Fred Hutch Cancer Center

Familial Syndromes

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UW Medicine

Familial Cancer Characteristics

- For any given tumor type, ~1/8 is familial.
- Positive family history:
  - Typically autosomal dominant.
  - Less often autosomal recessive, which is more characteristic of a pediatric syndrome.
- New autosomal dominant germline mutations common due to reduced genetic fitness.
- Usually an earlier age of onset.
- Risk for multiple metachronous primary tumors (e.g., bilateral tumors for paired organs).

1/8 of Adults with Solid Tumors Have a Germline Disorder

JAMA Oncology | Original Investigation

Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients With Hereditary Cancer Syndrome

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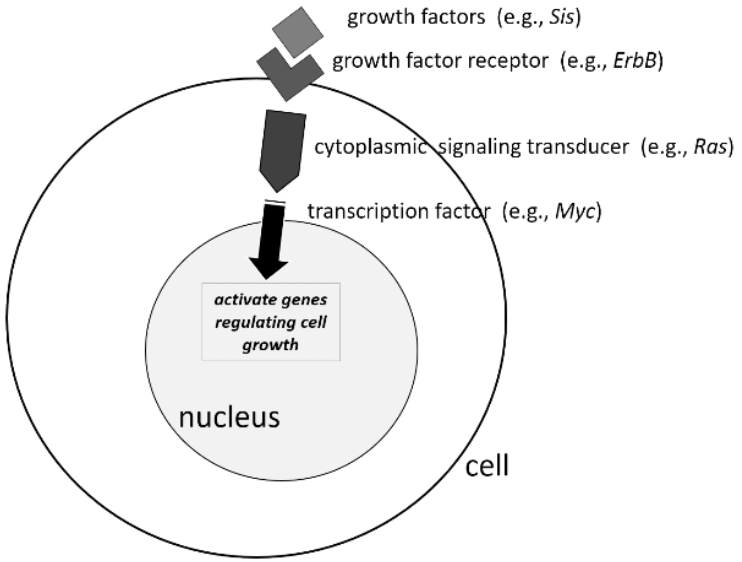
"1 in 8 patients had a pathogenic germline variant, half of which would not have been detected using a guideline-based approach. Nearly 30% of patients with a high-penetrance variant had modifications in their treatment based on the finding"

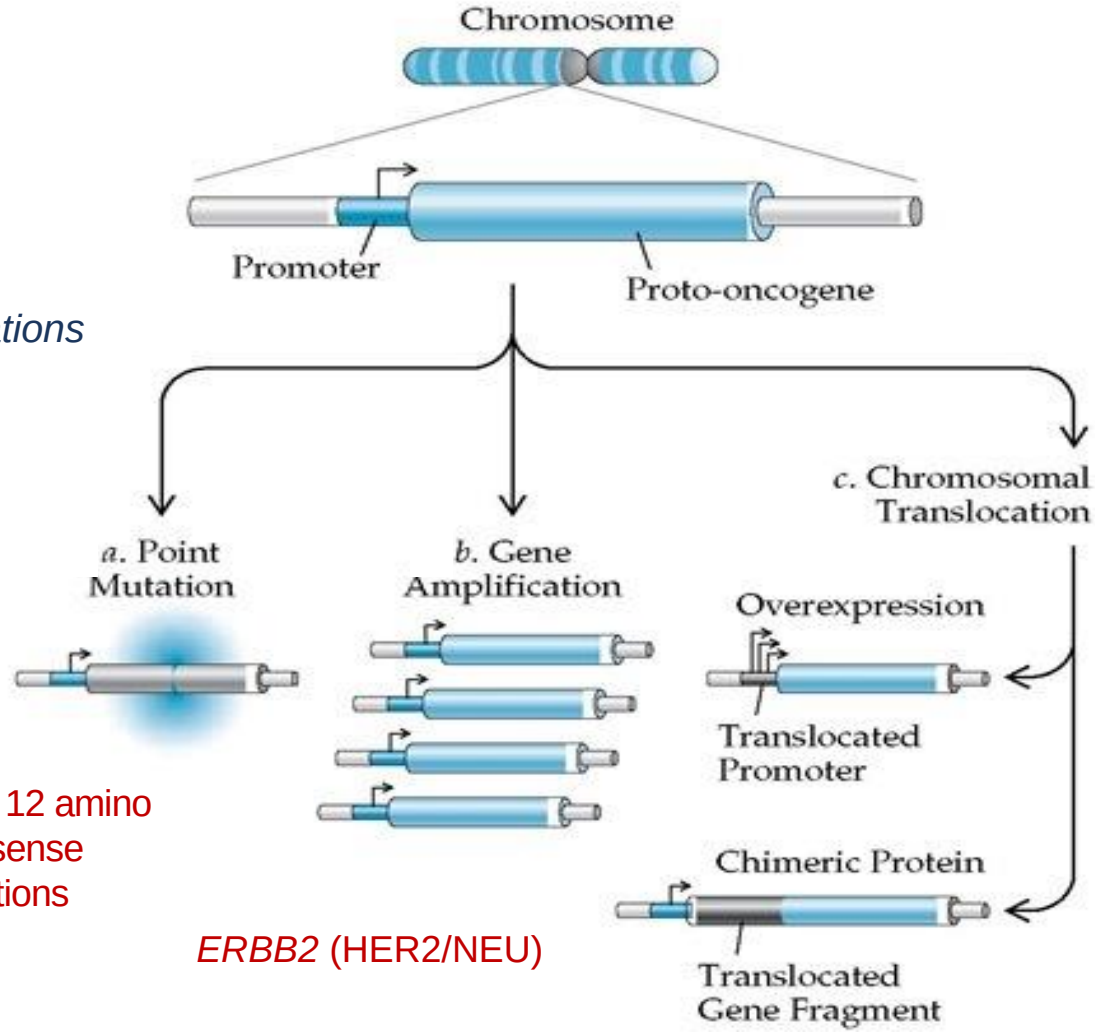
Characteristics of Oncogenes

- Identified as transforming genes of animal retroviruses.
- An activated form of a cellular gene (proto-oncogene). In contrast, the oncogenes of DNA-based tumor viruses (such as Human Papillomavirus (HPV)) do not have cellular homologs.
- Act dominantly at the cellular level, which means only one allele need be mutated.
- Mutations are somatic and seldom inherited. (Two exceptions are *RET*, responsible for MEN2, and *MET*, cause of familial papillary renal cell carcinoma.)
- Usually involved in growth factor signal transduction.



How a Proto-oncogene Transforms into an Oncogene

*Mutations **activate** proto-oncogenes, whereas mutations **in**activate tumor suppressor genes.*



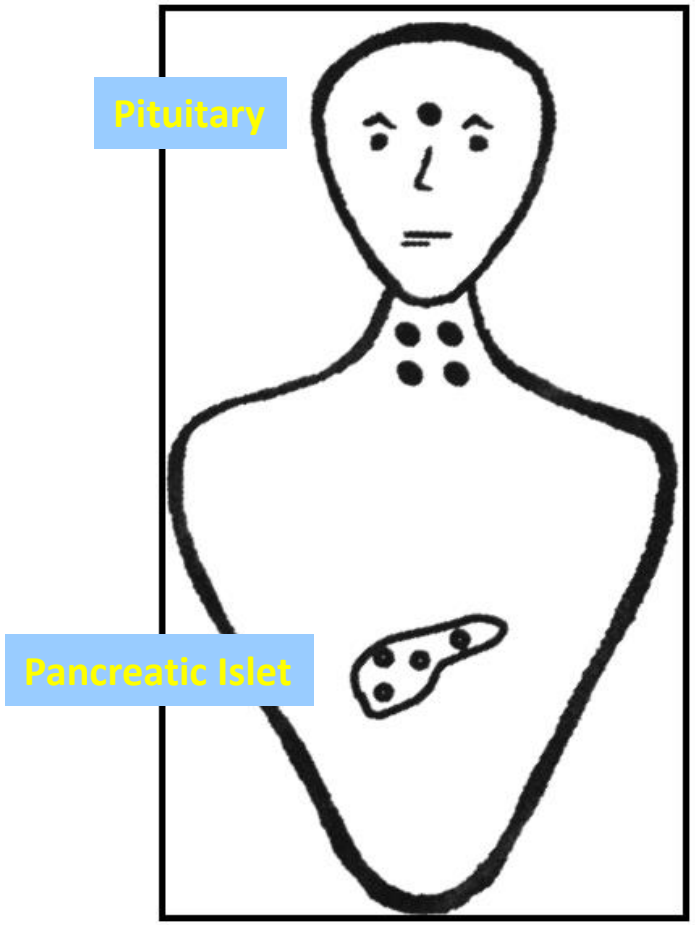
KRAS codon 12 amino acid missense substitutions

ERBB2 (HER2/NEU)

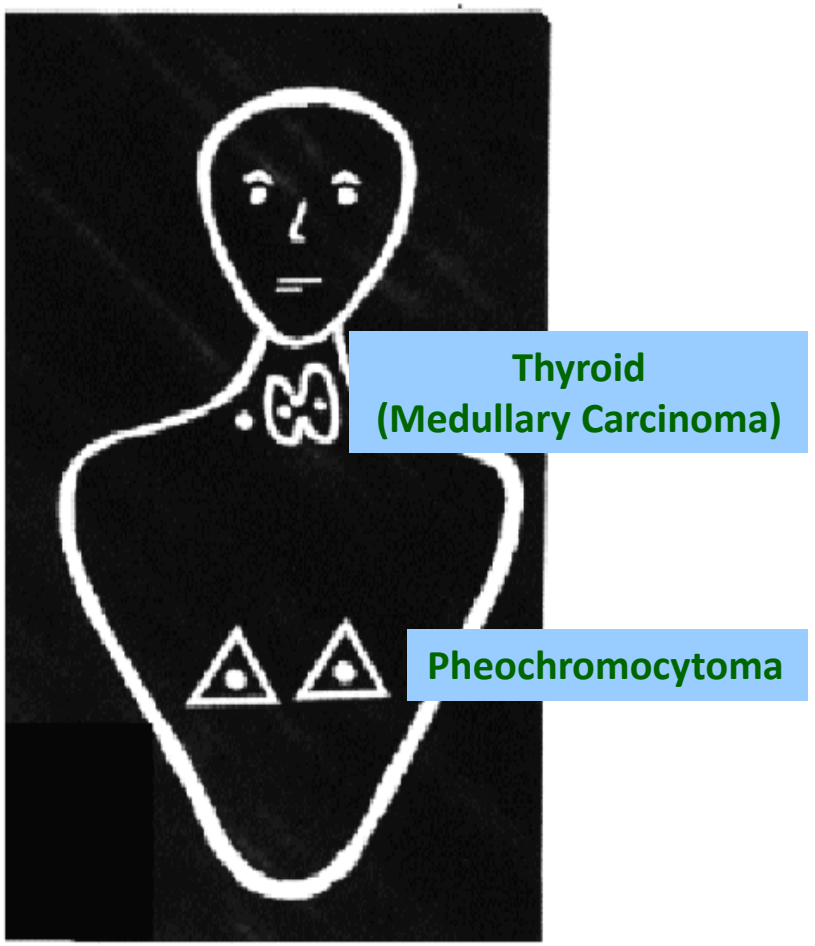
(all somatic)

T(9;22) Philadelphia chromosome

Gain of Function Mutations in *RET* Proto-Oncogene Cause Multiple Endocrine Neoplasia 2 (MEN2)



