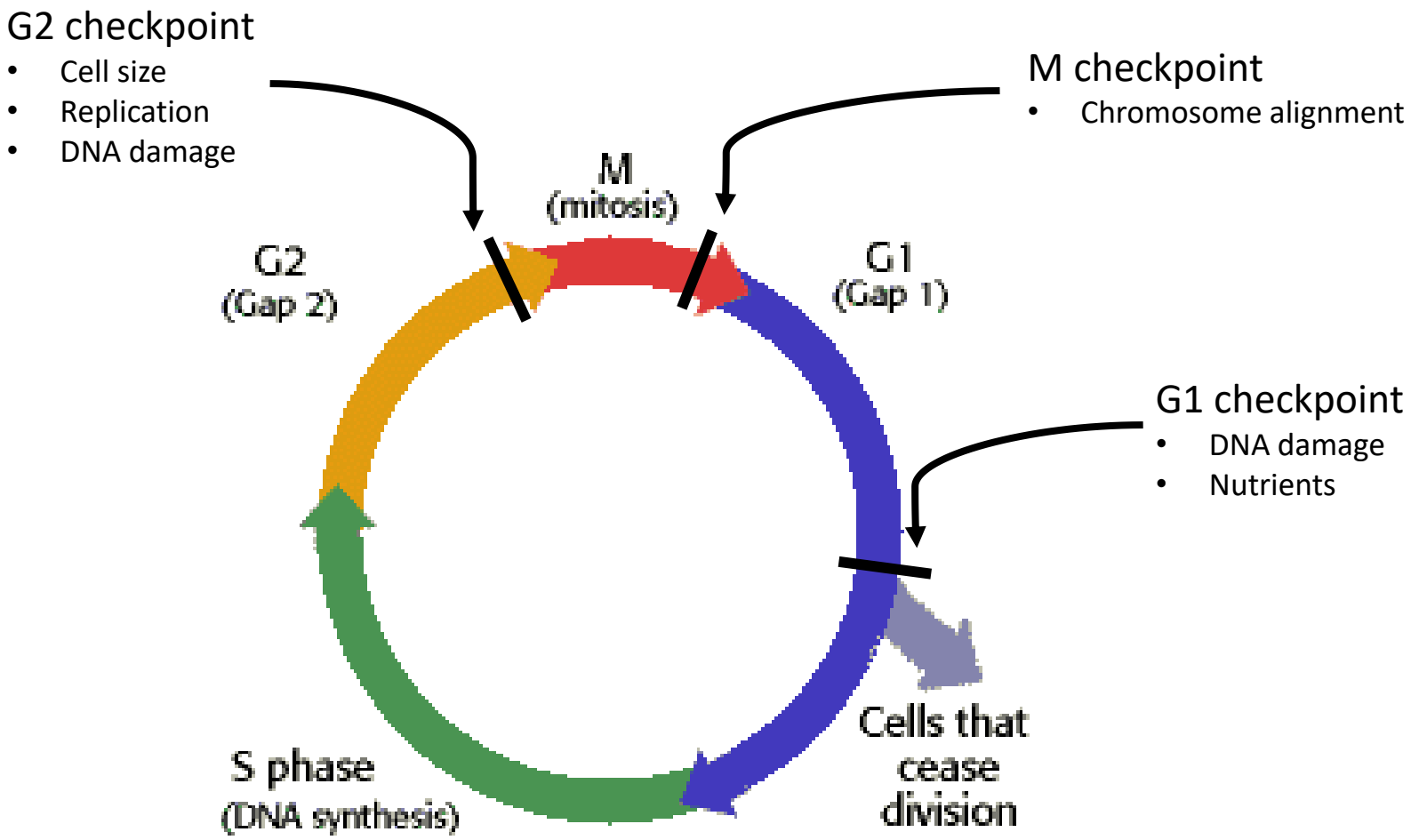
Παθογενετικοί μηχανισμοί και σύνδρομα προδιάθεσης του καρκίνου

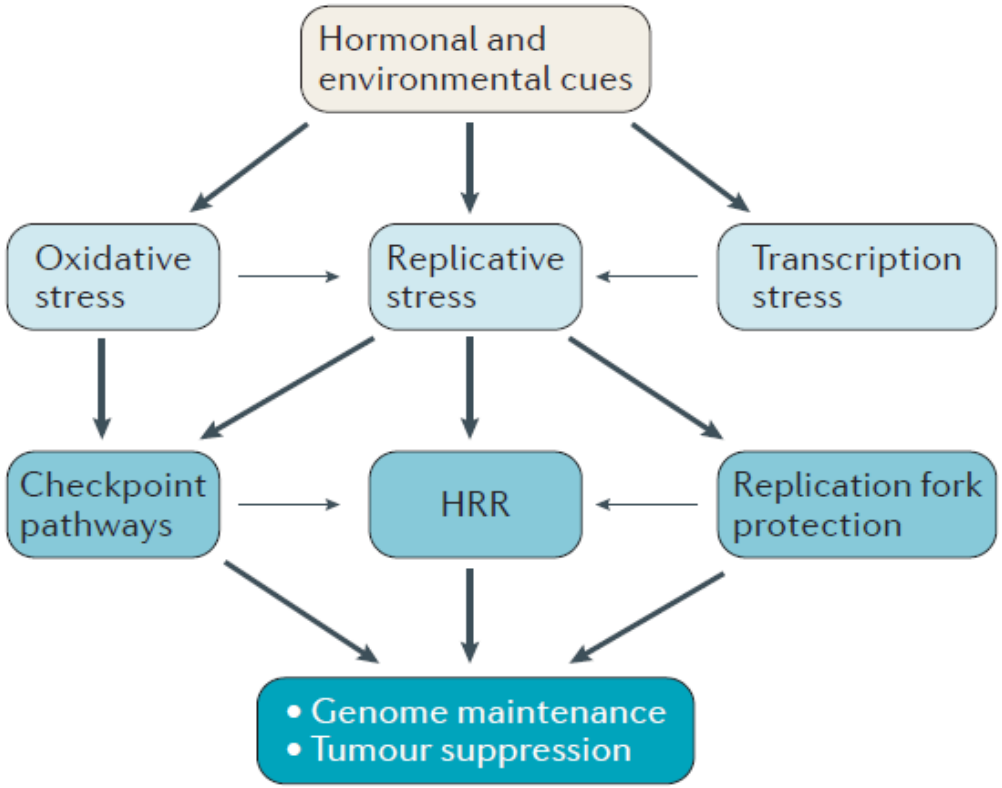
Πανεπιστημιακή Αιματολογική Ογκολογική Μονάδα (ΠΟΑιΜ)
Α’ Παιδιατρική Κλινική ΕΚΠΑ

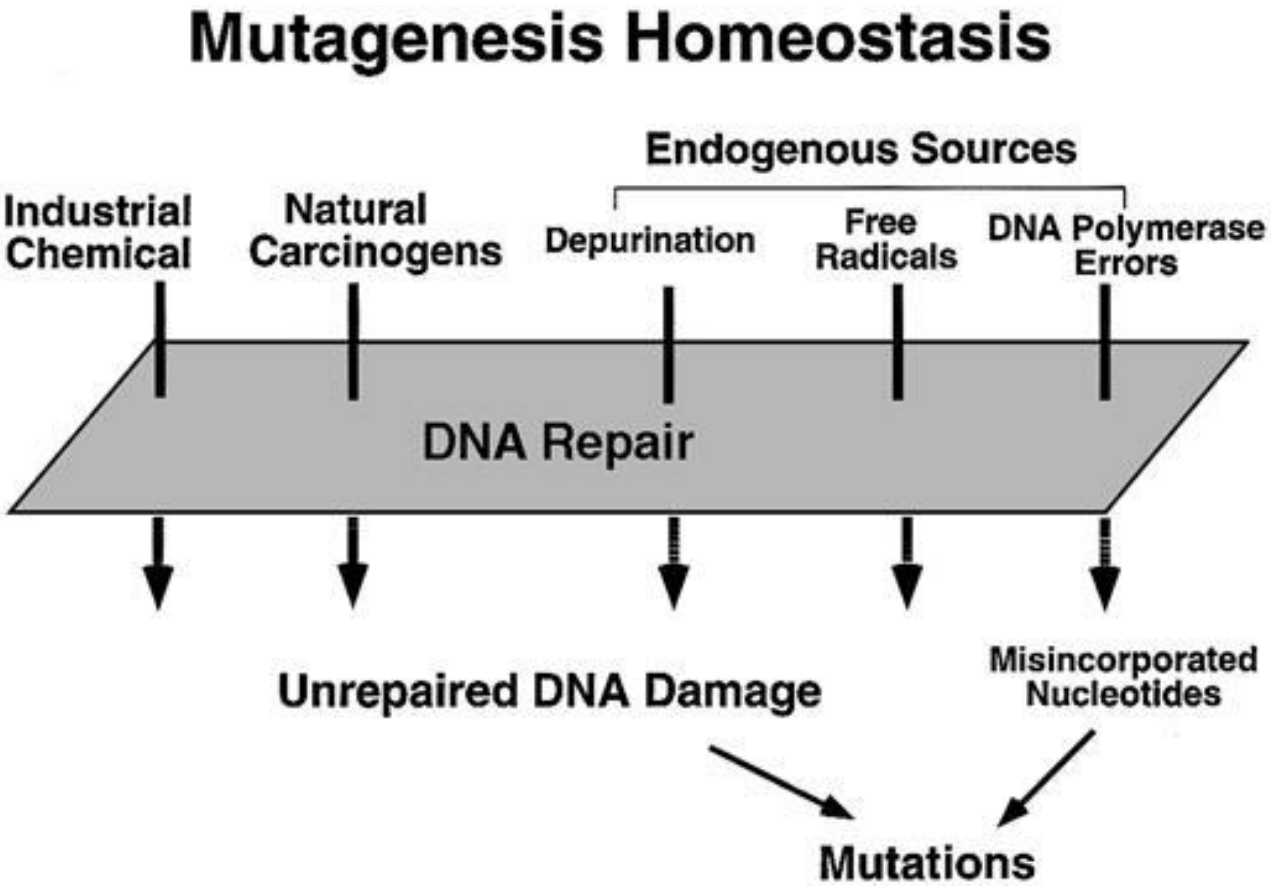
Κατερίνα Κατσιμπάρδη, MD, PhD
Γλεντής Σταύρος, PhD

Κυτταρικός κύκλος



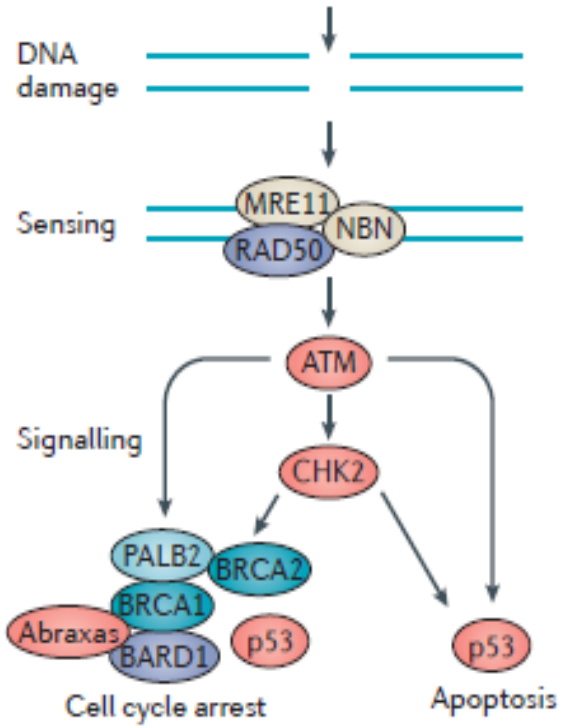
Σωματικές Μεταλλάξεις



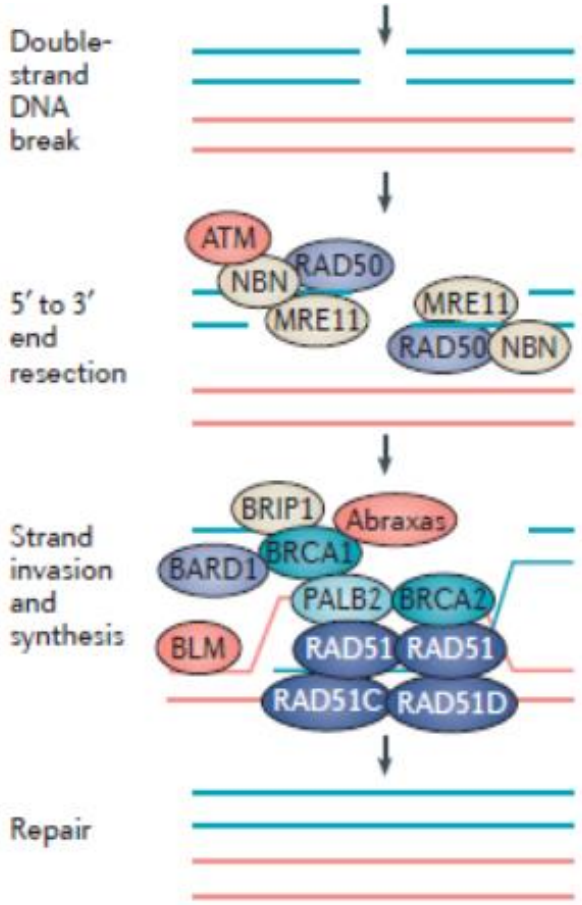


Μονοπάτια γενομικής σταθερότητας (Genome maintenance)

