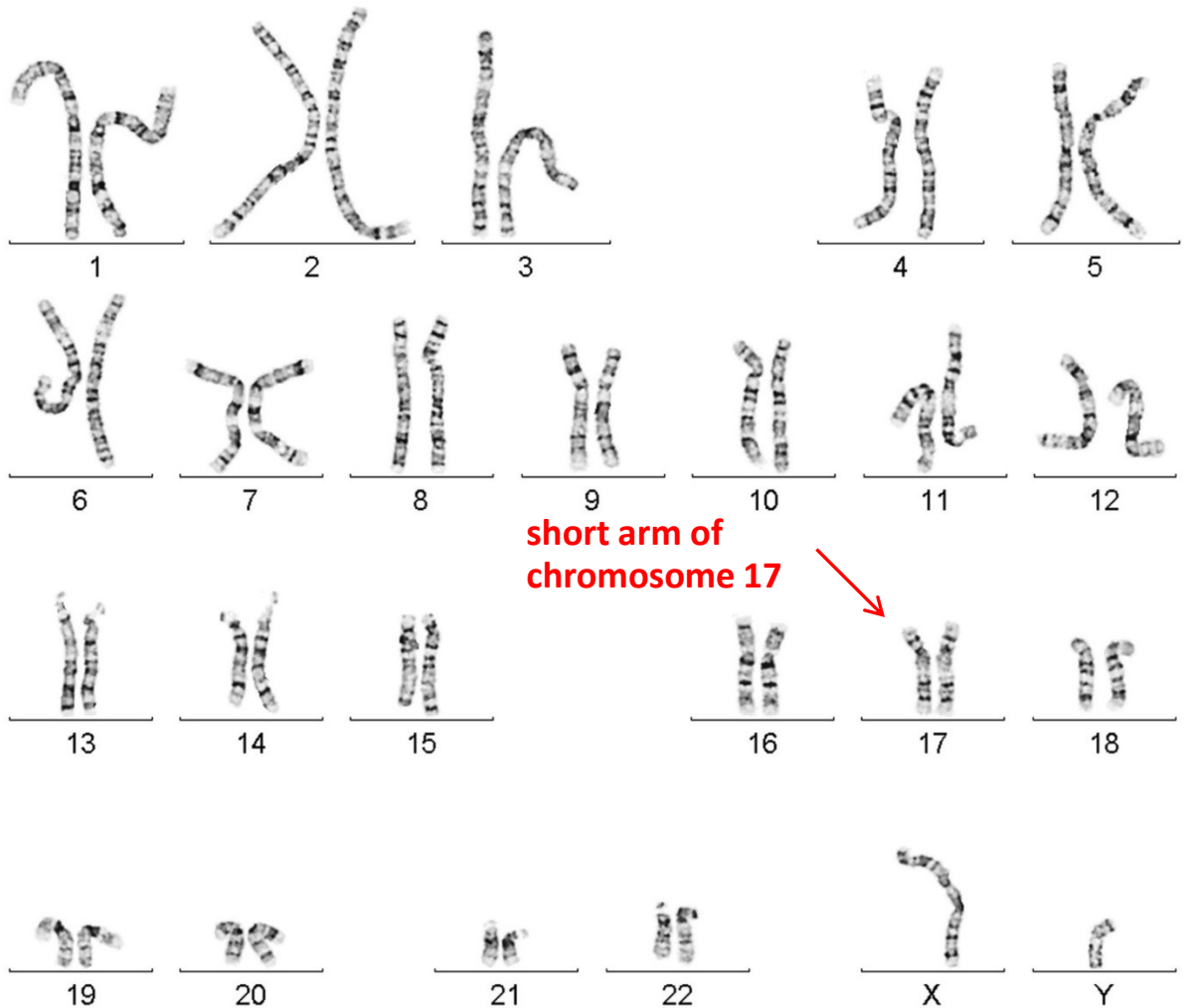
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X
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short arm of
chromosome 17

TP53 mutation screening criteria

(modified Li-Fraumeni syndrome criteria by Chompret)