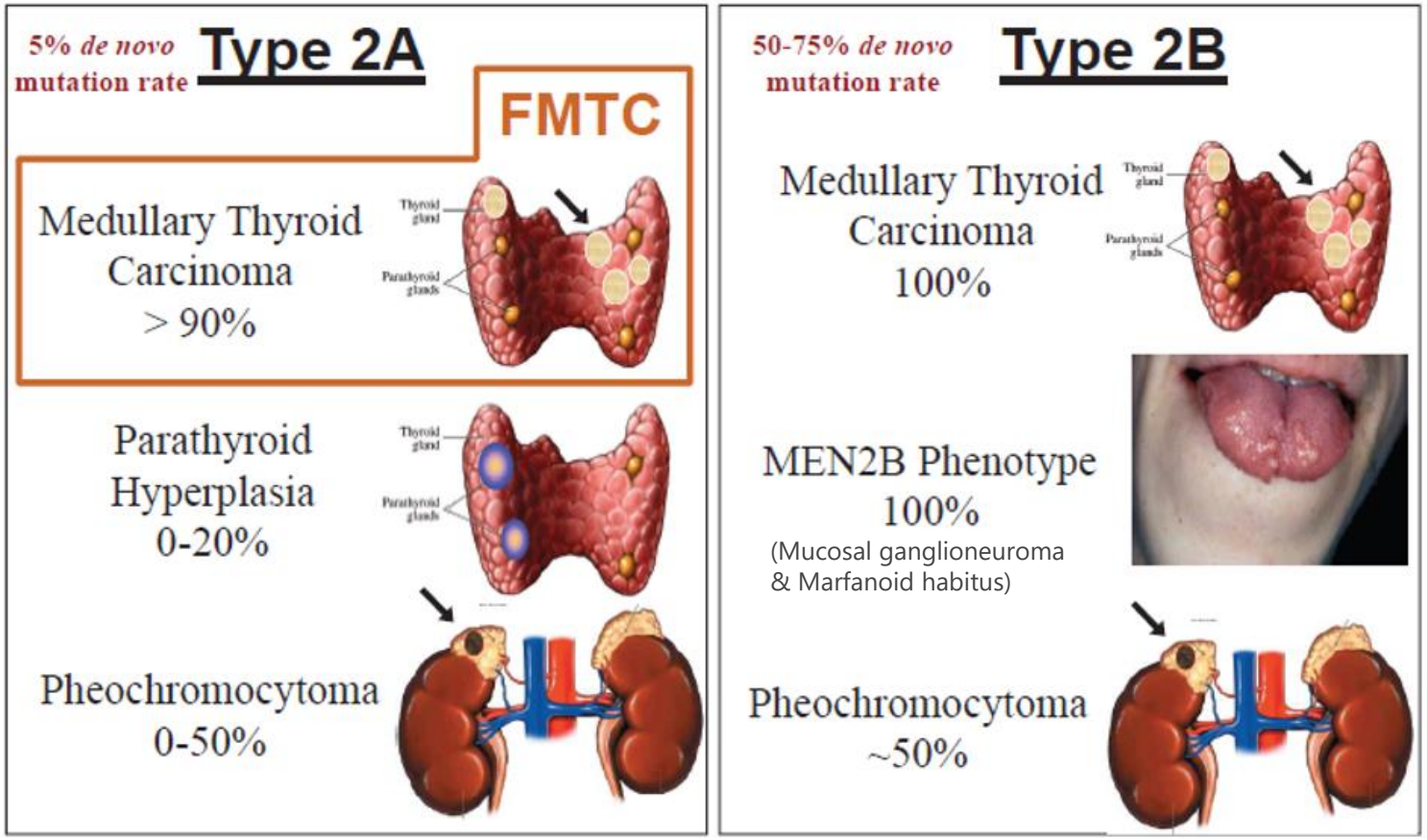
MEN1 (*MEN1* – TS gene)



MEN2 (*RET* – proto-oncogene)

MEN2 (*RET*)

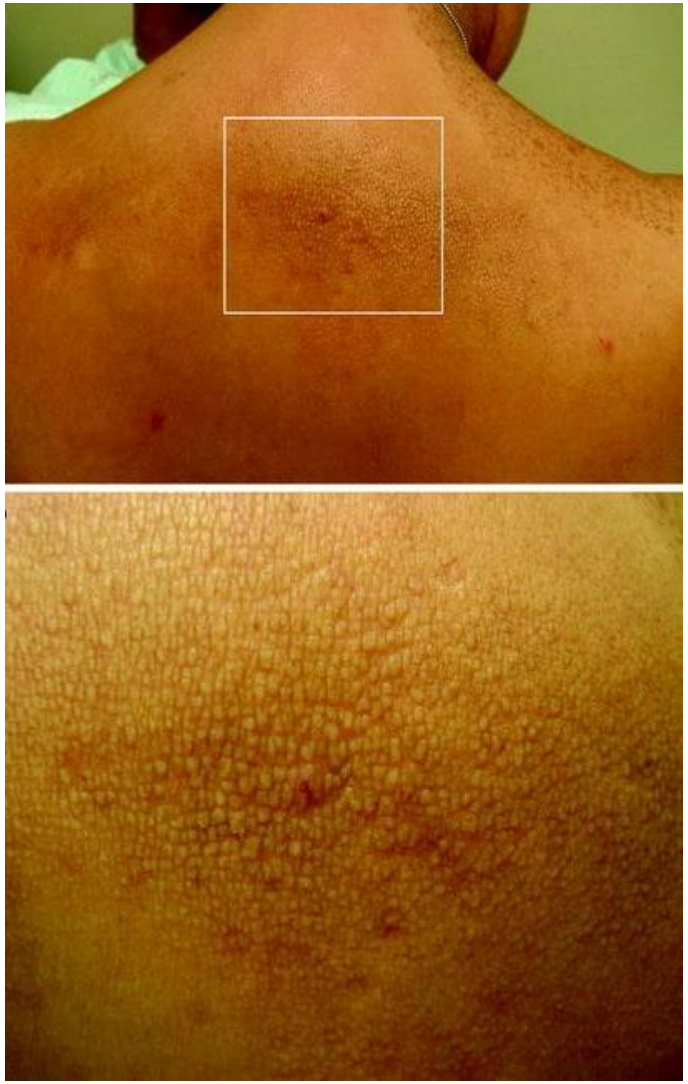
- All Medullary thyroid cancer (MTC) should have *RET* analysis.
- 25% of all MTC are hereditary, more often bilateral and multifocal.
- New germline mutations especially common for MEN2B.



Gilbert Cote (MD Anderson)

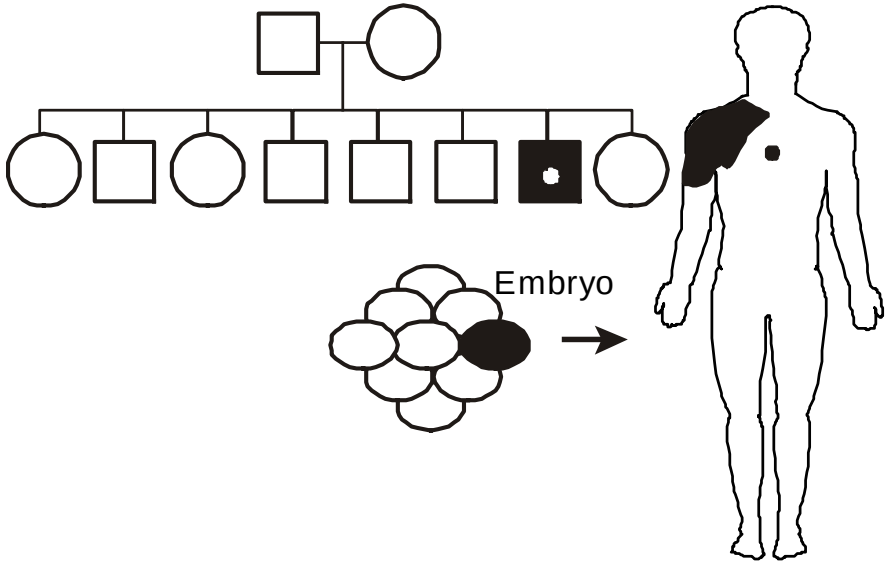
Cutaneous Lichen Amyloidosis

Feature of MEN2A



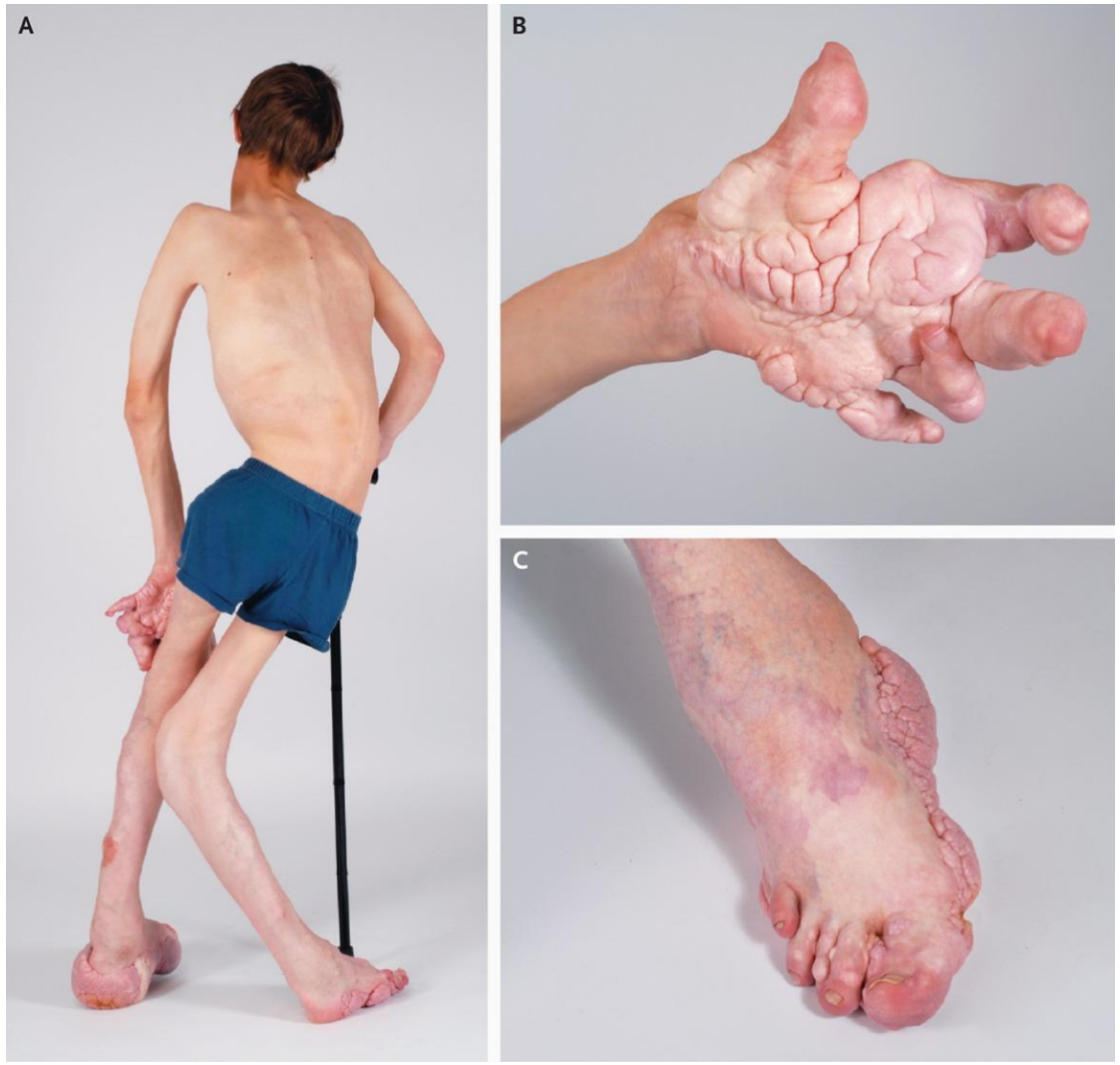
Daly, Merck Manual

Mosaic, otherwise Lethal Germline Proto-Oncogene Mutations



- Germline mutation is presumably embryonic lethal.
- Arises post-zygotically in a subset of cells during embryonic development.
- Not heritable and strictly sporadic.
- ‘Port wine stain’ (Sturge-Weber syndrome) is one such type of disorder and is caused by mutation of *GNAQ*, which encodes part of the Gq alpha subunit involved in intracellular signaling.
- *GNAQ* mutations occur in 45% of ocular melanoma.