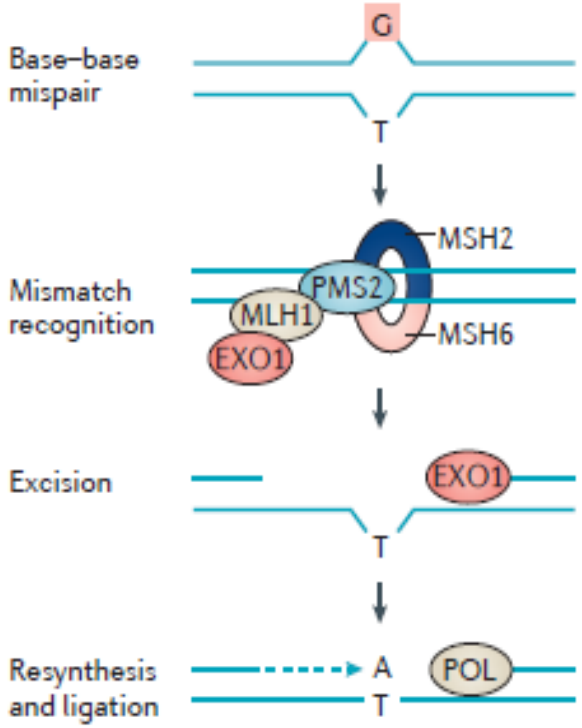
DNA damage checkpoint control



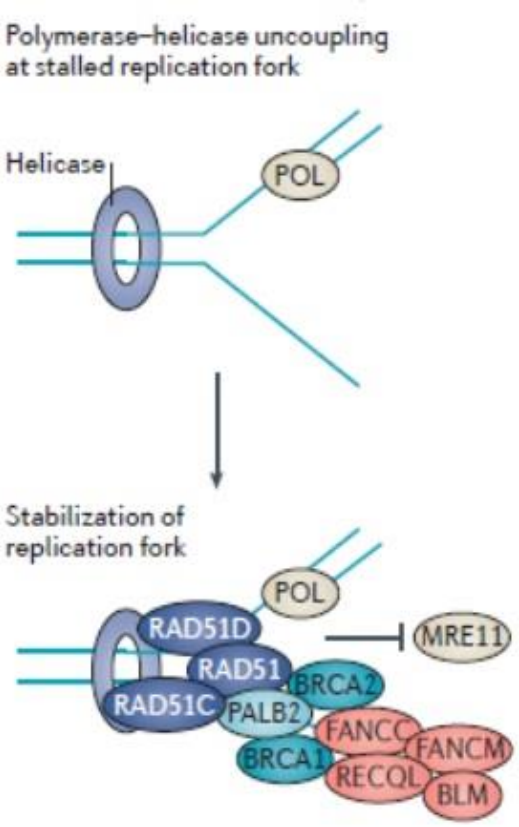
Homologous recombination repair



DNA mismatch repair

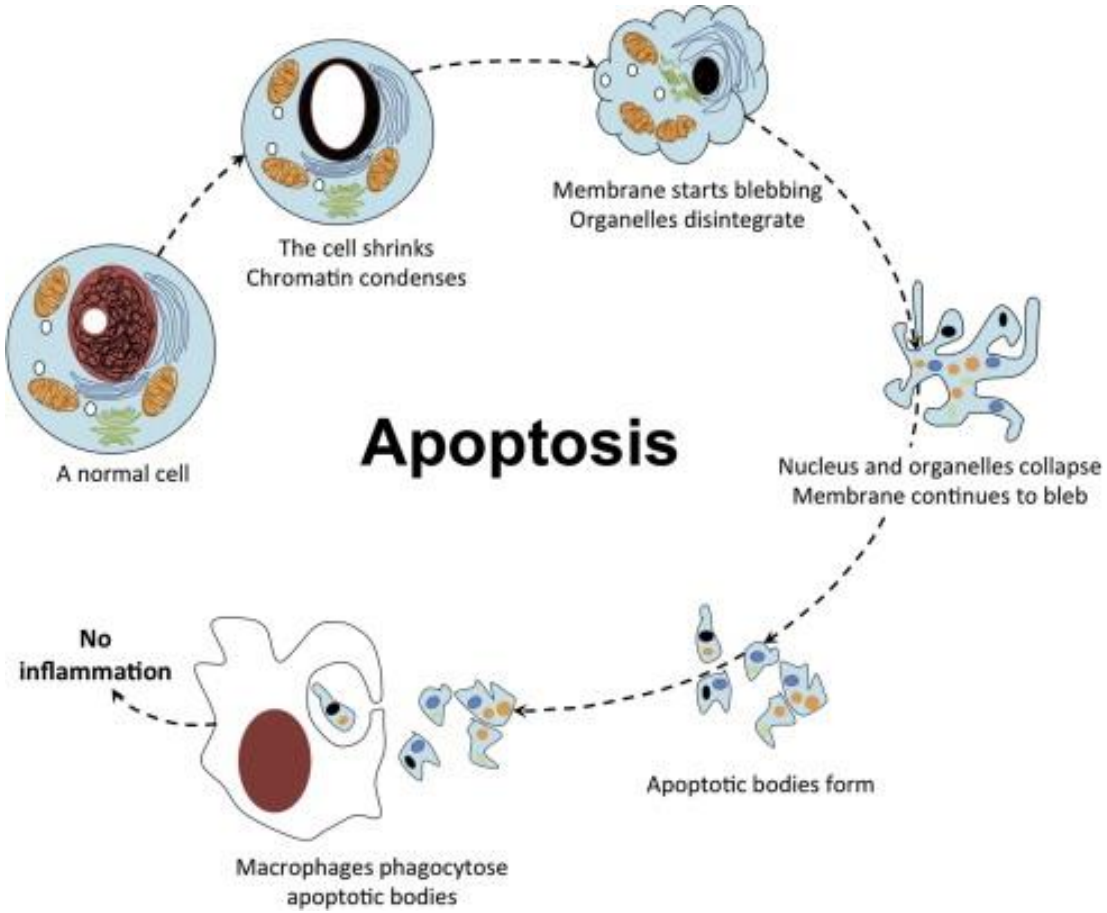


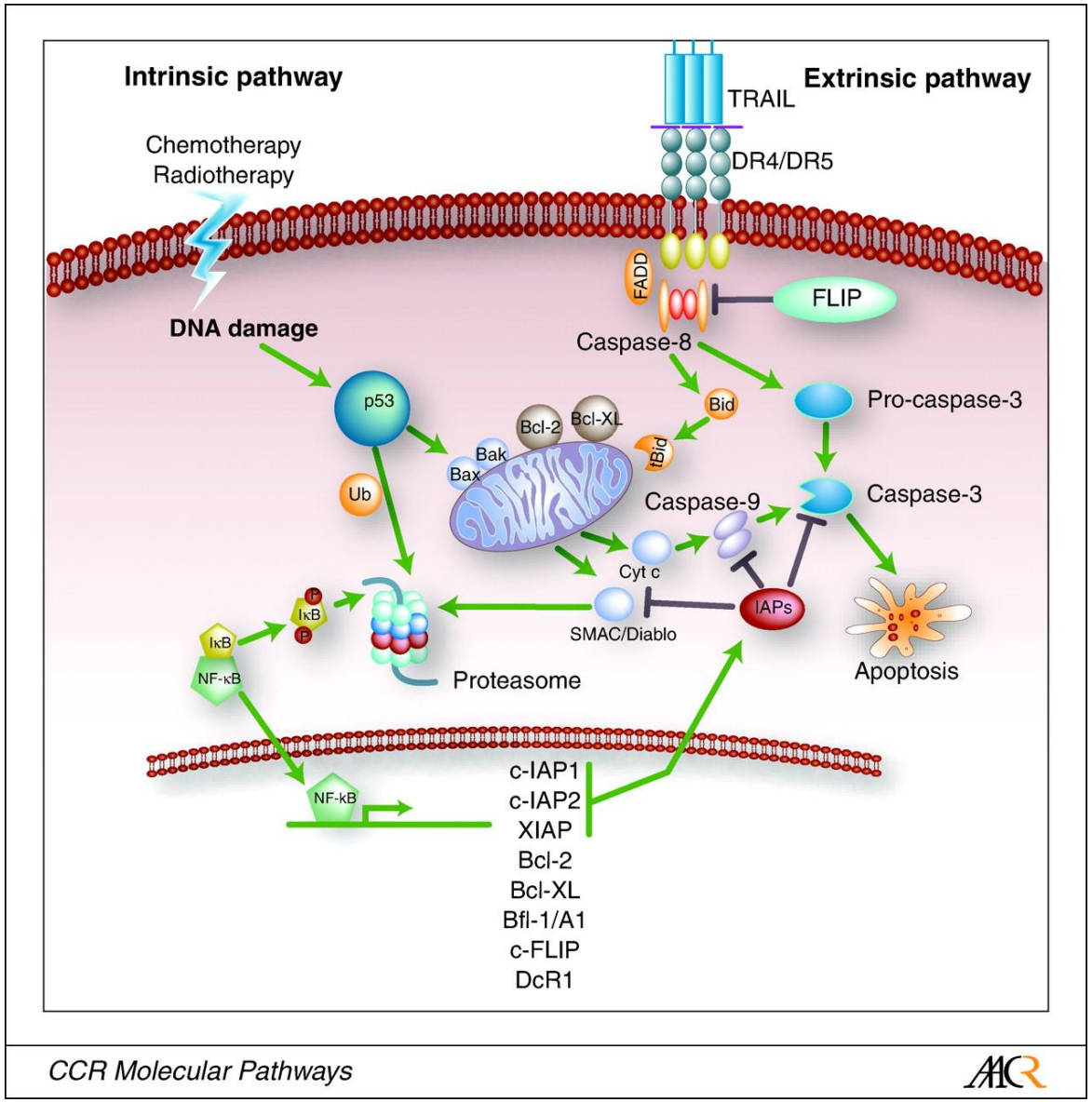
Replication fork stability



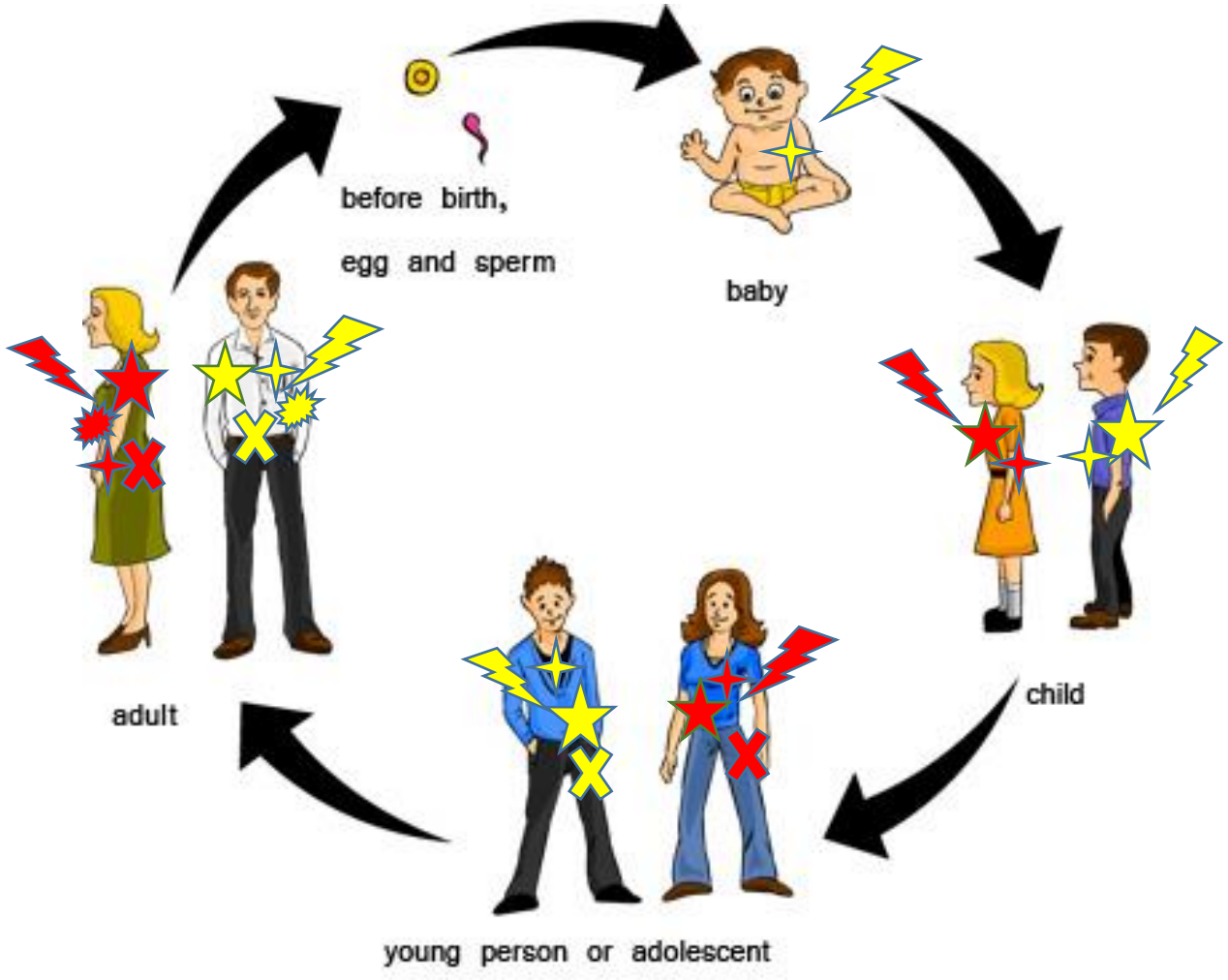
Nielsen *Nat Genet*, 2016

Απόπτωση


Apoptosis
A normal cell
The cell shrinks
Chromatin condenses
Membrane starts blebbing
Organelles disintegrate
Nucleus and organelles collapse
Membrane continues to bleb
Apoptotic bodies form
No
inflammation
Macrophages phagocytose
apoptotic bodies

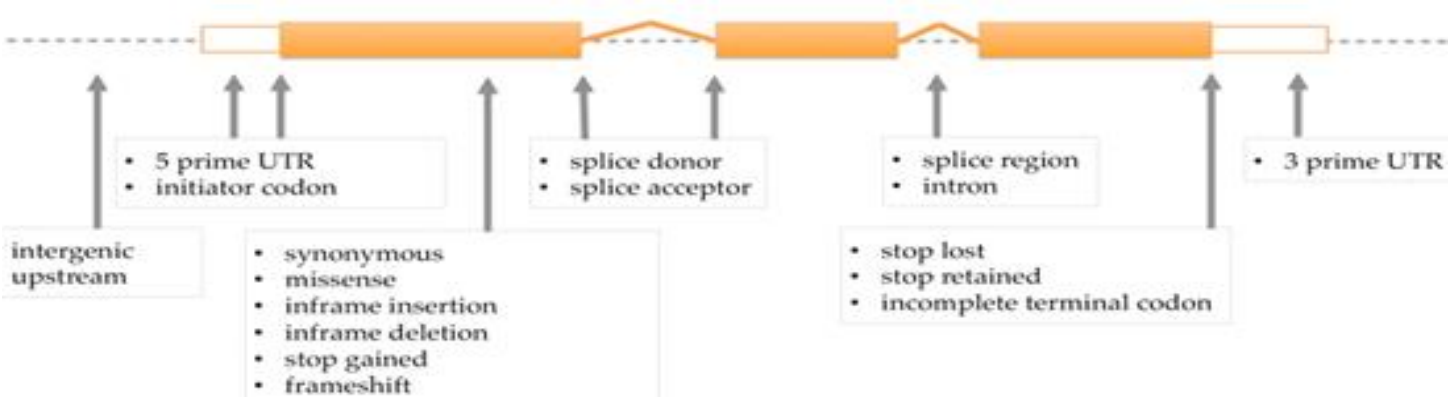

Intrinsic pathway
Extrinsic pathway
TRAIL
DR4/DR5
Chemotherapy
Radiotherapy
DNA damage