- proband with a tumor of the LFS spectrum under 46 years plus at least one first- or second degree rleative with a LFS-associated tumor
- proband with multiple tu,mors, out of which at least two belong to the LFS-associated tumors, first of which was diagnosed under 46 years
- Proband with adrenocortical carcinoma or a patient with breast cancer diagnosed under 36 years, without a *BRCA1* or *BRCA2* gene mutation, regardless of family history

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Selected dysmorphic syndromes associated with increased risk of malignancies

Syndrome	Gene	Asociované neoplazie
Sotos syndrom	*NSD1*	leukemias, lymphomas
Fanconi anemia	*FANCA, FANCC, FANCD* and other	hematological malignancies (MDS, leukemias)
Ataxia teleangiectasia	*ATM*	chronic lymfocytic leukemia, lymphomas of childhood
Nijmegen Breakage Syndrome	*NBS*	lymphomas (Burkitt lymphoma, DLBCL), breast cancer
Bloom syndrome	*BLM*	Non-Hodgin lymphomas, breast cancer

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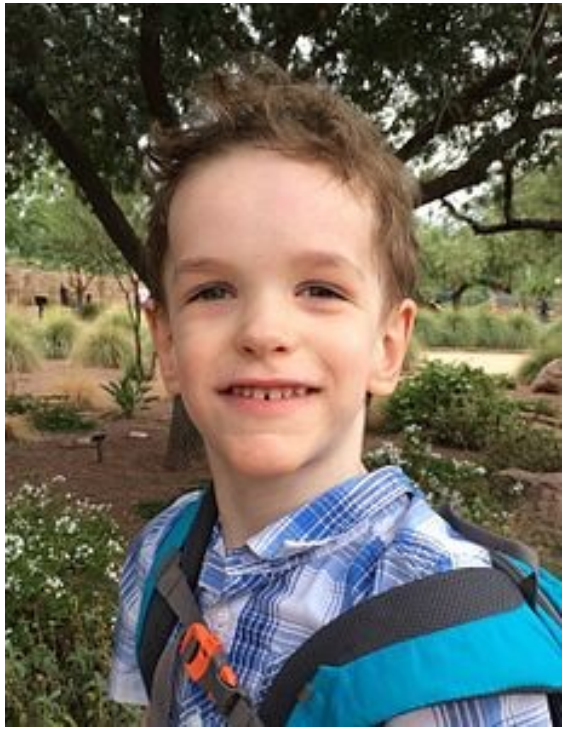
Sotos syndrome