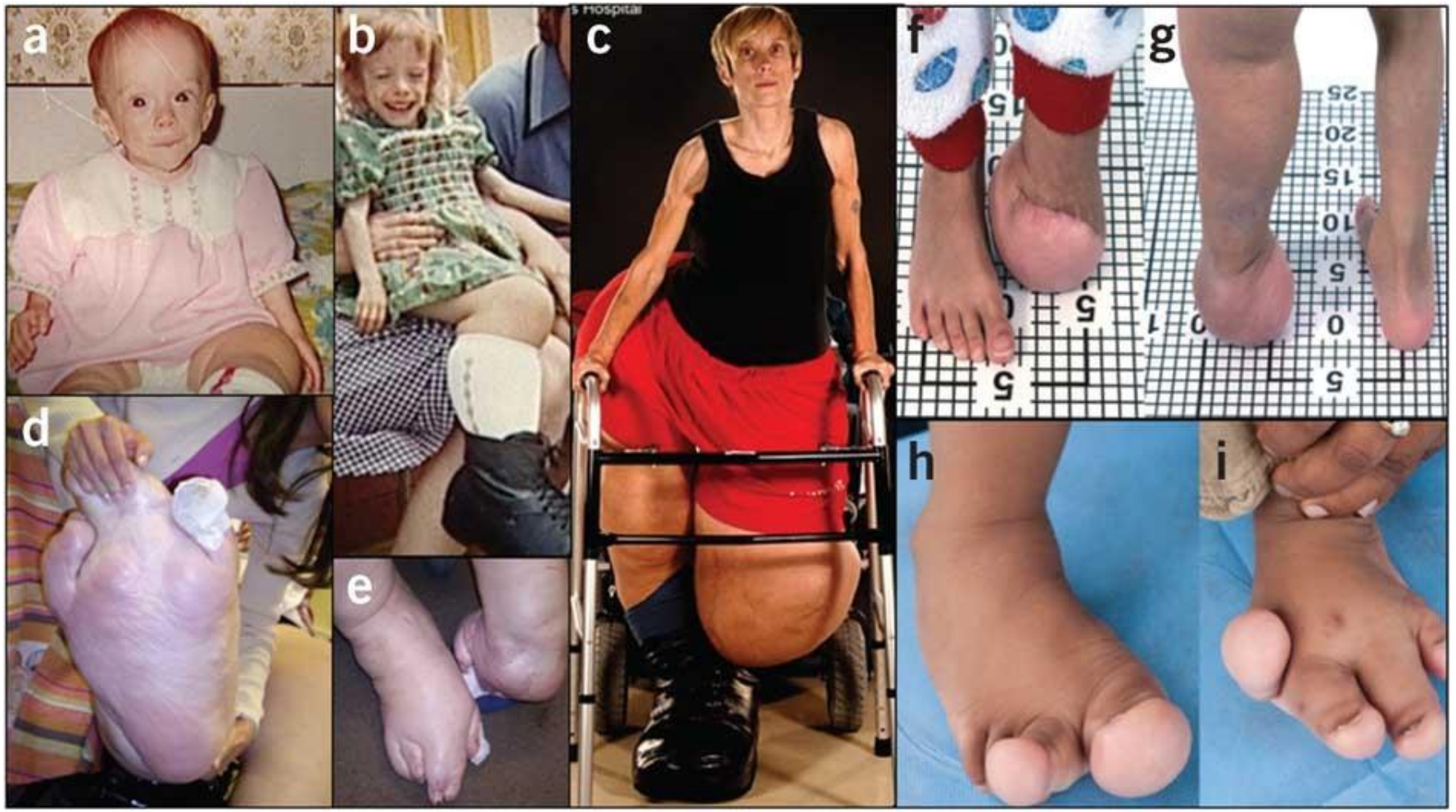
Activating *AKT* Mutations in Proteus Syndrome



Lindhurst et al. 2011 NEJM

26/29 patients had same *AKT* mutation (c.49G→A, p.Glu17Lys)

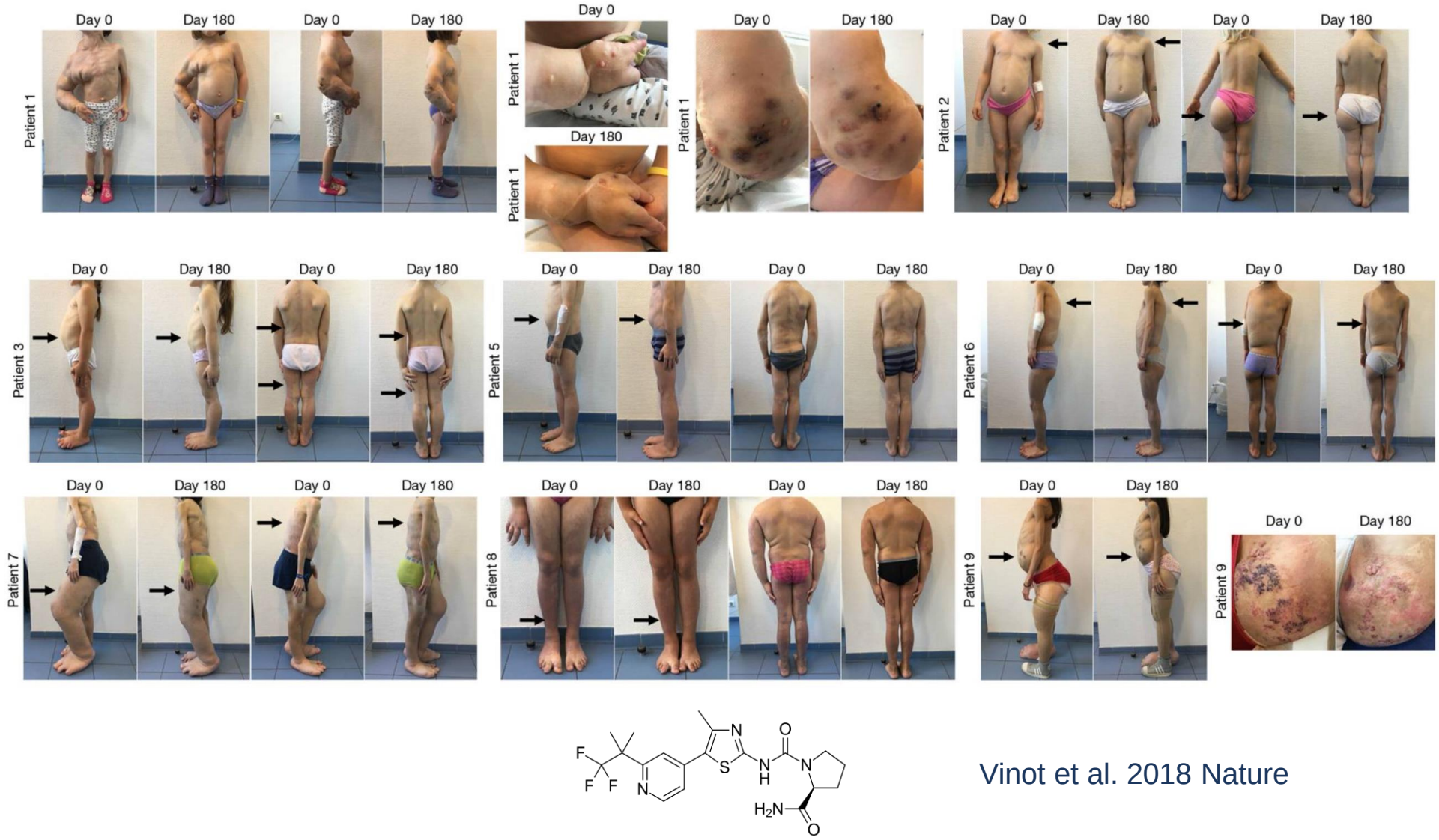
Fibroadipose Hyperplasia (CLOVES Syndrome*) with Somatic Activating Mutations in *PIK3CA*



Lindhurst et al. 2012
Nature Genetics

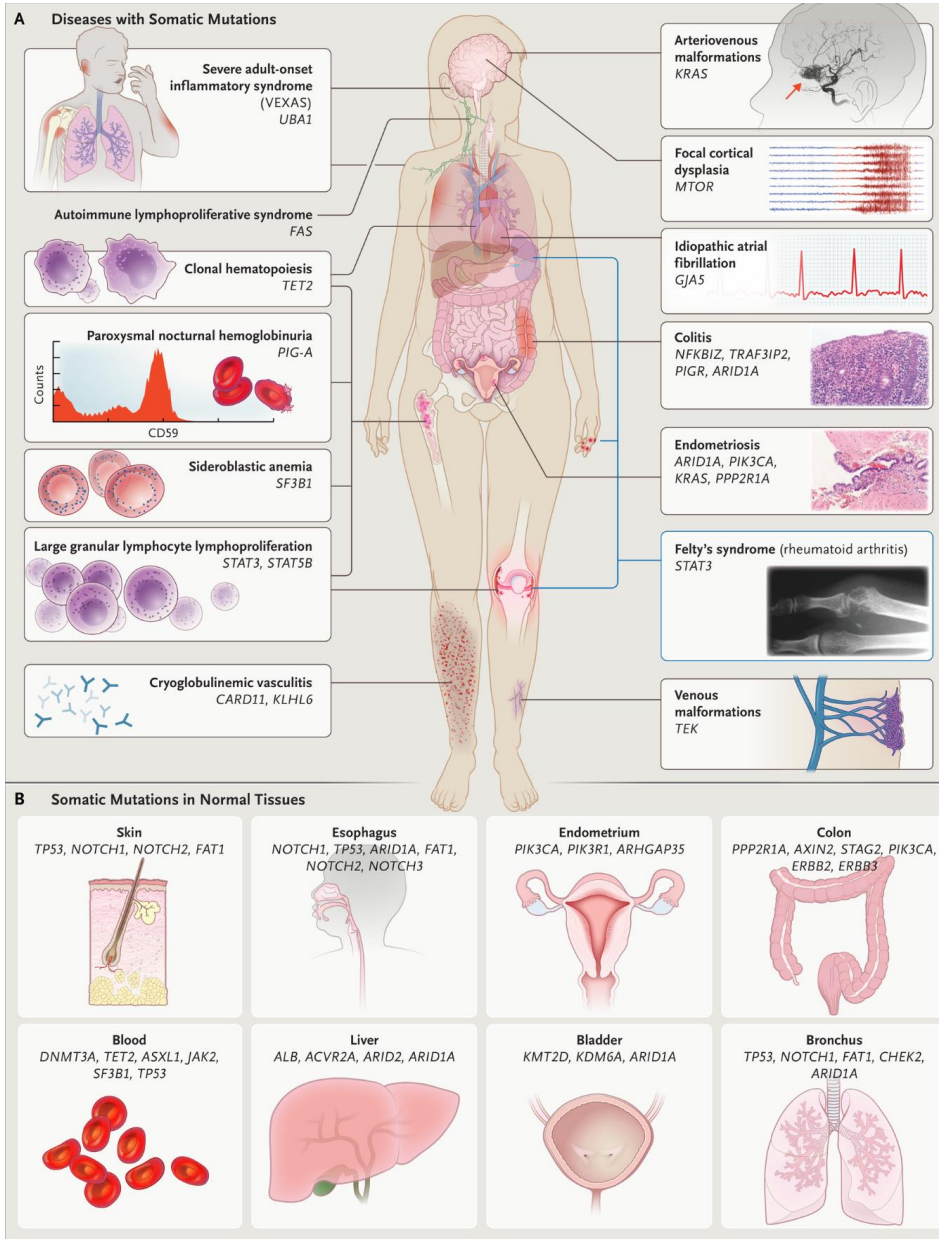
(*Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal naevi, Scoliosis/skeletal and spinal syndrome)