FADD
FLIP
Caspase-8
p53
Bid
Pro-caspase-3
Bcl-2
Bcl-XL
Bak
Bax
tBid
Ub
Caspase-9
Caspase-3
Cyt c
IκB
NF-κB
SMAC/Diablo
IAPs
Proteasome
Apoptosis
c-IAP1
c-IAP2
XIAP
Bcl-2
Bcl-XL
Bfl-1/A1
c-FLIP
DcR1
CCR Molecular Pathways
AACR

Ο κύκλος της ζωής του ανθρώπου



***Accumulation of mutations as we grow**

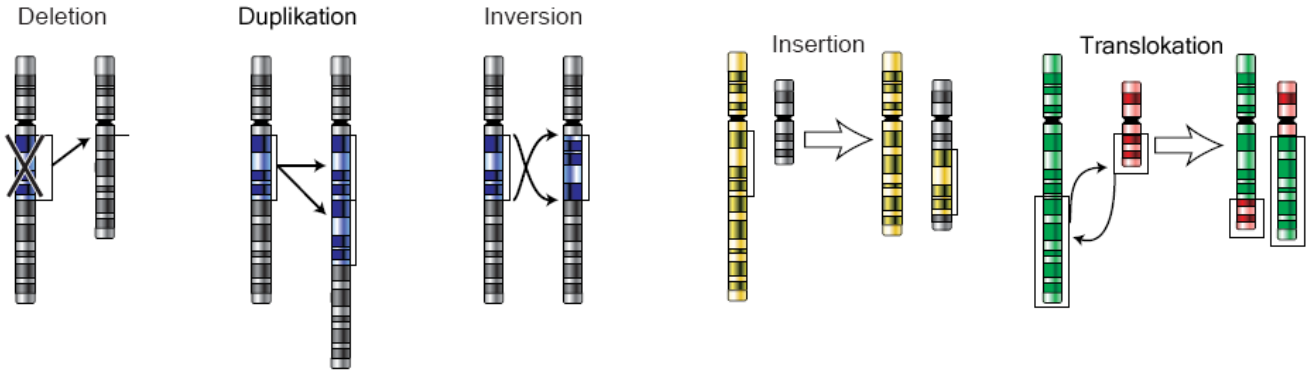
Είδη (σωματικών) μεταλλάξεων



Truncated protein → StopGain, Indel, splice

Altered amino acid → Missense

Altered expression → UTR, promoters

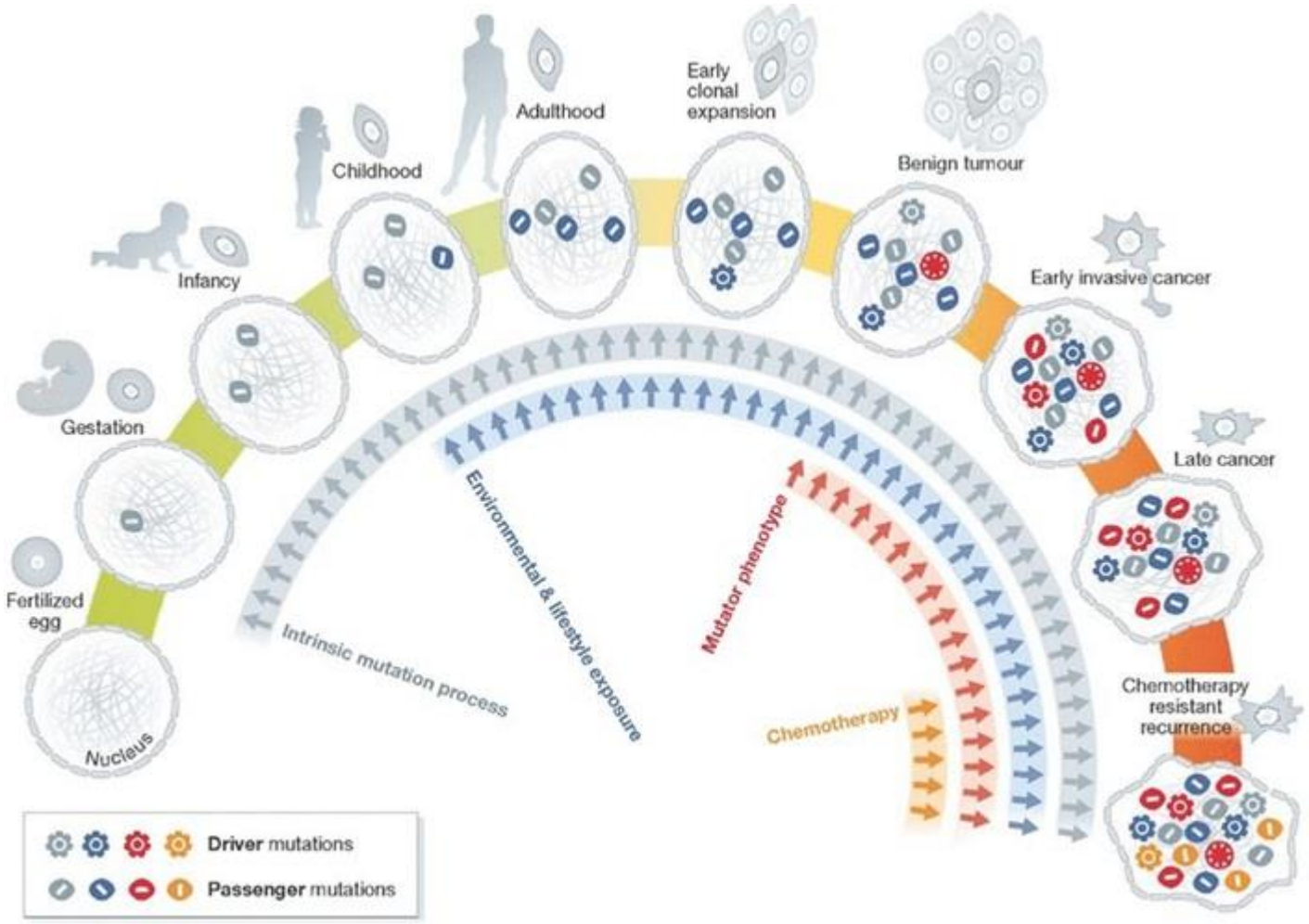


Deletion of many genes → Deletion, translocation

Altered expression → All abnormalities

"Novel" genes → Translocation, fusion

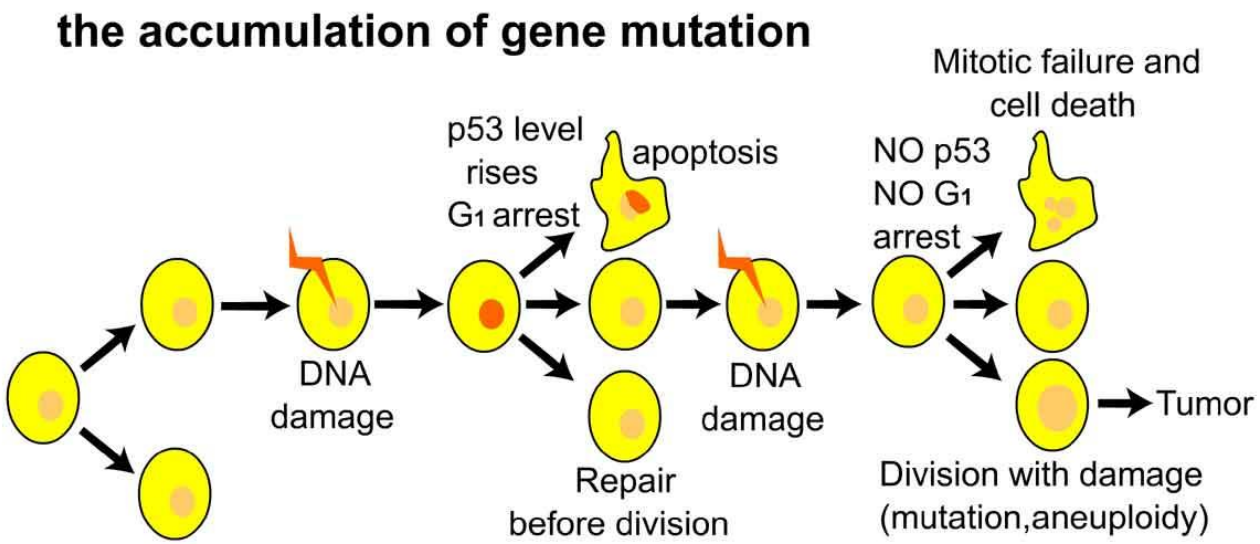
Μεταλλάξεις «Οδηγοί» και «επιβάτες»