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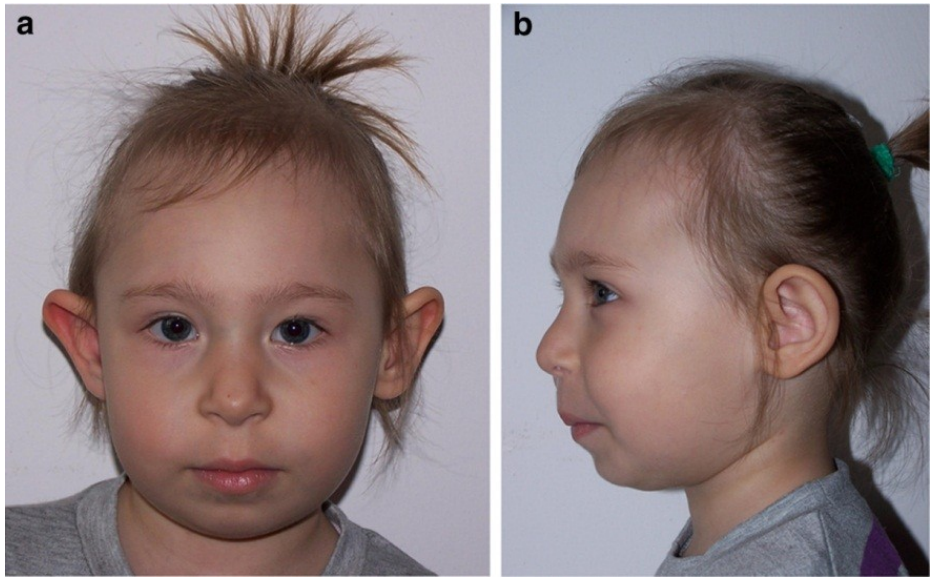
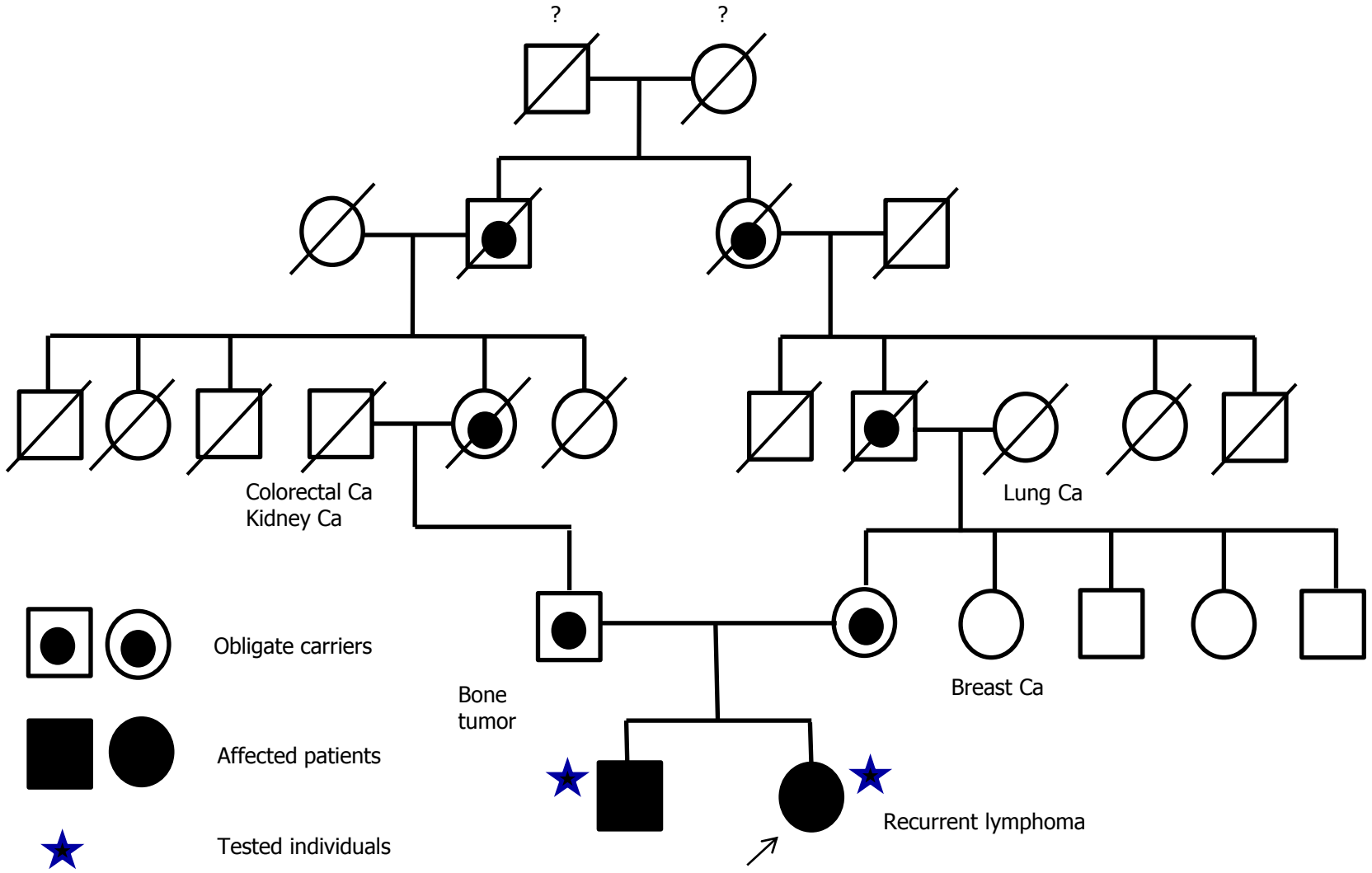
Nijmegen Breakage Syndrome



MUNI
MED

Bloom syndrome

MUNI MED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Colorectal Ca
Kidney Ca
Lung Ca
Breast Ca
Bone
tumor
Recurrent lymphoma
Obligate carriers
Affected patients
Tested individuals

MUNI
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Lékařská fakulta Masarykovy univerzity
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