Clinical Trial with PI3K Inhibitor, Alpelisib (BYL719)



Vinot et al. 2018 Nature

Somatic Mutations in Many Organs

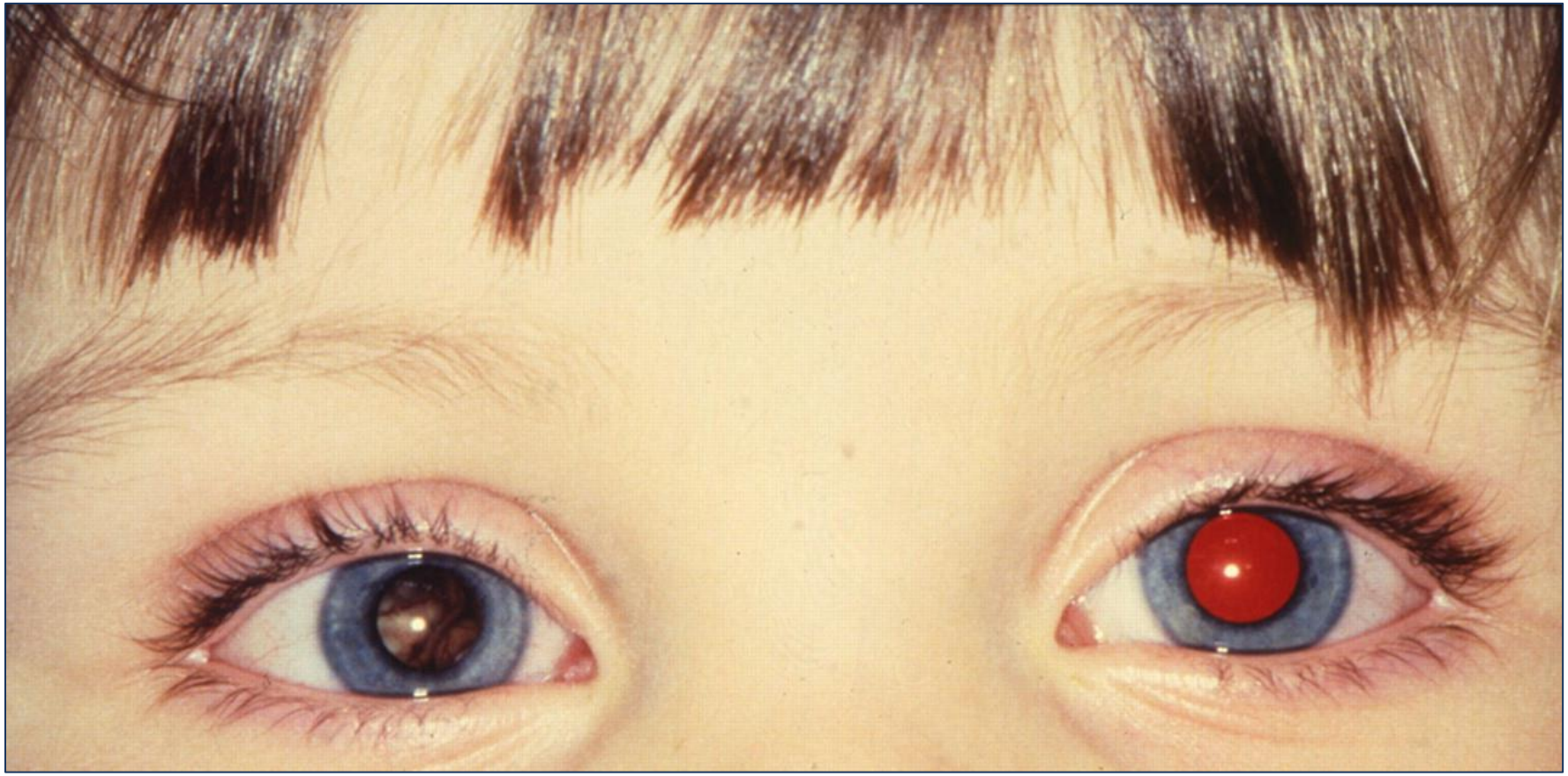


Mustjoki & Young, 2021 NEJM

Characteristics of Tumor Suppressor (TS) Genes

- Identified as genes responsible for autosomal dominant human tumor syndromes.
- Recessive at cellular level, means both alleles must be inactivated.
- For familial cases, the mutation in one allele is germline and the mutation in the other allele is acquired (somatic). For sporadic (non-familial) cases, both mutations are acquired.

Retinoblastoma



Leukocoria

Alfred Knudson's Two-Hit Model of Tumor Suppressor Gene Inactivation

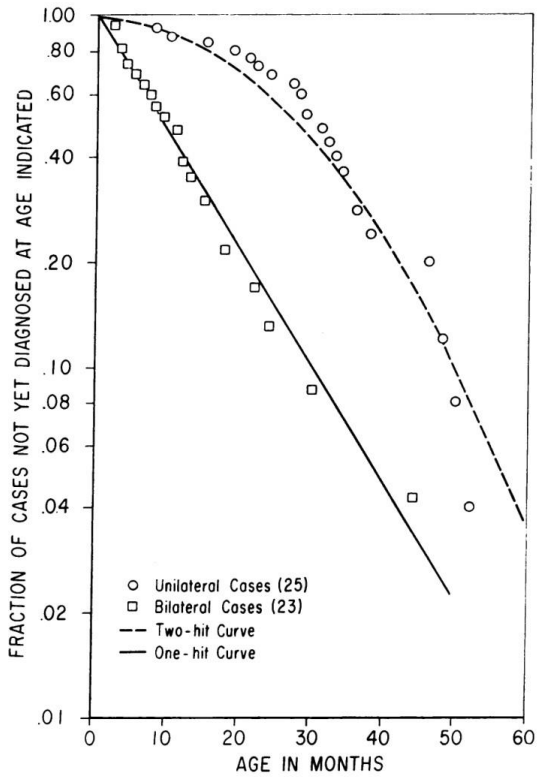


FIG. 1. Semilogarithmic plot of fraction of cases of retinoblastoma not yet diagnosed (S) vs. age in months (t). The one-hit curve was calculated from $\log S = -t/30$, the two-hit curve from $\log S = -4 \times 10^{-5} t^2$.

Knudson 1971 PNAS

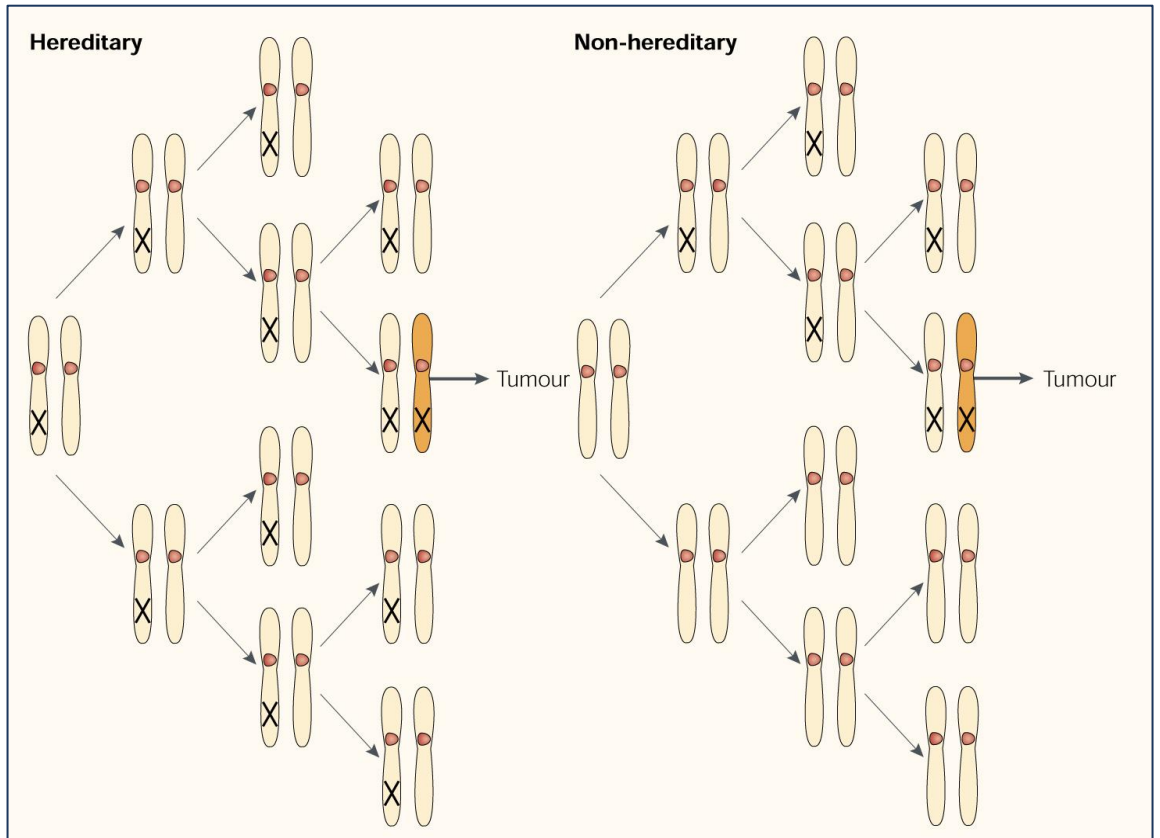
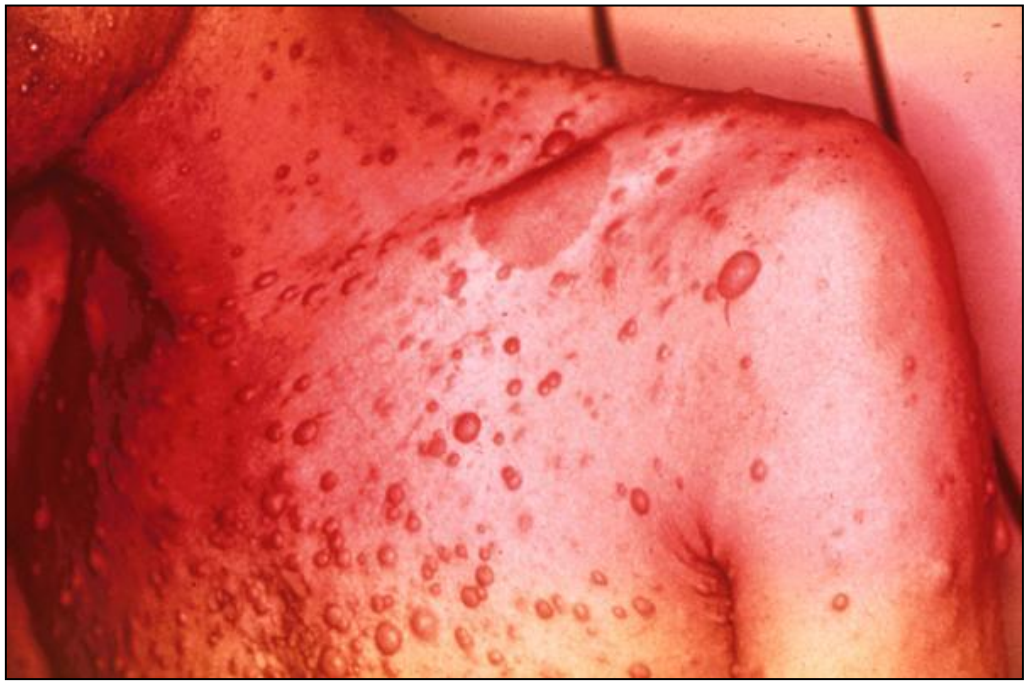


Figure 4 | **Two-hit tumour formation in both hereditary and nonhereditary retinoblastoma.** A 'one-hit' clone is a precursor to the tumour in nonhereditary retinoblastomas, whereas all retinoblasts (indeed, all cells) are one-hit clones in hereditary retinoblastoma.