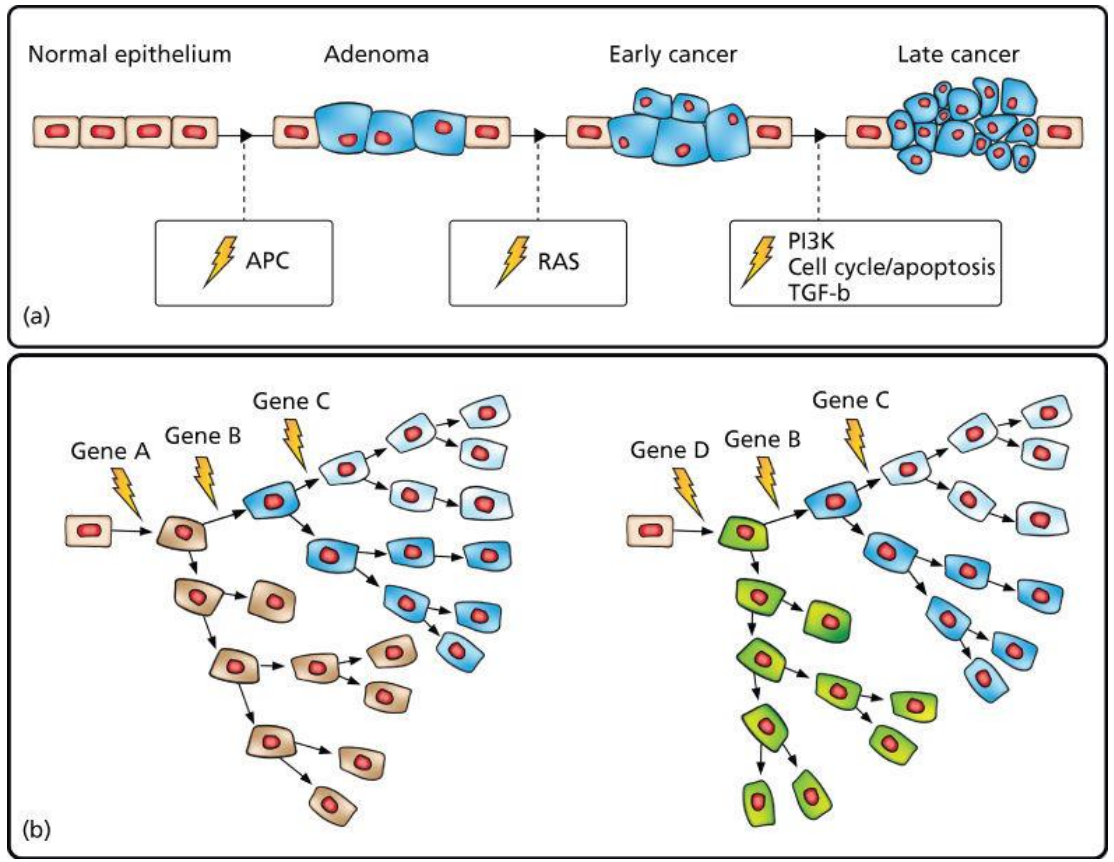


- Drivers confer tumor progression, cell proliferation and fitness selection
- Passengers do not confer to cancer phenotypes

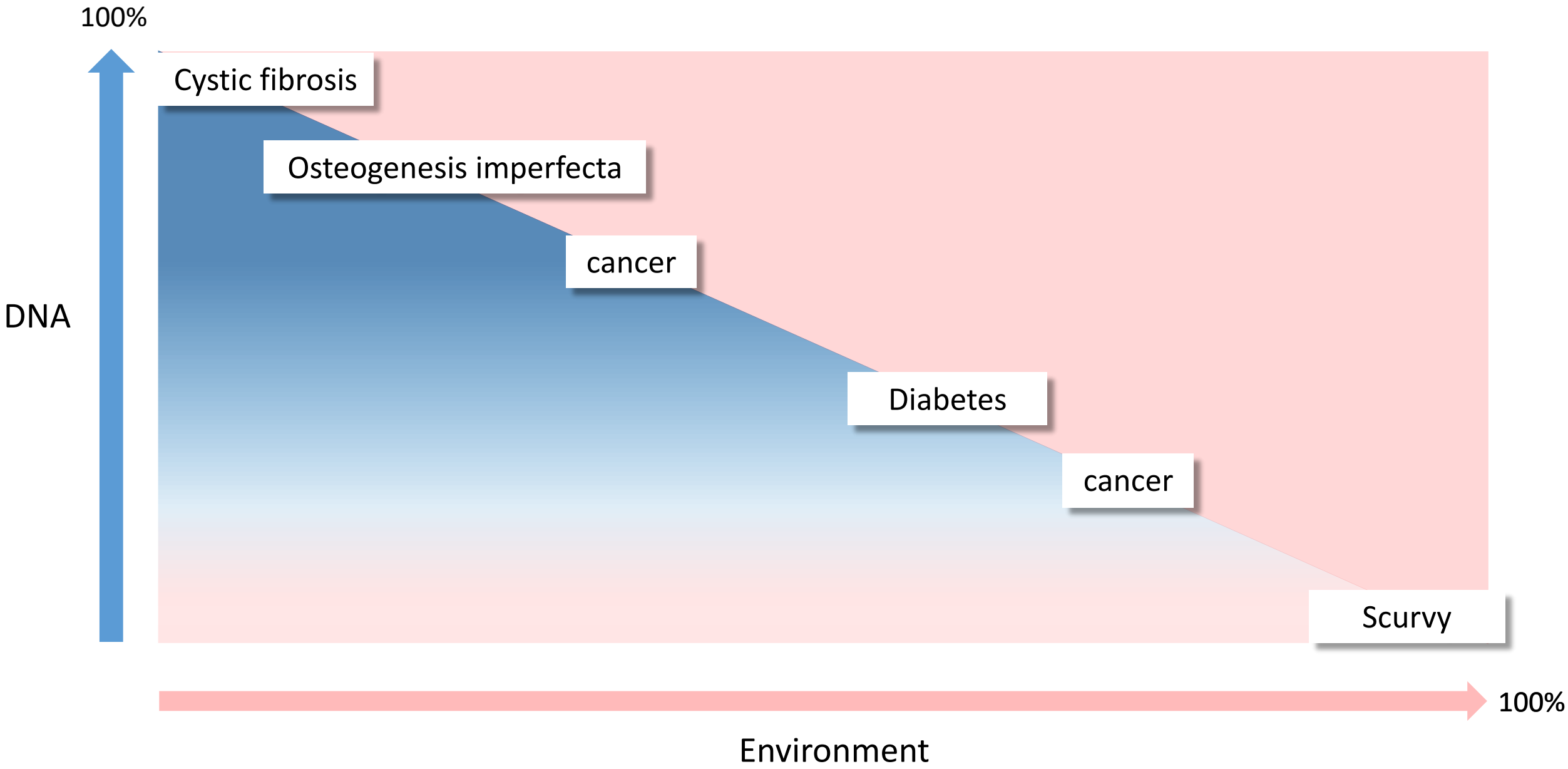
*Deleterious drivers may suppress cancer progression

Συσσώρευση μεταλλάξεων για την δημιουργία του όγκου



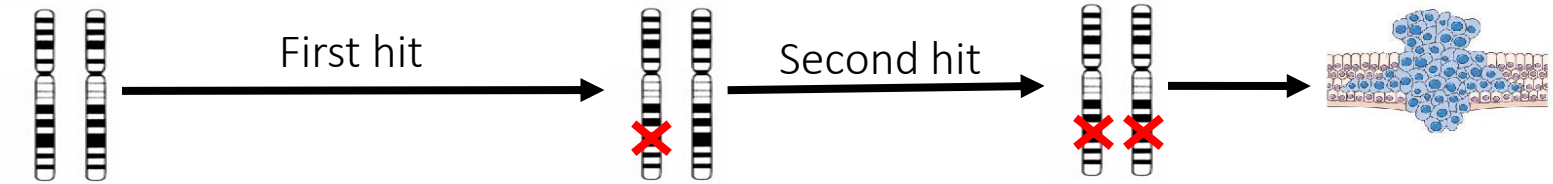


Contribution of genetic and environmental factors to human diseases

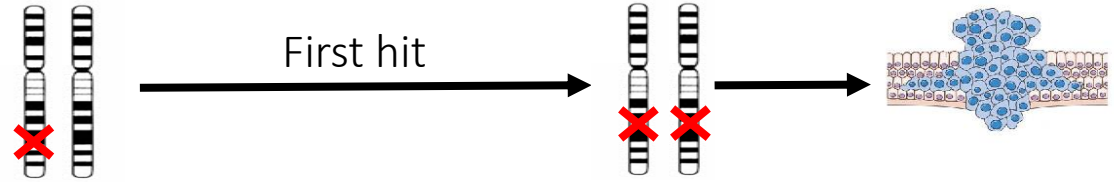


The two-hit hypothesis in hereditary cancer

Sporadic Cancer :



Hereditary cancer:

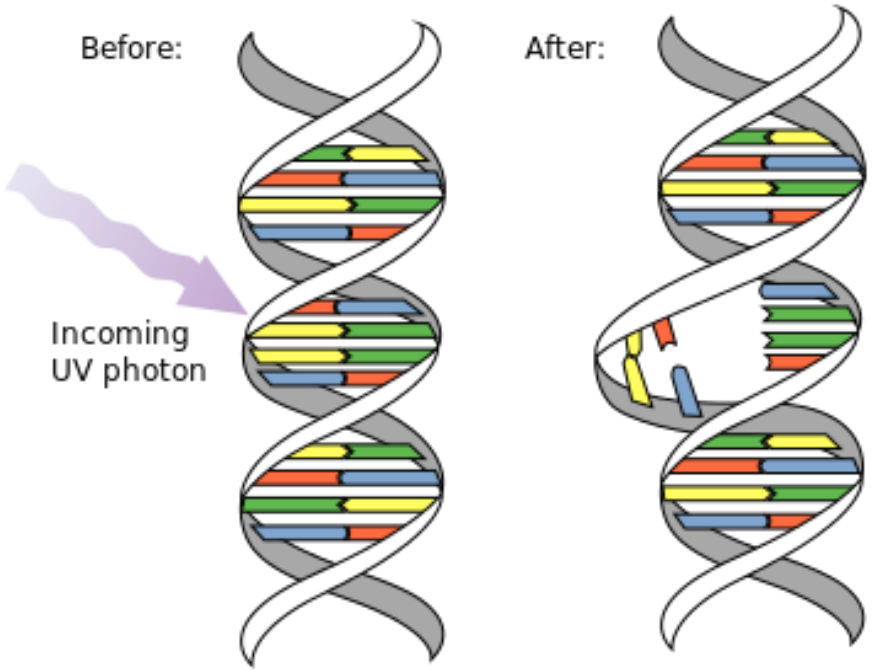


DNA test for genetic predisposition

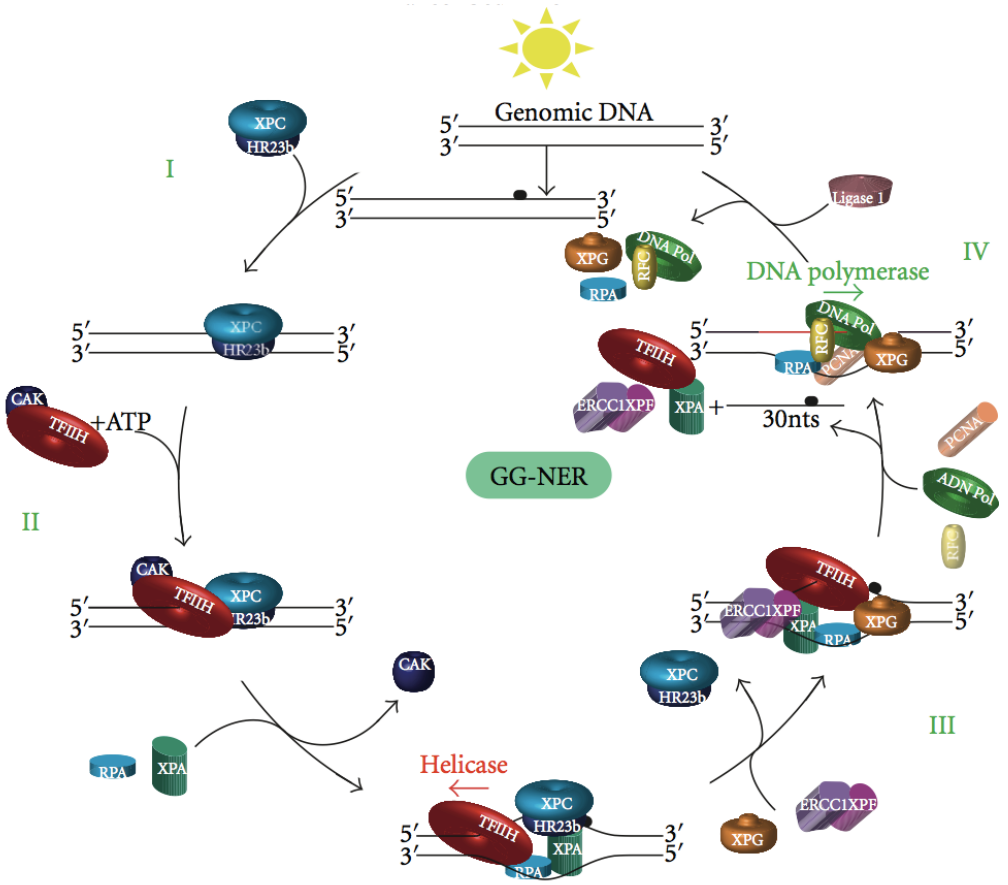
Δράση μονοπατιού NER

Το μονοπάτι NER ενεργοποιείται όταν ανιχνεύονται διμερή πυριμιδίνων κατά την διάρκεια της ελέγχου βλαβών του DNA.

Pyrimidine dimers (T,C)



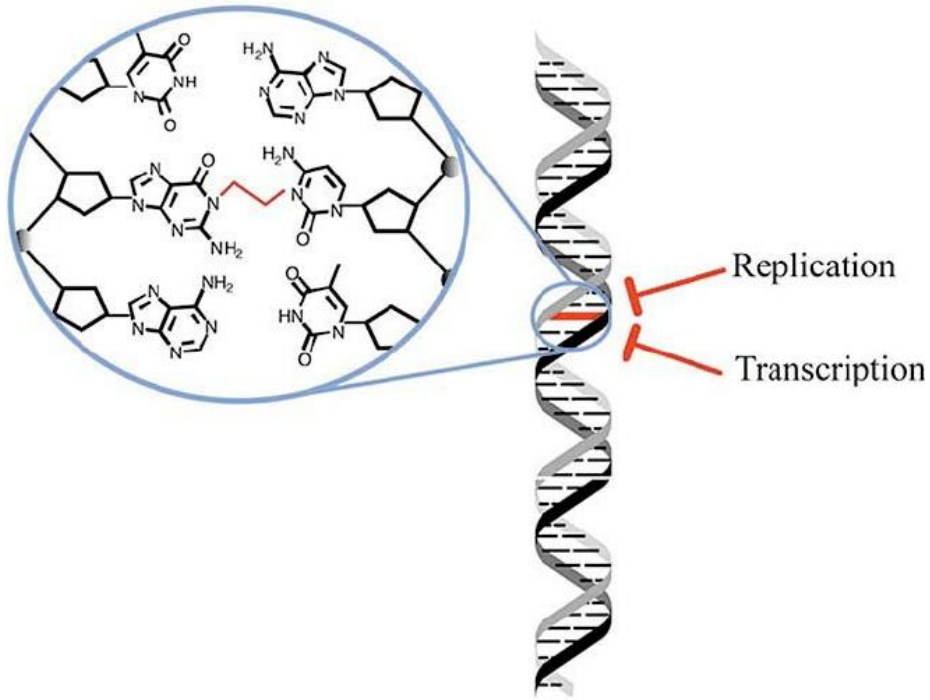
Nucleotide Excision Repair Pathway



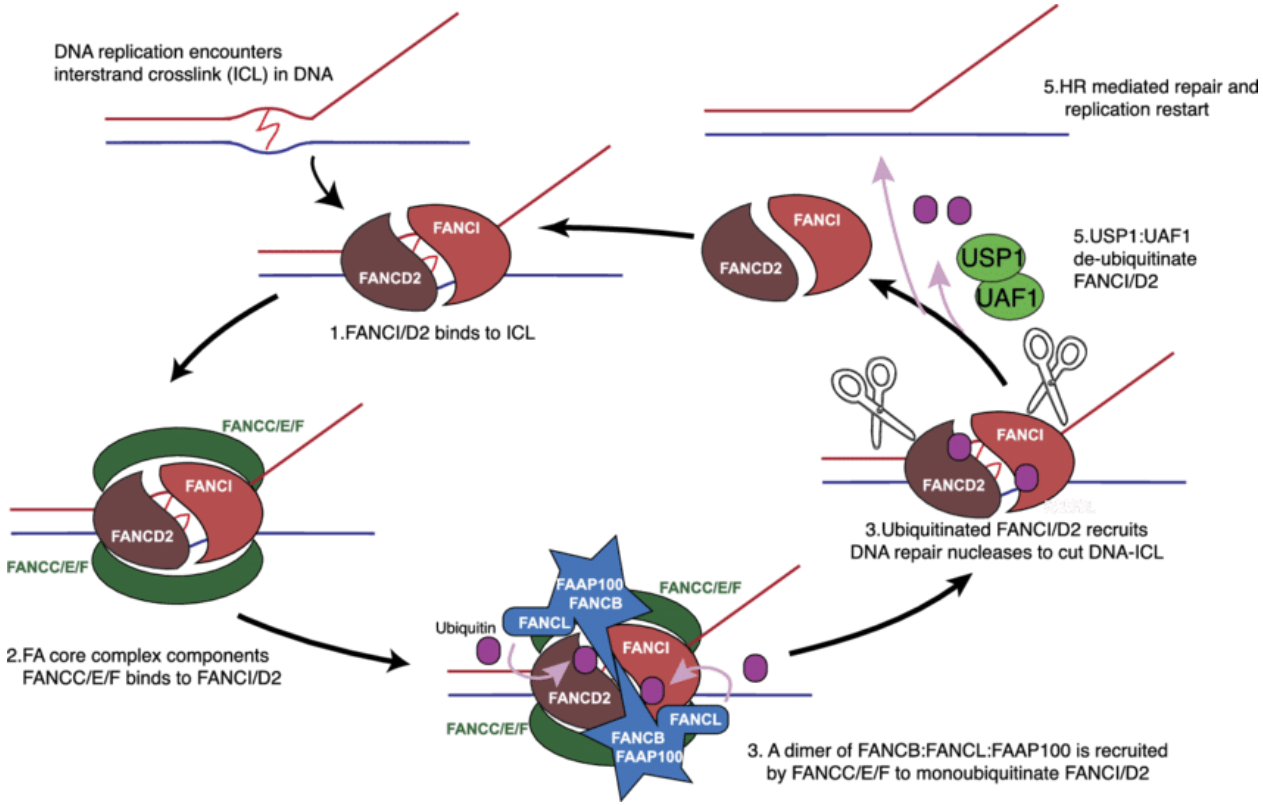
Δράση μονοπατιού Fanconi Anaemia

Το μονοπάτι FA ενεργοποιείται κυρίως όταν ανιχνεύονται μεταλλάξεις “interstrand cross-links” κατά την διάρκεια της αντιγραφής του DNA.

Interstrand cross-links



Fanconi Anaemia pathway

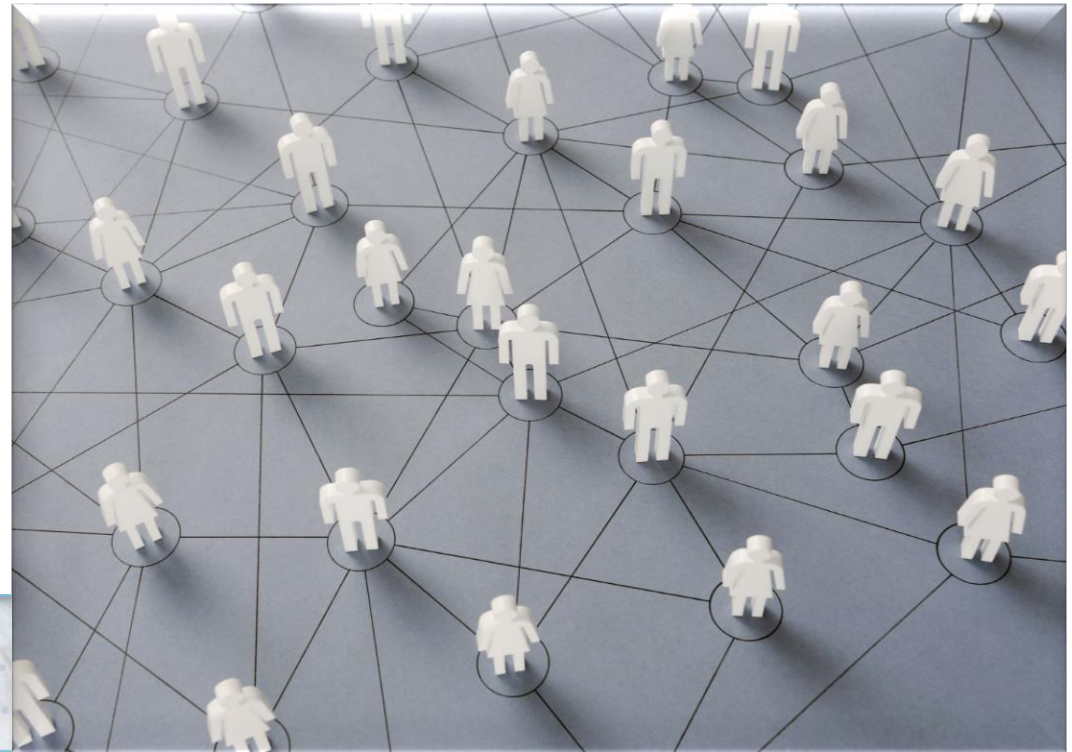


Pediatric Cancer Predisposition: Surveillance

Katerina Katsibardi, MD, PhD

Pediatric Hematology/Oncology Unit (POHemU)
Head: Prof. Antonis Kattamis

1st Department of Pediatrics, University of Athens
Aghia Sophia Children's Hospital
Athens, Greece



1ο Πανελλήνιο Υβριδικό Συνέδριο Ιατρικής Γενετικής (με Διεθνή συμμετοχή)

Pediatric Cancer Predisposition

10%: of children have an underlying cancer predisposition syndrome

- P/LP germline variants: 12% of patients
  (1.507 children and AYAs < 29 years with solid tumors)

- 7 – 8% of patients <20 years had P/LP variants

- ***TP53*** - adrenocortical cancer

✓ children: 50-80%

✓ AYAs: 13%

✓ adults: 5.8%

Toss A et al. Current Oncology Reports 2022;24:843–860.
Gröbner SN et al. Nature 2018;555(7696):321–7.

Pediatric Cancer Predisposition: general issues

- **Selection criteria** to identify patients with cancer predisposition syndrome (CPS).
- **Optimal timing** of genetics referral and testing for children at risk.
- **Surveillance and counseling** over time as children mature.
- **Transition** to adult cancer predisposition care.