Knudson 2001 Nat Rev Cancer

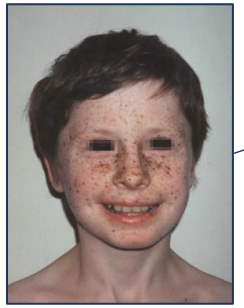
Neurofibromatosis Type 1 (*NF1*)

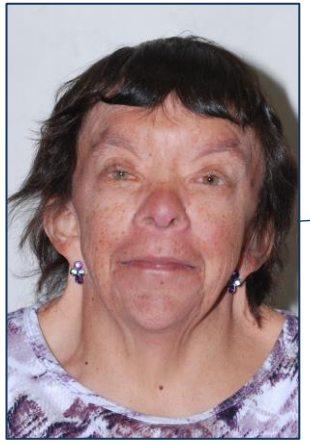


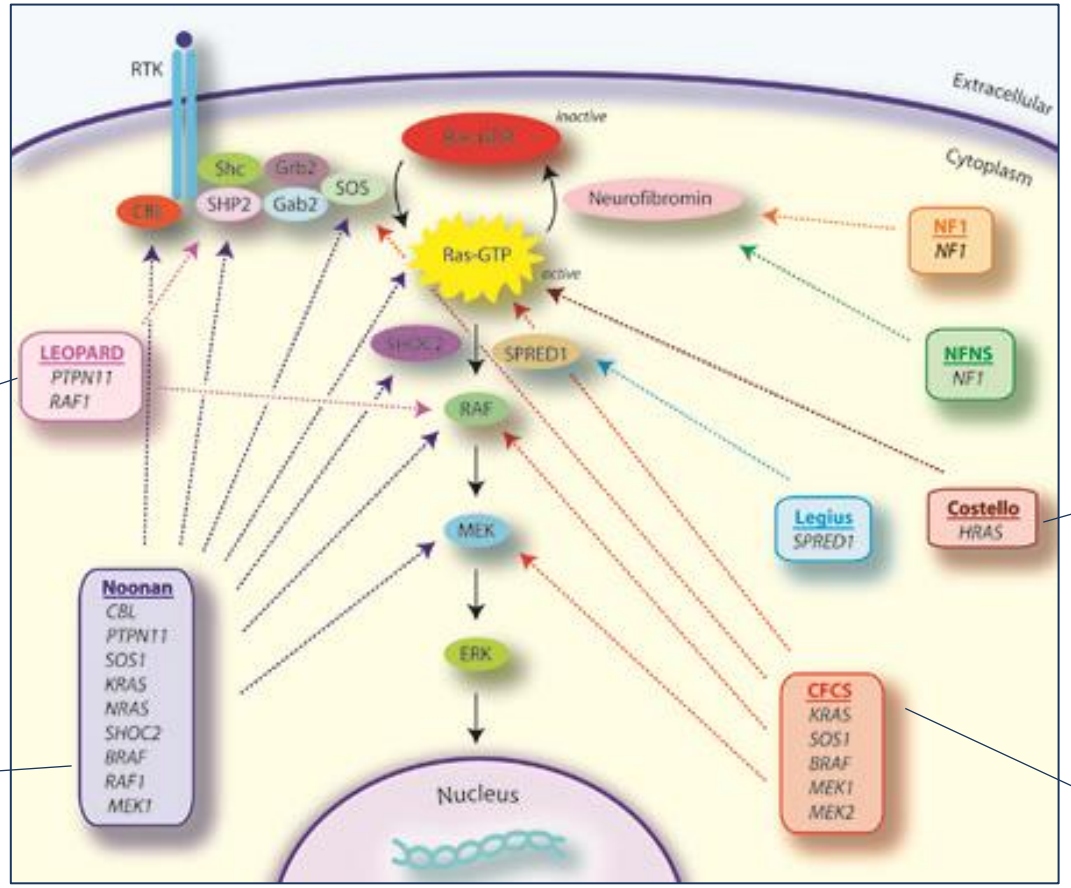
- Autosomal dominant.
- “Café-au-lait” macules.
- Freckling in axillary and inguinal skin folds.
- Occasional malignant tumors (neurofibrosarcomas, schwannomas, gliomas, pheochromocytomas, and chronic myelomonocytic leukemia).
- Mutations in *NF1*, a large gene (60 exons, >300 kb of DNA), encoding a GAP (GTPase activating protein).
- Each lesion is a direct read-out of the second hit

NF1 Is Just One of Many Distinct yet Similar “RASopathies”

GEFs (guanine nucleotide exchange factors)



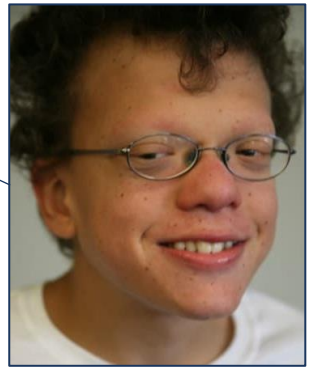




RAS-MAPK Signal Transduction Cascade

Ekvall et al. 2011 AJMG

GAPs (GTPase activating protein)



CFCS - Cardiofaciocutaneous syndrome

Li Fraumeni Syndrome (*TP53*)

Core cancers:

- Brain
- Choroid plexus carcinoma
- Breast cancer
- Sarcoma
- Adrenocortical carcinoma
- Bronchoalveolar cancer
- GI malignancy
- TP53 mutations are found in >90% of peds & adult low-hypodiploid ALL and these are constitutional (Li-Fraumeni) in 43% of the pediatric cases

When to suspect:

- Young breast cancer <35
- Strong family history of core cancers
- All adrenocortical carcinomas
- All sarcomas <45 years

Li Fraumeni Syndrome Management

- Risk of cancer in women ~100%, men 75%.
- Risk reduction options include bilateral mastectomy.
- Avoid ionizing radiation (i.e., X-ray/CT).
- Screening (Toronto Protocol vs NCCN or AACR)
  - Annual breast MRI, beginning @ 20-25y.
  - Annual whole body MRI (not CT).
  - Annual brain MRI .
  - q6m Abdominal US, CBC, LDH, ESR.
  - Annual dermatology exam.
  - Upper/lower endoscopy, beginning @ 25y.
- Consideration of metformin for chemoprophylaxis.

Sharks Get Cancer

Elephants Don’t Get Cancer

Table 1. Cause of Death in 644 Elephants[a]

Age Range, y	Total Necropsies	No. of Elephants							Observed % With Cancer (95% CI)	Inferred % With Cancer (95% CI)
		Euthanized, Noncancer	Noncancer Disease	Exogenous Mortality	Euthanized, Unspecified	Disease, Unspecified	Euthanized, Cancer	Cancer		
0-5	125	15	77	28	1	2	0	2	1.60 (0.00-4.24)	2.40 (0.00-5.44)
6-15	83	20	36	19	4	1	1	2	3.61 (0.00-8.02)	6.02 (0.58-11.47)
16-25	121	35	48	25	7	2	2	2	3.31 (0.00-6.69)	4.96 (0.86-9.05)
26-35	108	27	51	15	8	4	3	0	2.78 (0.00-6.11)	3.70 (0.00-7.60)
36-45	94	32	27	13	12	5	0	5	5.32 (0.47-10.16)	6.38 (1.18-11.58)
46-55	70	14	23	7	7	17	1	1	2.86 (0.00-7.37)	5.71 (0.00-11.59)
≥56	43	3	7	6	7	19	1	0	2.33 (0.00-8.16)	6.98 (0.00-15.29)
Lifetime, 0-≥56	644	146	269	113	46	50	8	12	3.11 (1.74-4.47)	4.81 (3.14-6.49)

[a] Observed cancers are reported as the percentage of deaths annotated as being caused by cancer or by euthanasia due to cancer. Inferred cancer risk assumes that cancer occurs at the same fraction of deaths in cases with unspecified causes as those with specified causes. Exogenous causes of mortality include accidents (eg, falling in the enclosure) and animal fights that cause fatal injury.

Abegglen et al. 2015 JAMA

Speculate Why They Don’t

One way to think about it:

Elephants are big, but their cells are generally the same size as a human or mouse.

So, they must have more cells.

But baby elephants start out from a zygote. So, they must undergo more cell divisions.

If you do the math, elephants would undergo as many or more cell divisions by the time they are a young adult as a human would during an entire lifetime.

Since most DNA errors are associated with cell division, and elephants have both undergone more cell divisions and have more cells, they must have evolved a mechanism for reducing DNA errors.

Elephants Have 40 copies of *TP53*

TP53 -- Guardian of the genome. If it is lost, then cell division proceeds unchecked, even if there are mutations that need to be repaired.

It is the single most commonly mutated gene in cancer, often biallelic inactivating mutations but also dominantly-acting mutations occur.

It behaves as a tumor suppressor gene.

Li-Fraumeni syndrome is a rare autosomal dominant tumor suppressor gene syndrome that requires two hits. The first is hereditary, so the second hit has a good chance of occurring.

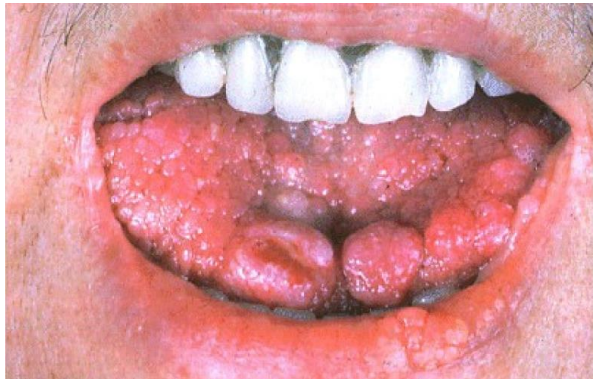
Even if an elephant had a germline mutation in one copy of TP53, it would need 39 more hits! Not very likely. Elephants have duplicated their TP53 gene many times throughout the genome.