Who to refer for genetic testing?

Knapke et al. (2012): **29%** of patients are considered for referral to a cancer genetics clinic.

Druker et al. (2017): **all** children with cancer given the limitations of current referral and genetic testing criteria.

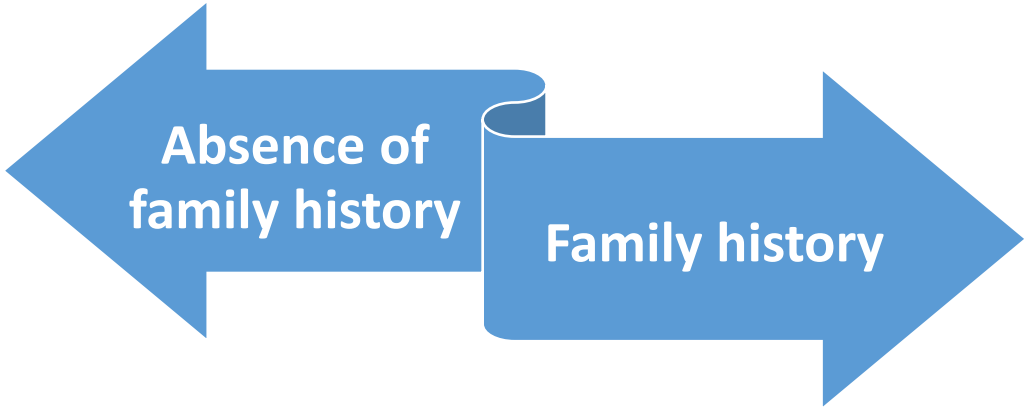
34% of high/moderate penetrance variants:

unexpected based on patient's diagnosis and previous history.

Knapke S et al. Pediatr Blood Cancer. 2012;58:85-89.
Druker H et al. Clin Cancer Res. 2017;23(13):e91-e97.
Fiala E et al. Nat Canc er 2021;2:357-36.

Points of entry: family history

- ≥ 2 malignancies at childhood age (≤ 18 years of age)
- a first degree relative (parent or sibling) with cancer < 45 years of age
- ≥ 2 second degree relatives with cancer < 45 years of age on the same side of the family
- the parents of the child with cancer are related, i.e. consangious



Family history alone does not adequately identify children with CPSs.

- de novo variants or parental germline mosaicism.
- low penetrance, recessive inheritance, small or young families.

Zhang J et al. N Engl J Med 2015;373:2336–46.
Parsons DW et al. JAMA Oncol 2016;2:616–24.

Inclusion criteria

- positive family history
- high genetic risk solid tumor types
- multiple primary tumors
- physical findings and clinical features (non-oncological)
- treatment toxicity (Ataxia Telangiectasia, Gorlin syndrome)

- classic lip pigmentation: Peutz–Jeghers syndrome.
- >3 cafe au lait macules: neurofibromatosis type 1 and biallelic mismatch repair deficiency.
- multiple, bilateral congenital hypertrophy of the retinal pigment epithelium: familial adenomatous polyposis.

Jongmans MC et al. Eur J Genet Med 2016;59:116–25.
Druker H et al. Clin Cancer Res. 2017;23(13):e91-e97.

Pediatric solid tumors: genetic evaluation regardless of family history

SMARCB1
SMARCA4
TP53

Central and peripheral nervous system tumors	Non-CNS solid tumors	Renal and genitourinary tumors (non-rhabdoid)
Acoustic/vestibular schwannoma	Adrenocortical carcinoma	Botryoid-type embryonal rhabdomyosarcoma
Atypical teratoid/rhabdoid tumor	Anaplastic rhabdomyosarcoma	Cystic nephroma
Choroid plexus carcinoma	Basal cell carcinoma	Gonadoblastoma
CNS hemangioblastoma	Carcinoid tumor	Gynandroblastoma
Malignant nerve sheath tumors	Cardiac rhabdomyoma	Juvenile granulosa cell tumor
Medulloblastoma (sonic hedgehog, desmoplastic, nodular)	Ciliary body medulloepithelioma	Large cell calcifying Sertoli-Leydig cell tumor (testicular)
Neurofibroma (two or more or one plexiform neurofibroma)	Gastrointestinal cancer	Ovarian Sertoli-Leydig cell tumor
Optic pathway glioma	Cribriform-morular variant of papillary thyroid cancer	Renal angiomyolipoma
Pineoblastoma	Desmoid tumor	Renal cell carcinoma
Pituitary blastoma	Endolymphatic sac tumors (ELST)	Renal sarcoma
Subependymal giant cell astrocytoma	Gastrointestinal stromal tumor (GIST)	Urothelial cell carcinoma
	Hepatoblastoma	Wilms tumor (bilateral/multifocal) → ***WT1***
	Malignant rhabdoid tumor	
	Medullary thyroid cancer	
	Melanoma	
	Multinodular goiter	
	Myxoma	
	Nasal chondromesenchymal hamartoma	
	Osteosarcoma (dx <10 y)	
	Parathyroid carcinoma	
	Pheochromocytoma/paraganglioma	
	Pleuropulmonary blastoma → ***DICER1***	
	Retinal hemangioblastoma	
	Retinoblastoma → ***RB1***	

Cancer types for clinical genetic evaluation

1) Cancers of adult age, which are extremely rare in the pediatric age group
i.e. colorectal cancer, ovarian cancer, pheochromocytoma, basal cell carcinoma etc.

2) Tumors highly correlated with specific syndrome(s)	**Syndrome**
Adrenocortical carcinoma	Li Fraumeni syndrome, BWS, MEN1, FAP
Atyp. teratoid malignant rhabdoid tumor	Rhabdoid Predisposition syndrome
Cerebellar gangliocytoma	*PTEN hamartoma tumor syndrome*
Choroid Plexus Carcinoma	Li Fraumeni syndrome
Endolymphatic sac tumors	Von Hippel-Lindau syndrome
Hemangioblastoma	Von Hippel-Lindau syndrome
Hepatoblastoma	FAP, BWS
Juvenile myelomonocytic leukemia	Neurofibromatosis type 1, Noonan syndrome, CBL germline syndrome, Constitutional Mosaic Trisomy 8
Low hypodiploid acute lymphoblastic leukemia	Li Fraumeni syndrome
Malignant peripheral nerve sheath tumor	Neurofibromatosis type 1
(Malignant) Schwannoma	Neurofibromatosis type 1 and 2, Schwannomatosis, Carney complex
Medullary thyroid carcinoma	MEN2
Medulloblastoma (in particular < 3 years of age)	FAP, Gorlin syndrome, germline mutations in *SUFU*
Optic pathway glioma	Neurofibromatosis type 1
Ovarian Sertoli-Leydig cell tumor	DICER1 syndrome
Pleuropulmonary blastoma	DICER1 syndrome
Pineoblastoma	DICER1 syndrome
Pituitary blastoma	DICER1 syndrome
Retinoblastoma	Retinoblastoma predisposition syndrome

BWS = Beckwith Wiedemann syndroom; FAP = Familial Adenomatous Polyposis

50%
TP53

Jongmans CJ M et al. Eur J Med Genet 2016;59:116-25.

Pediatric Cancer Working Group of the American Association for Cancer Research (AACR)

- Consensus recommendations for cancer **surveillance** of children and adolescents with heritable cancer predisposition (Boston, Massachusetts, 10/2016).
- 50 most common syndromes that predispose to cancer in the first 20 years of life.
- Clinicians, not only genetics professionals, decide for cancer genetic referral, using:
  - National Comprehensive Cancer Network guidelines (https://www.nccn.org/professionals/physician_gls/default.aspx).
  - GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1116/).

Brodeur M B et al. Clin Cancer Res 2017;23:e1-e5.
Bashford M et al. Genet Med 2019;21:2844.


Genetics inMedicine | ADDENDUM

Addendum: A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment

Michael T. Bashford, MD[1], Wendy Kohlman, MS[2], Jessica Everett, MS[3], Ashley Parrott, MS[4] and Toni I. Pollin, MS, PhD[5] for the Practice Guidelines Committee of the National Society of Genetic Counselors and the Professional Practice and Guidelines Committee of the American College of Medical Genetics and Genomics

Genetics in Medicine (2019) 21:2844; https://doi.org/10.1038/s41436-019-0586-y

Children with a CPS should undertake surveillance ?

- **Recommended:** ≥5% risk of developing cancer during the first 20 years of life and when effective screening modalities exist.
- **Not recommended:** < 1% risk of developing cancer during the first 20 years of life.
- Grey zone- discussed on an individual basis: 1% - 5% cancer risk during childhood.

Brodeur M B et al. Clin Cancer Res 2017;23:e1-e5.
Bashford M et al. Genet Med 2019;21:2844.

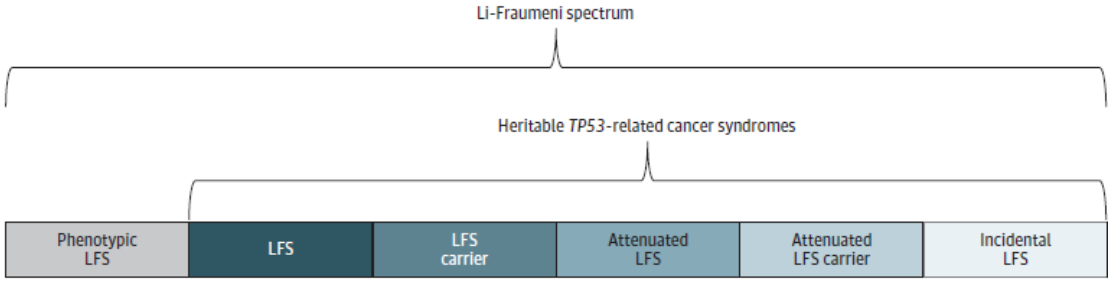
When to follow the surveillance recommendations

- Pathogenic variant detected in cancer-predisposing gene.

- Clinical criteria met for a syndrome, but genetic testing not pursued.

- Clinical criteria met for a syndrome, but no pathogenic variant detected.

✓ 50% risk (parent/sibling with syndrome), but genetic testing not (yet) pursued.

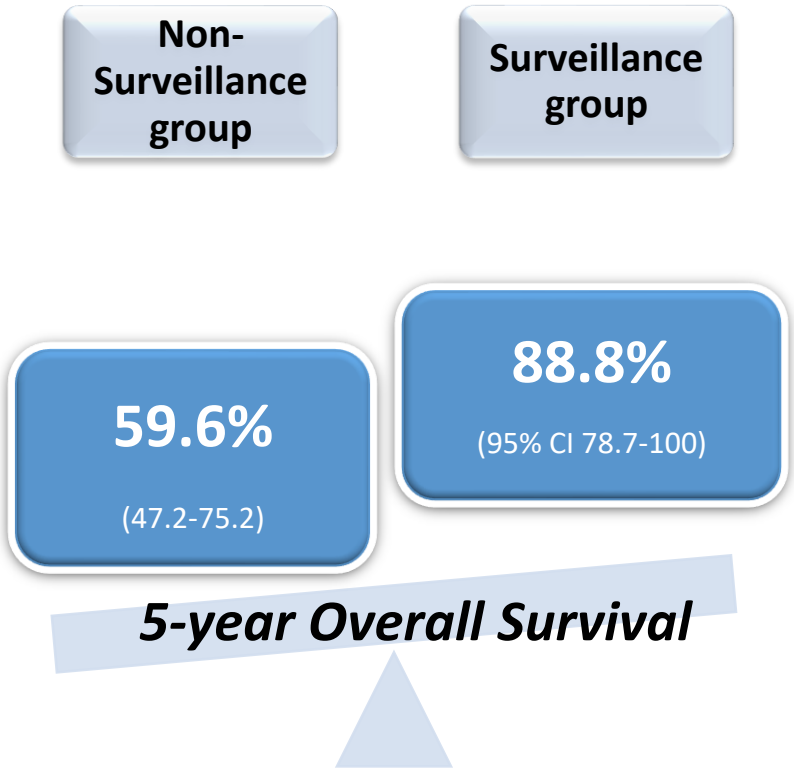


Druker H et al. Clin Cancer Res 2017;23:e91-e97.
Kratz CP et al. JAMA oncol 2021; e1-e6.