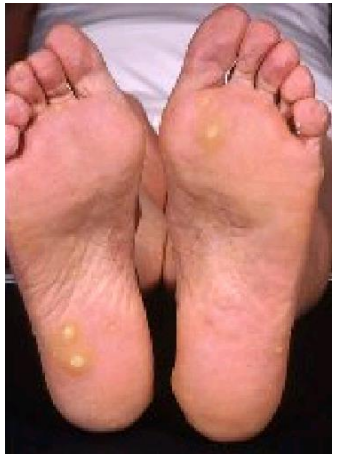
Cowden Syndrome

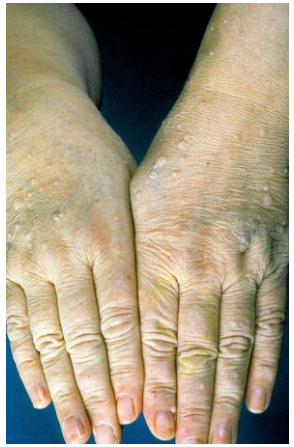
- Germline mutation in *PTEN* (less often, *PIK3CA* or *AKT1*)
- Cancer risks
  - Breast cancer - 85% lifetime risk
  - Thyroid disease in 75% of Cowden patients
    - Multinodular goiter
    - Epithelial thyroid cancer follicular>papillary
  - Endometrial Cancer
  - Colorectal Cancer
- Physical features
  - Developmental Delay
  - Head circumference >59cm
  - Papillomas on skin and mucosa
  - Dysplastic gangliocytoma of cerebellum
  - Skin lesions such as acral keratoses, trichilemmomas

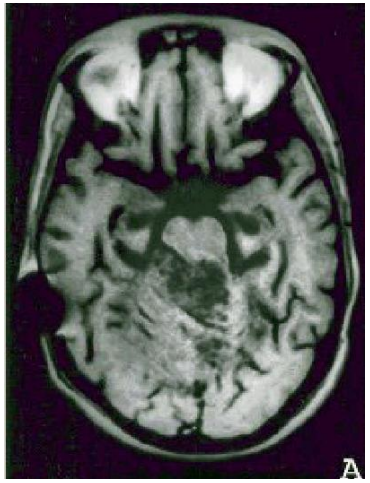
- Surveillance
- Annual thyroid ultrasound from childhood
- High risk breast screening MRI/mammography @30
- Colonoscopy @35, q5years
- Renal ultrasound @40
- Endometrial biopsy@30
- Annual dermatologic exam

R. Kim, Princess Margaret Cancer Center
& Wikimedia/Madhero88









Lynch Syndrome and DNA Mismatch Repair

- Autosomal dominant.
- Predisposes to numerous types of carcinomas, esp. of the colon, accounts for ~3-5% of all colon cancer.
- Genomic instability of repeated sequences had been noted in tumors from patients. Pattern of instability reminiscent of phenotype in yeast with deficiency in DNA mismatch repair.
- DNA mismatch repair genes are highly conserved from *E. coli* through yeast to humans.
- Somatic mutations of mismatch and other DNA repair genes appears important in sporadic cases, because genomic instability of repeated sequences is also noted in many non-familial cases.
- A mutation in a DNA repair gene could lead to a cascade of mutations in many other genes, including tumor suppressor and proto-oncogenes.

Amsterdam Criteria for Lynch Syndrome

- Three or more relatives with histologically verified Lynch syndrome-associated cancers (CRC, cancer of the endometrium or small bowel, transitional cell carcinoma of the ureter or renal pelvis), one of whom is a first-degree relative of the other two and in whom familial adenomatous polyposis (FAP) has been excluded.
- Lynch syndrome-associated cancers involving at least two generations.
- One or more cancers were diagnosed before the age of 50 years.

"3-2-1 rule" (3 affected members, 2 generations, 1 under age 50)

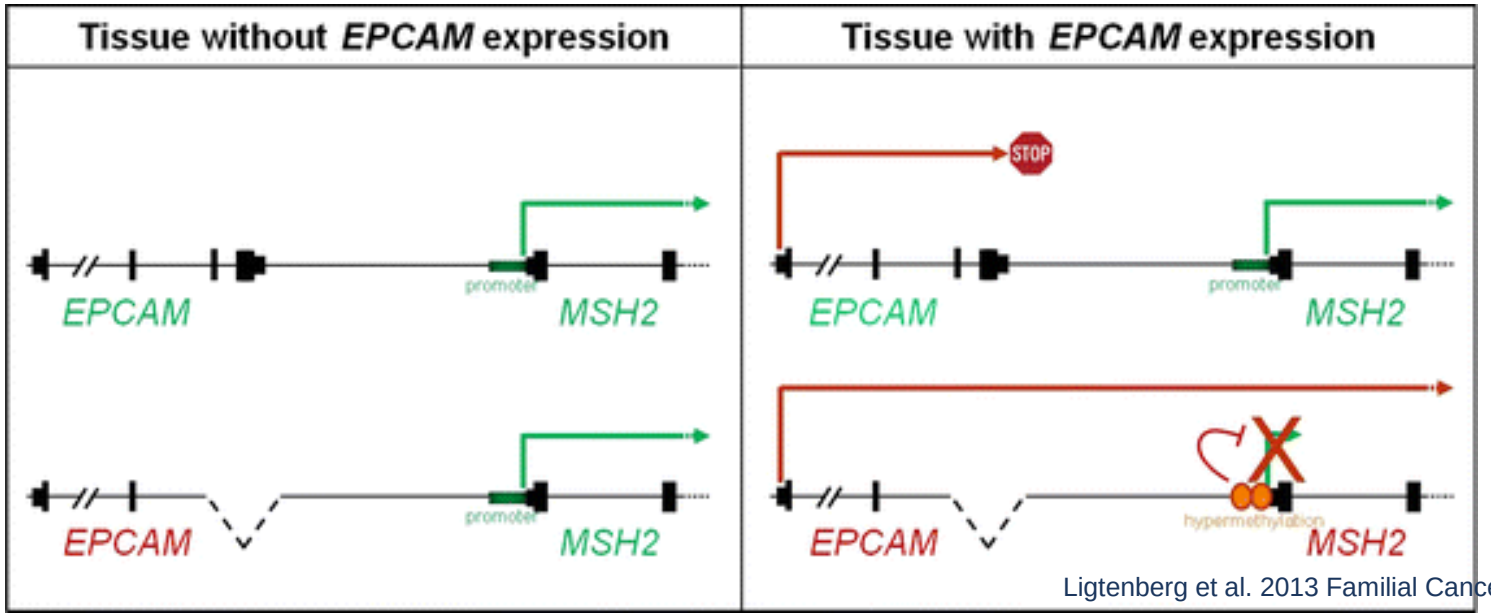
Lynch Syndrome vs Familial Adenomatous Polyposis (FAP)

Feature	Lynch Syndrome	FAP (*APC*)	Attenuated FAP (*APC*)	MAP (*MUTYH*)
# Polyps	0-50 usually	>100	10-99	5 to >700
Inheritance	autosomal dominant	autosomal dominant	autosomal dominant	autosomal recessive
Cancer(s)	colon, endometrial, gastric, ovarian	colon, small bowel, other	colon, small bowel	colon
Median onset age (years)	44-61 cancer	39 cancer (16 polyps)	50-55 cancer	47 cancer
DNA repair phenotype	MSI+ (microsatellite instability)	CIN+ (chromosomal instability – not clinically testable)	-	MSI-

DNA Mismatch Repair Genes

E. Coli	Human	Location	% of Lynch
MutS	*MSH2*	2p16	30%
	MSH6	2p16	7-10%
MutL	*MLH1*	3p21.3	60%
	PMS2	7p22	<5%

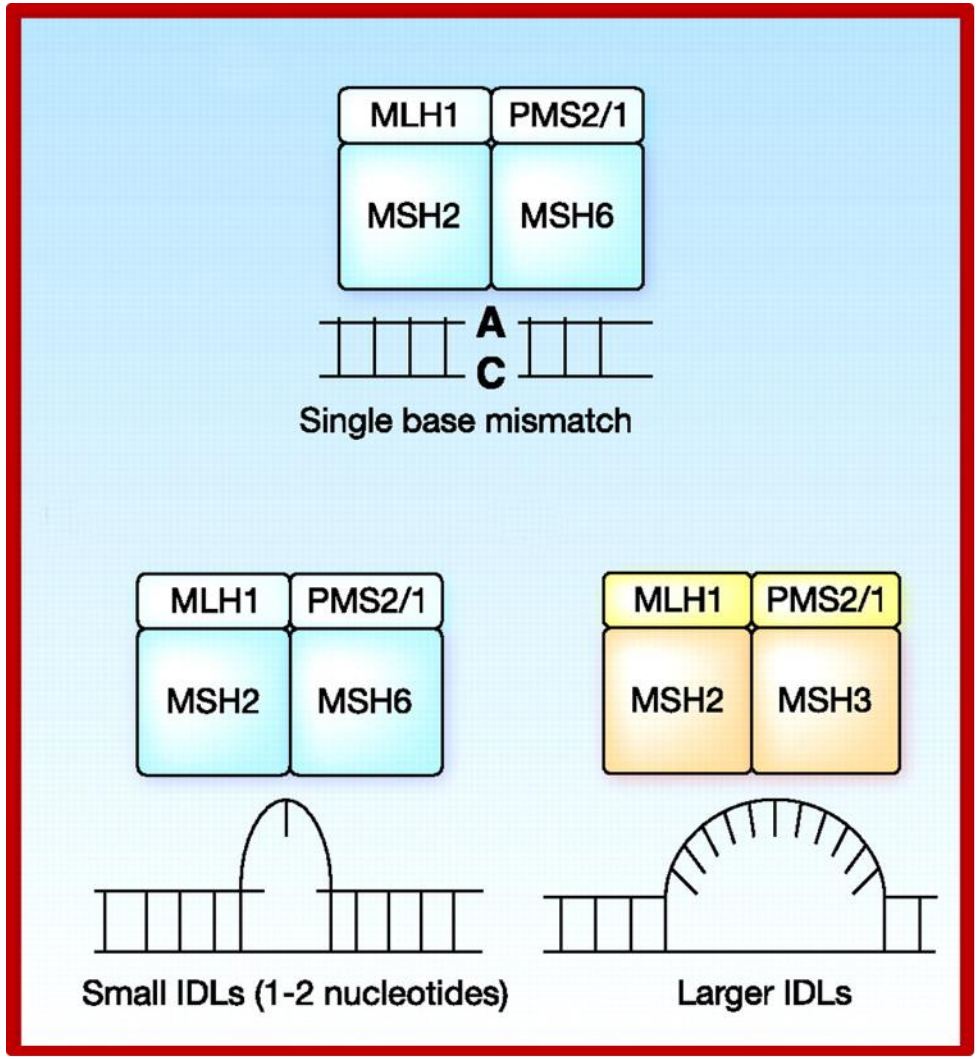
EPCAM Deletions with Intact, Non-expressed *MSH2*



Ligtenberg et al. 2013 Familial Cancer

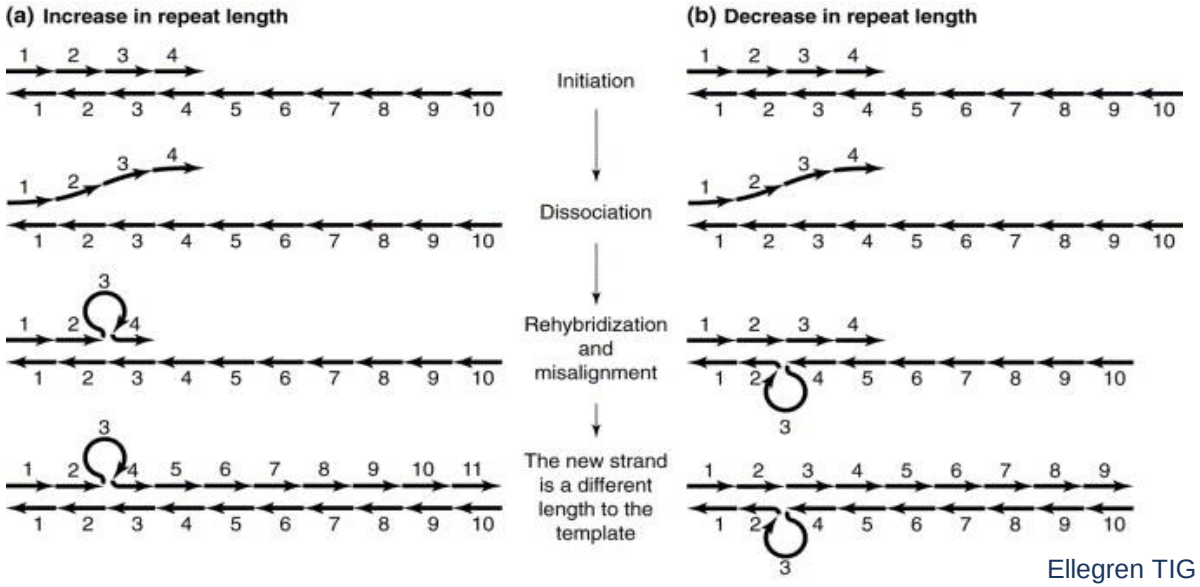
Mutation deleting a transcriptional stop signal in an upstream gene (EPCAM) leads to hypermethylation and loss of expression of MSH2

Schematic of DNA Damage Recognized by the Mismatch Repair (MMR) Pathway



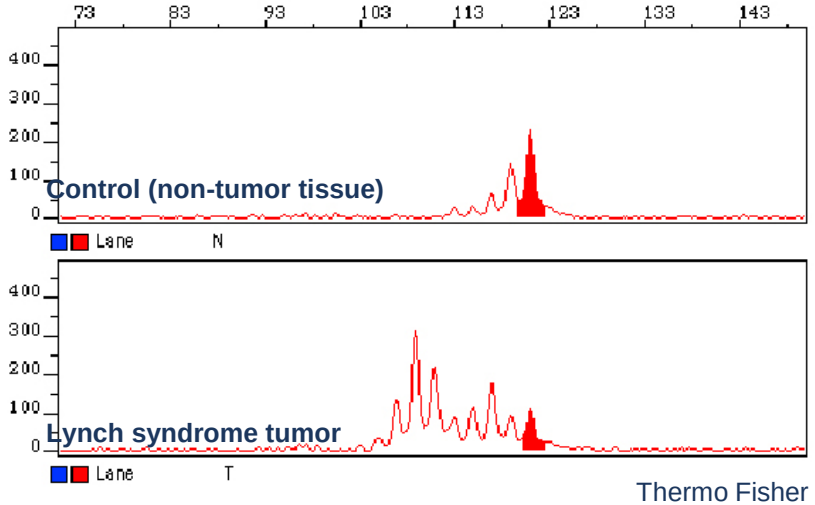
Martin et al. 2010 Cancer Research

Microsatellite Instability (MSI)



Ellegren TIG 2000

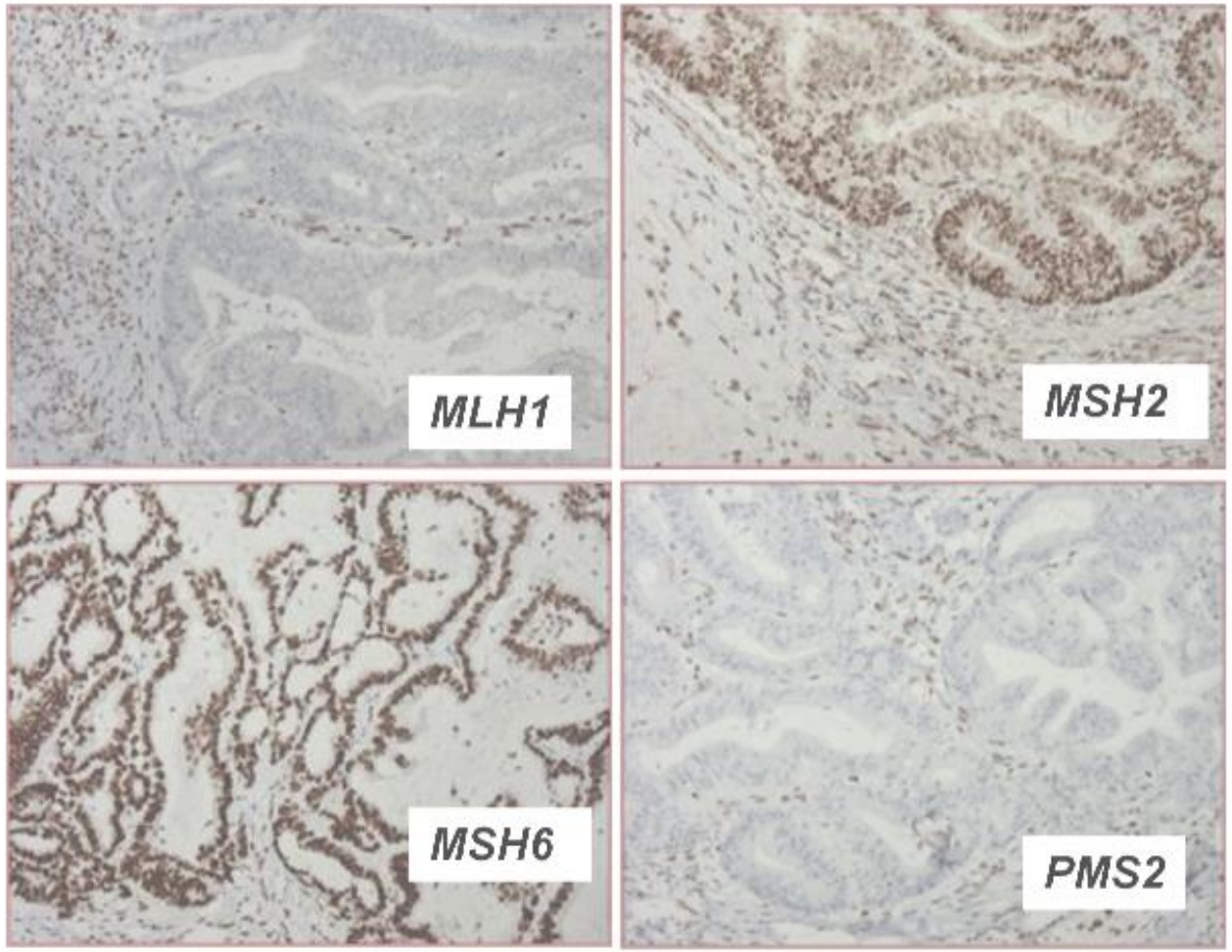
5-marker microsatellite panel with
100% sensitivity and specificity
(one marker shown as example)



Thermo Fisher

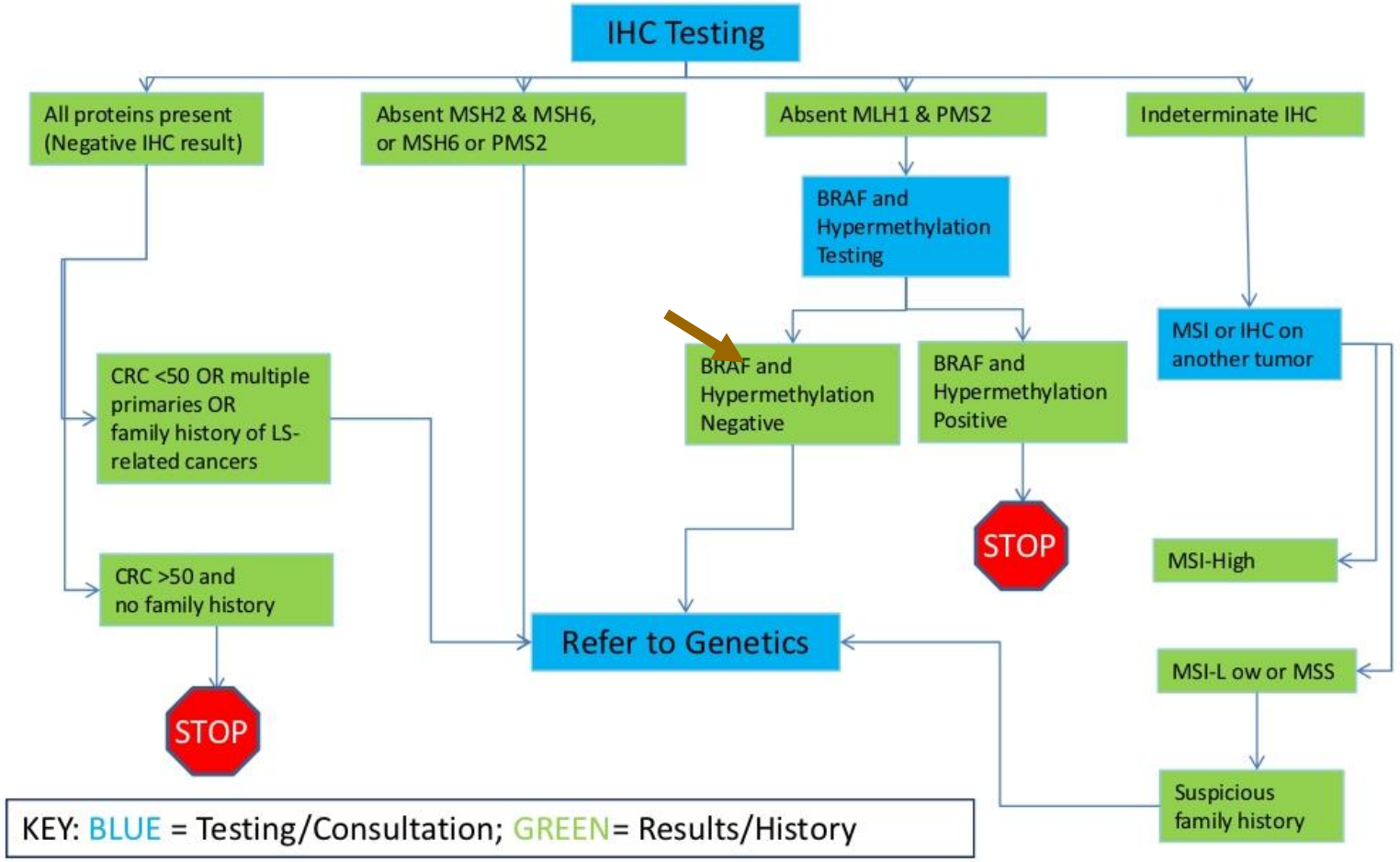
Immunohistochemistry (IHC)

IHC ≠ MSI !