Surveillance improves outcome

Early identification of tumors when smaller and less likely to be metastatic improves clinical outcome:

- 89 carriers (asymptomatic) of *TP53* pathogenic variants.
- 66%: surveillance for 32 months (median).
  - 40 asymptomatic tumors detected in the surveillance group.



Villani A et al. Lancet Oncol 2016;17:1295-305.

Cancer Surveillance Considerations

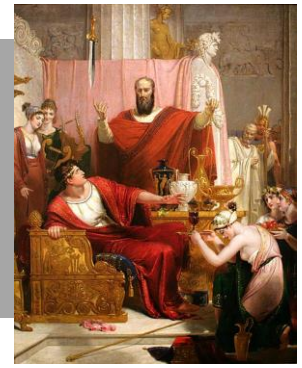
- How often should screening be performed?
- At what age should screening start and if/when should it stops?

  at the time of initial assessment.

  revisit in the mid- to late teenage years and when family planning.
- Should the screening procedures (frequency or type) change over time with age to account for changes in cancer risk?
- Disseminate information to relatives.
- Implication of family members.

McCullough LB. Pediatr Blood Cancer 2016;63: 511–5.

Psychological issues related to surveillance



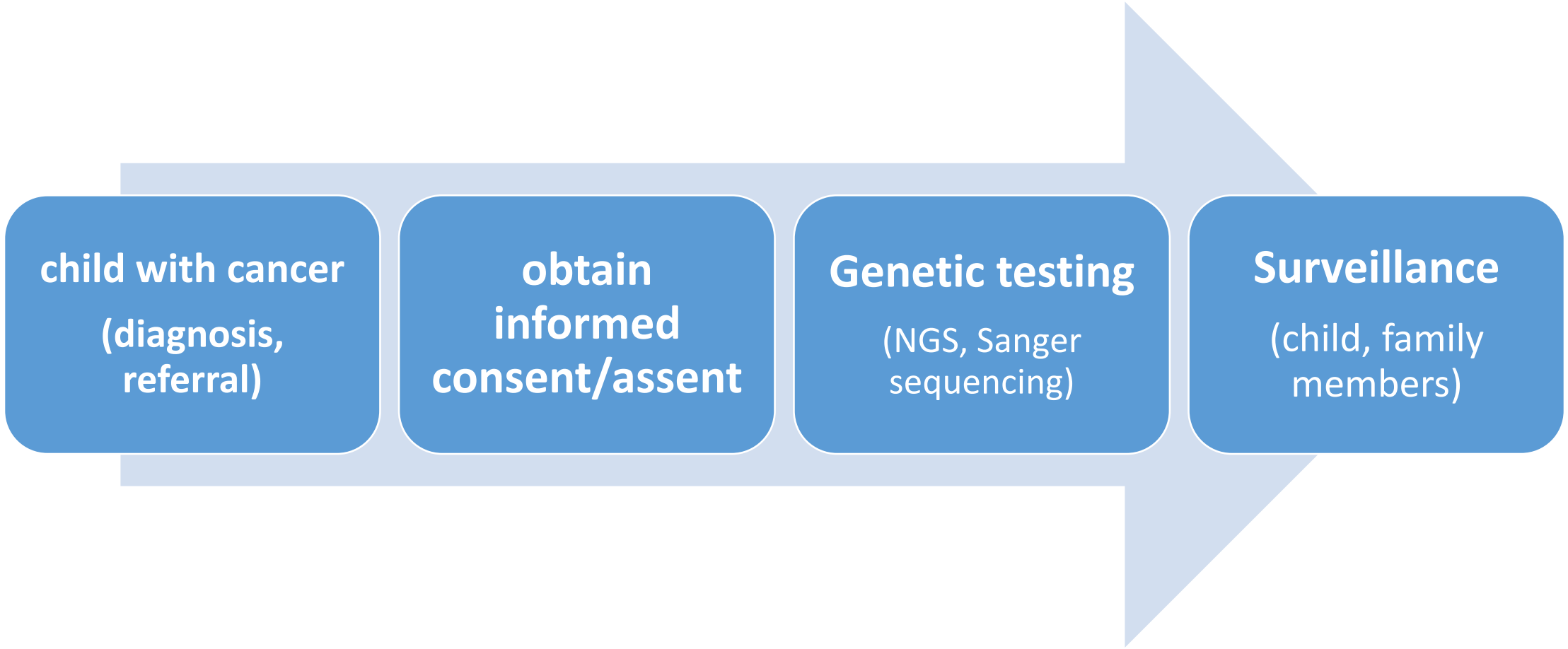
- Sense of empowerment and control.
- Relief (when negative test).
- Sense of trust and support with the surveillance team: when a new tumor diagnosis is made.

- **"Scanxiety":** often-debilitating anxiety in the period of imaging studies.
- Cancer distress, reduced satisfaction with care, impact on the quality of life.

  - Not established surveillance for many pediatric cancers.
  - Lack of information regarding optimal surveillance protocols.
  - High frequency of exams, inconclusive outcomes.
  - Costs of complex specialty care.

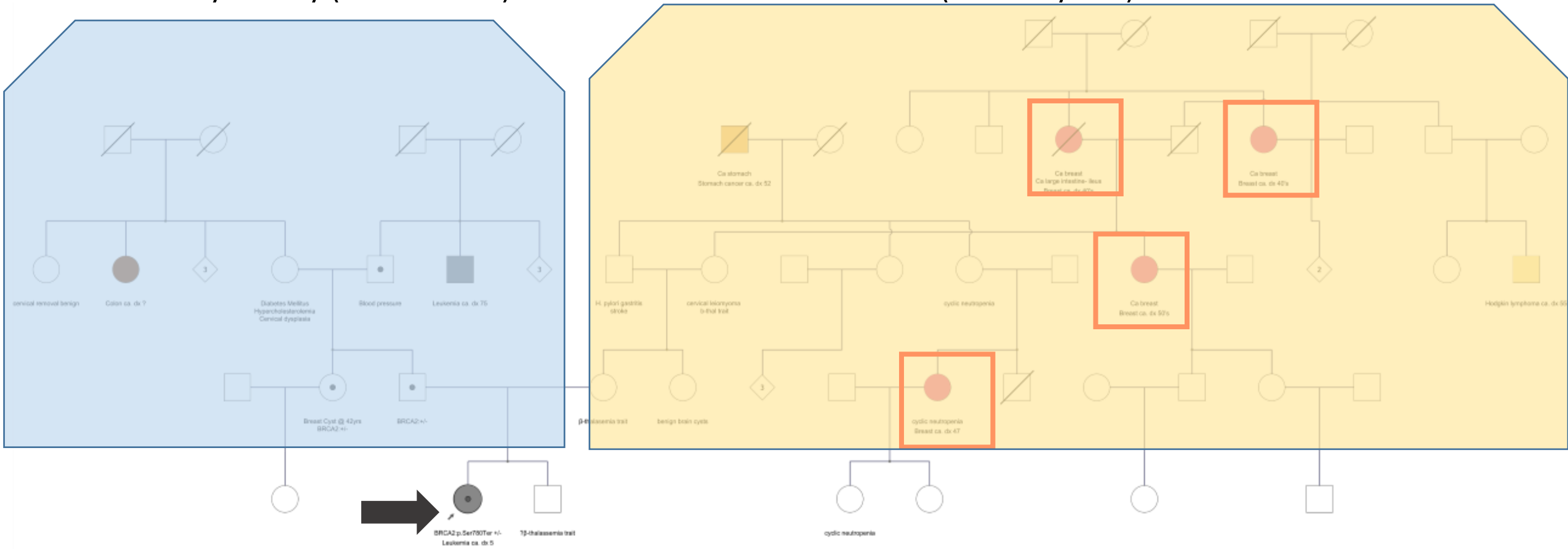
Malkin D et al. Clin Cancer Res 2017;23:e133-e137.
Desrosiers RL et al. Pediatr Blood Cancer 2019;66:e27907.

Surveillance in pediatric cancer patients in POHem CPS Unit



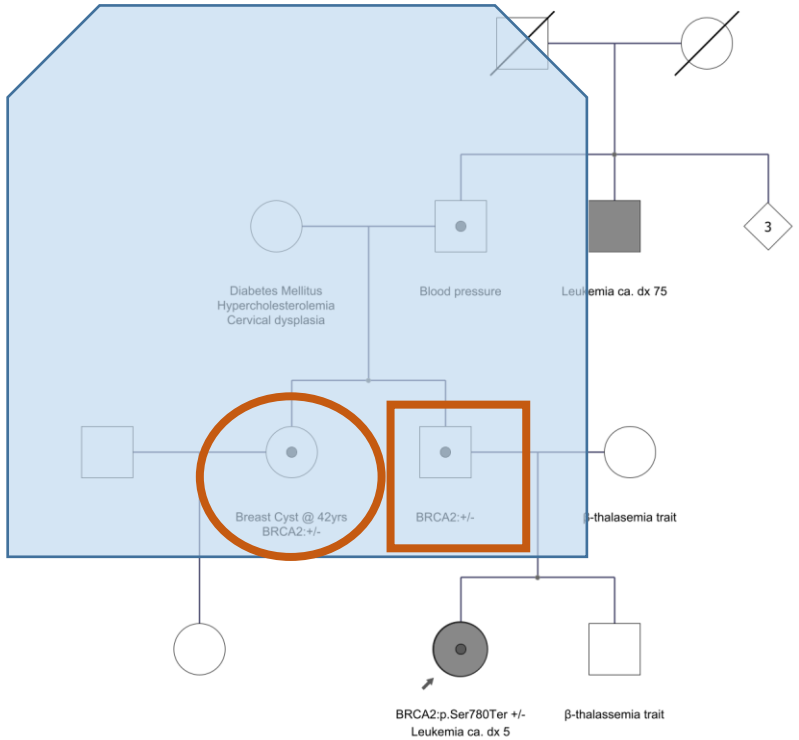
Patient with Acute Lymphoblastic Leukemia

- 5 years old, pro-common B-ALL, 46XX, somatic deletion *IKZF1* (ex 4-7)
- family history (mother side): 4 members with breast cancer (40 – 50 years)



Genetic testing: results

Gene (Transcript)	DNA substitution/ Protein (rsid)	Inheritance	Clinical significance
BRCA2 **(NM_000059)**	c.2339C>G/p.Ser780* (rs587781471)	heterozygous	pathogenic • Hereditary breast and ovarian cancer (HBOC) • pancreas, prostate • non HL



BRCA2 **(Class V pathogenic variant):**

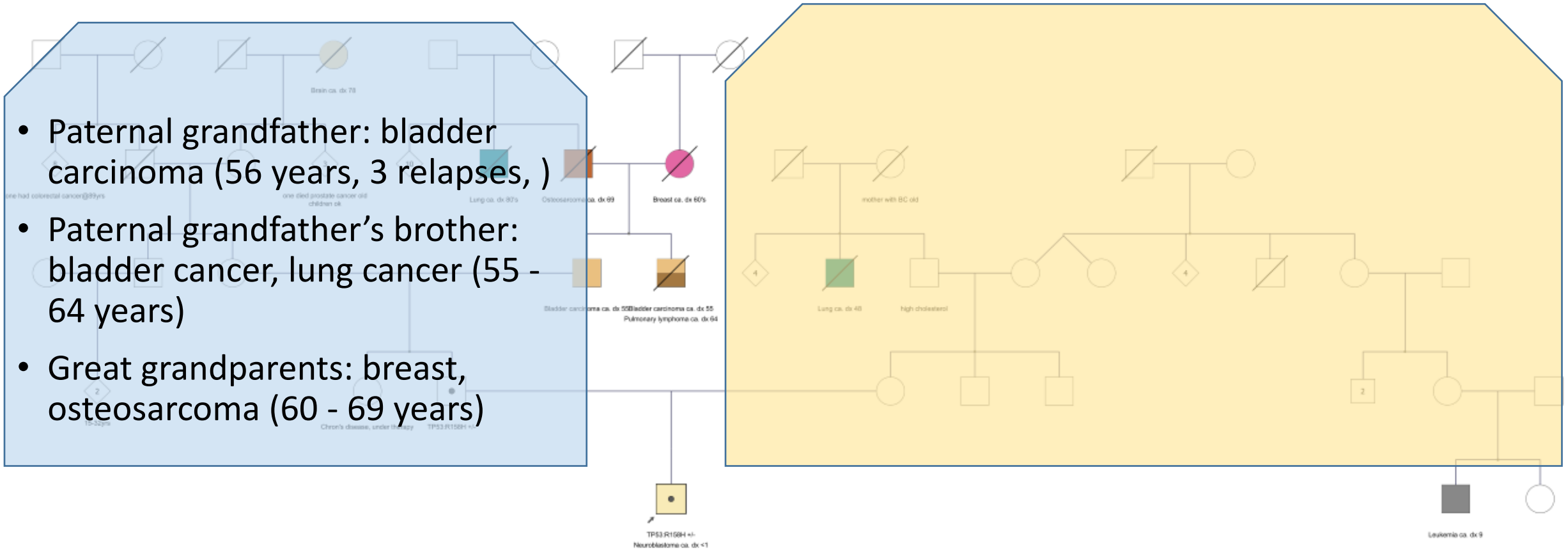
- ✓ **Patient**
- ✓ **Her father (asymptomatic)**
- ✓ **Paternal aunt (asymptomatic)**

Steps - Questions

- Inform the parents for the results.
- Referral for surveillance programme in the father and the parental aunt.
- Should the patient be informed about the results of the genetic testing? When?
- When should surveillance start for our patient?

Patient with neuroblastoma (Ms): 11 months, MYCN(-)

- Paternal grandfather: bladder carcinoma (56 years, 3 relapses,)
- Paternal grandfather's brother: bladder cancer, lung cancer (55 - 64 years)
- Great grandparents: breast, osteosarcoma (60 - 69 years)



Steps - Decisions

- Inform the parents for the results.
- Referral for surveillance programme in the father.

- Mother: 12th week of gestation.
  - Trophoblast for prenatal diagnosis (embryo: *TP53*).

The parents decided to terminate the pregnancy.

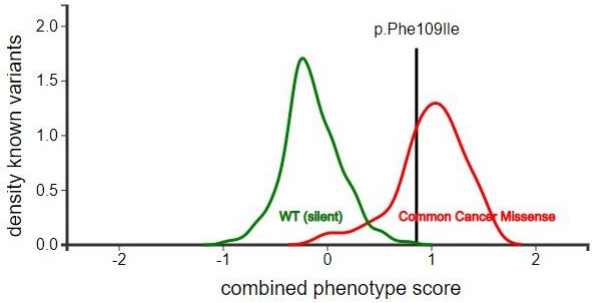
Discuss the risks for future children in the family, options for preimplantation genetic diagnosis, prenatal diagnosis.

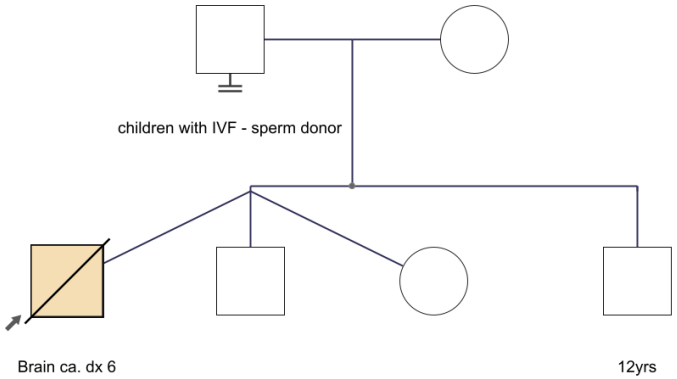
Patient with SHH-medulloblastoma

Gene (Transcript)	DNA substitution/ Protein (rsid)	Inheritance	Clinical significance
TP53 (NM_000546)	c.325T>A/ p.Phe109Ile	heterozygous	Likely pathogenic

Functional analysis of F109I variant – IARC database

Reference amino acid	Phe
Protein change	p.Phe109Ile
Combined phenotype score	0.854 ± 0.218
# of IARC somatic mutations (human tumors)	0
# of IARC germline mutations (LFL/LFS individuals)	0
# of ExAC germline mutations (unselected individuals)	0
Transcriptional activity in yeast (% of wild-type)	14.7%
Mutation probability (COSMIC Signature 1 percentile)	44.41%





- ✓ **Patient**
- ✓ **Brother and sister (asymptomatic) from the triplet pregnancy (sperm donor)**

Steps - Surveillance

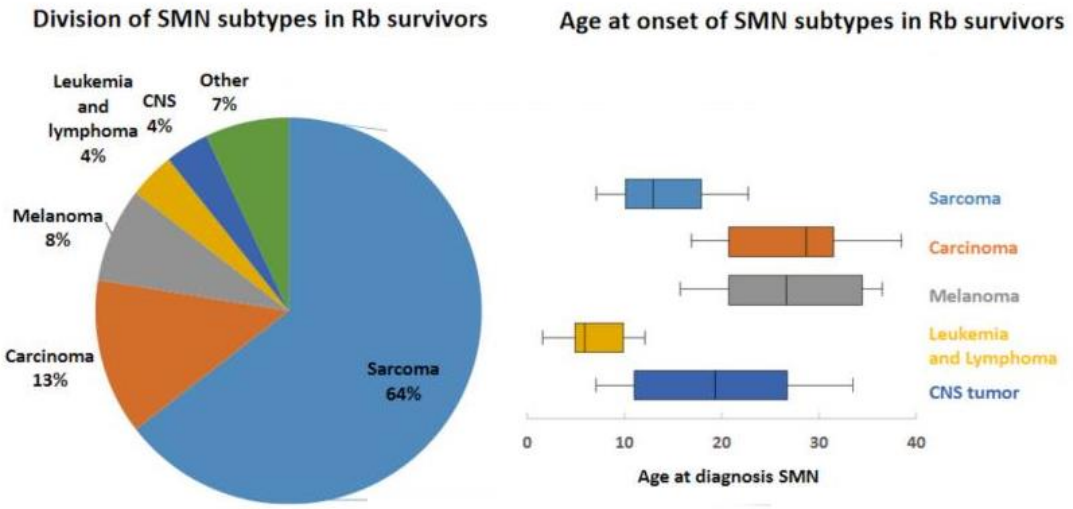
- Inform the parents for the results.
- Incorporate brother and sister in the surveillance programme of our clinic.
- Inform the National IVF Committee and the Center of IVF.

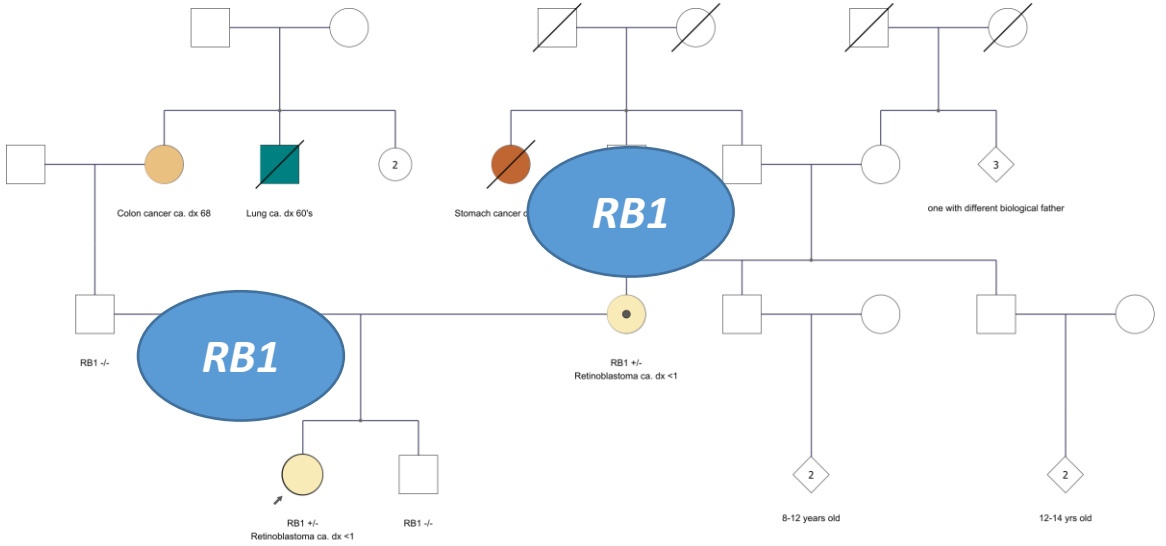
Surveillance of LFS

- individuals carrying a pathogenic *TP53* variant.
- individuals fitting the "classic clinical definition" of LFS, without a pathogenic *TP53* variant.
- lifelong screening, starting as soon as a genetic or clinical diagnosis are established.
- screening modalities change depending on the sex and age of the patient.
- Families with known *TP53* germline mutation: presymptomatic testing soon after birth to begin screening within the first months of life.

Bougeard G. J Clin Oncol 2015;33:2345-52.

Patient with Retinoblastoma: Surveillance



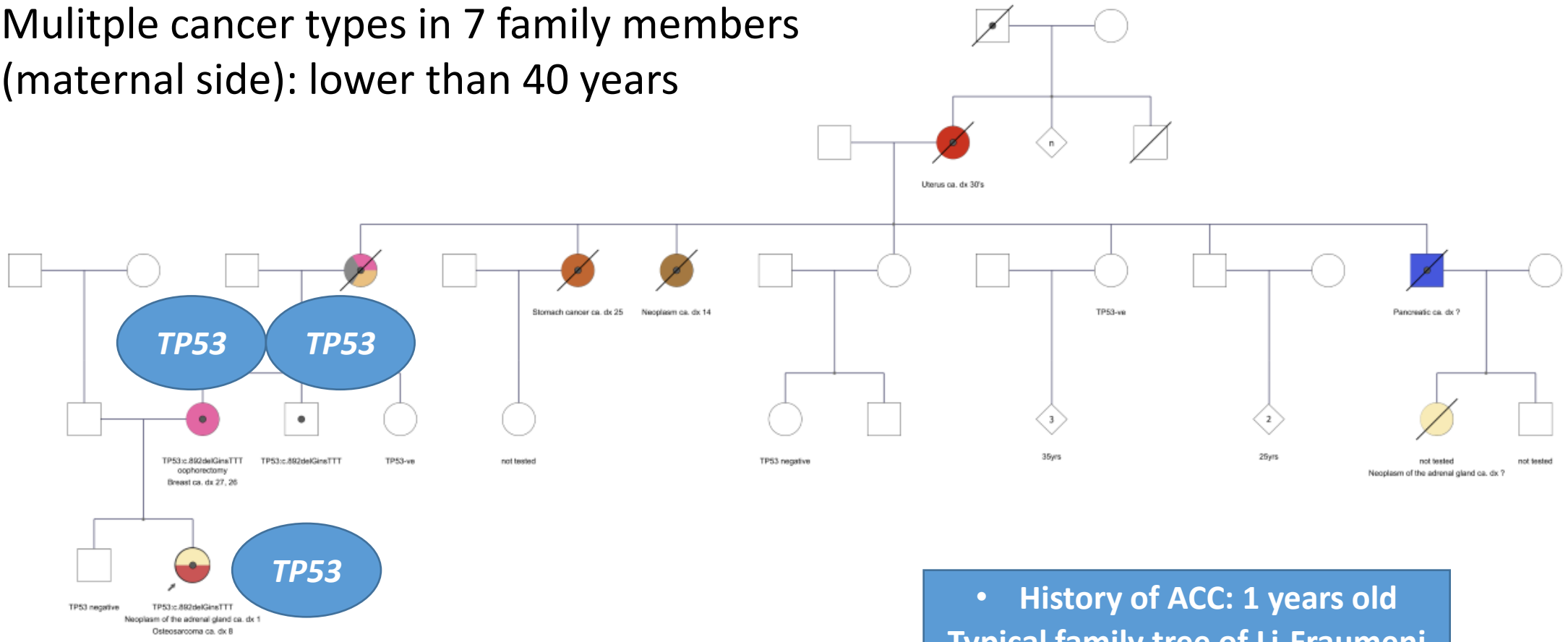


Mother: melanoma in situ in the first surveillance screening

Skalet AH et al. Ophthalmology. 2018;125:453-458.
Fabius A et al. Cancers. 2021;13:1200

Surveillance in an asymptomatic patient with *TP53*: Osteosarcoma

Mulitple cancer types in 7 family members (maternal side): lower than 40 years



- **History of ACC: 1 years old**

Typical family tree of Li-Fraumeni