Lynch Syndrome Screening Network

V600E *BRAF* Mutation Testing Informs IHC



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

Rectal Cancer Disappears After Experimental Use of Immunotherapy

Share

Sunday, June 5, 2022

Approximately 5 to 10% of rectal adenocarcinomas are mismatch-repair deficient, and these tumors have been shown to respond poorly to standard chemotherapy regimens, including neoadjuvant chemotherapy in locally advanced rectal cancer.[12-14] Immune checkpoint blockade alone has been shown to be highly effective as first-line treatment for patients with mismatch repair–deficient metastatic colorectal cancer, as well as for patients with treatment-refractory disease, with objective response rates of 33 to 55%, clinically significant durability of response, and prolonged overall survival.[15-17]

Memorial Sloan Kettering Cancer Center

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Hypermutation creates more neo-antigens

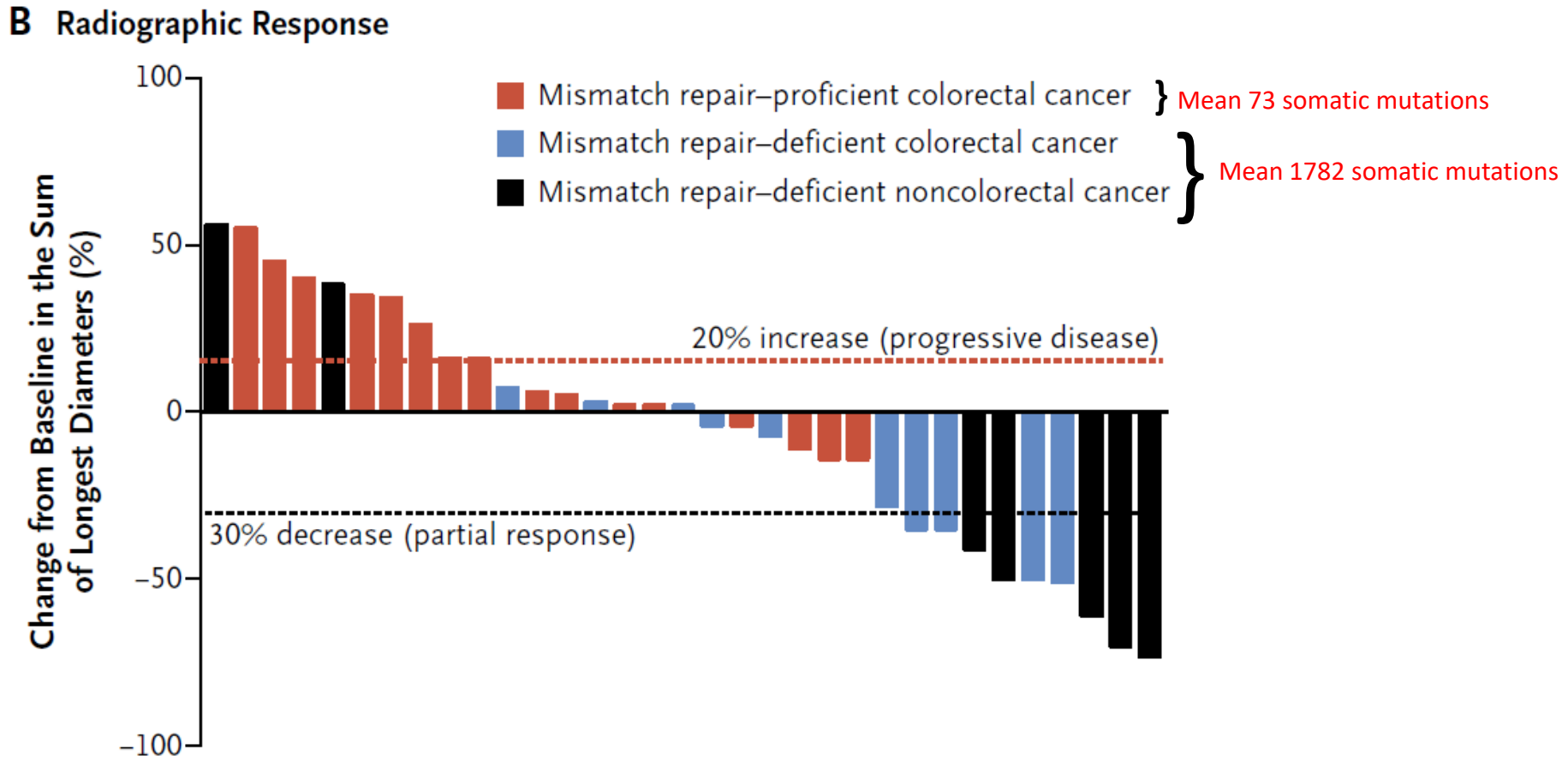
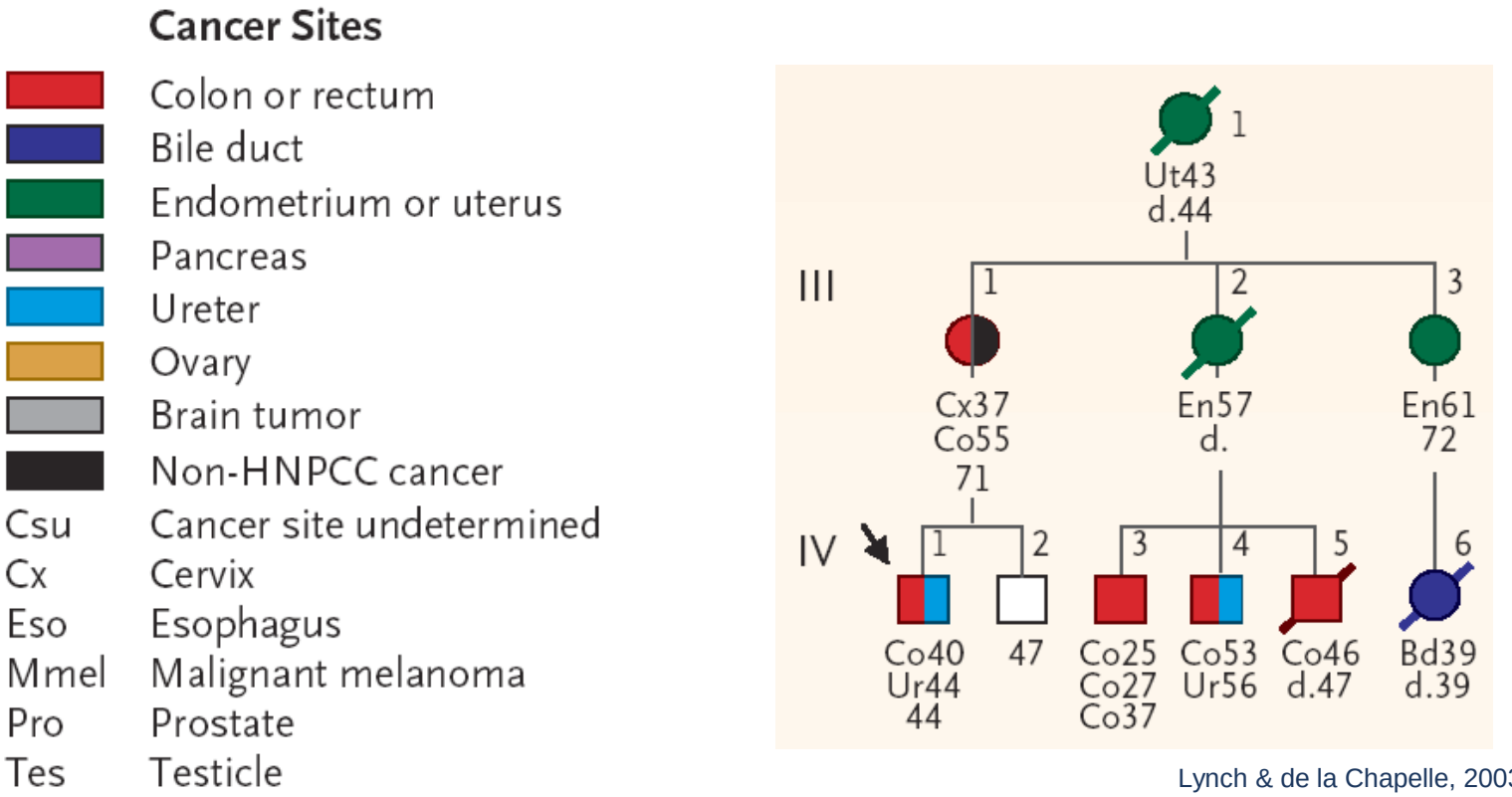


Figure 1. Clinical Responses to Pembrolizumab Treatment. Le et al. 2015 NEJM

Variable Expressivity in Lynch Syndrome



Lynch & de la Chapelle, 2003

Different types of cancer can occur in individuals from the same family with Lynch syndrome. Why?

Hereditary Breast/Ovarian Cancer Syndrome

BRCA1 mutation carriers

- Breast – 72 percent (95% CI 65 to 79 percent).
- Ovarian – 44 percent (95% CI 36 to 53 percent).

BRCA2 mutation carriers

- Breast – 69 percent (95% CI 61 to 77 percent).
- Ovarian – 17 percent (95% CI 11 to 25 percent) .
- Male breast cancer, pancreatic cancer, prostate cancer, melanoma…

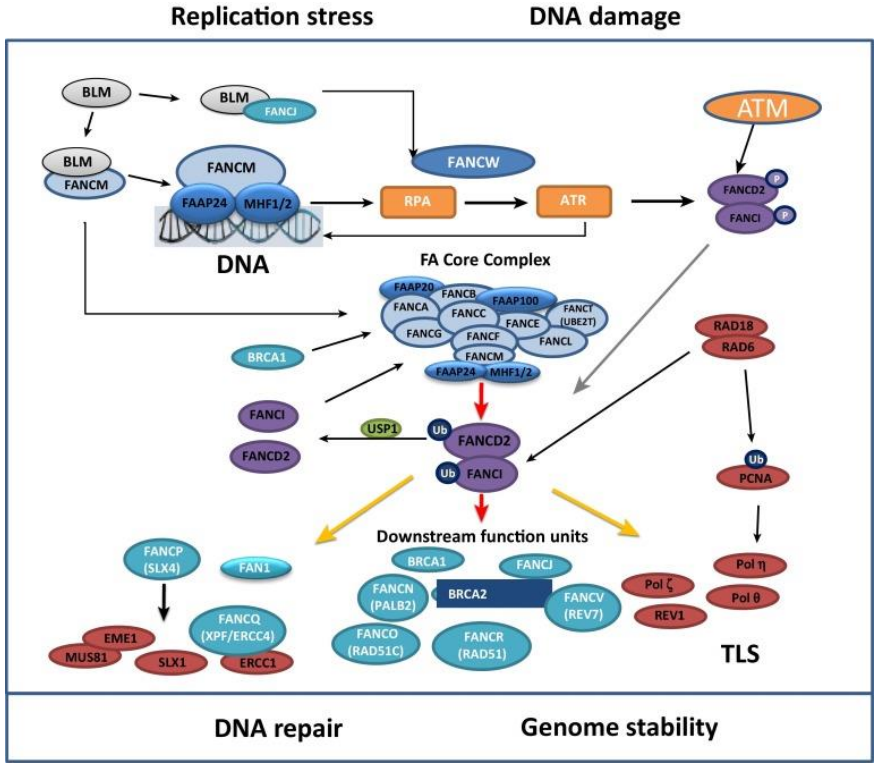
When to suspect

- Patient is from a *BRCA1/2* family.
- Ethnicity: Ashkenazi Jewish.
- Bilateral breast cancer.
- Age: under 35.
- Male Breast cancer.
- Invasive Serous Ovarian cancer.
- Medullary breast cancer ~11% BRCA1.
- Triple negative breast cancer <60 (NCCN).
- Strong family history of breast and ovarian cancer.
- Various guidelines of whom to test.

Management

- Surveillance.
- Risk reductive surgery.
- Chemoprevention.
- PARP inhibitors.

BRCA1/2 - Part of the Fanconi DNA Repair Complex



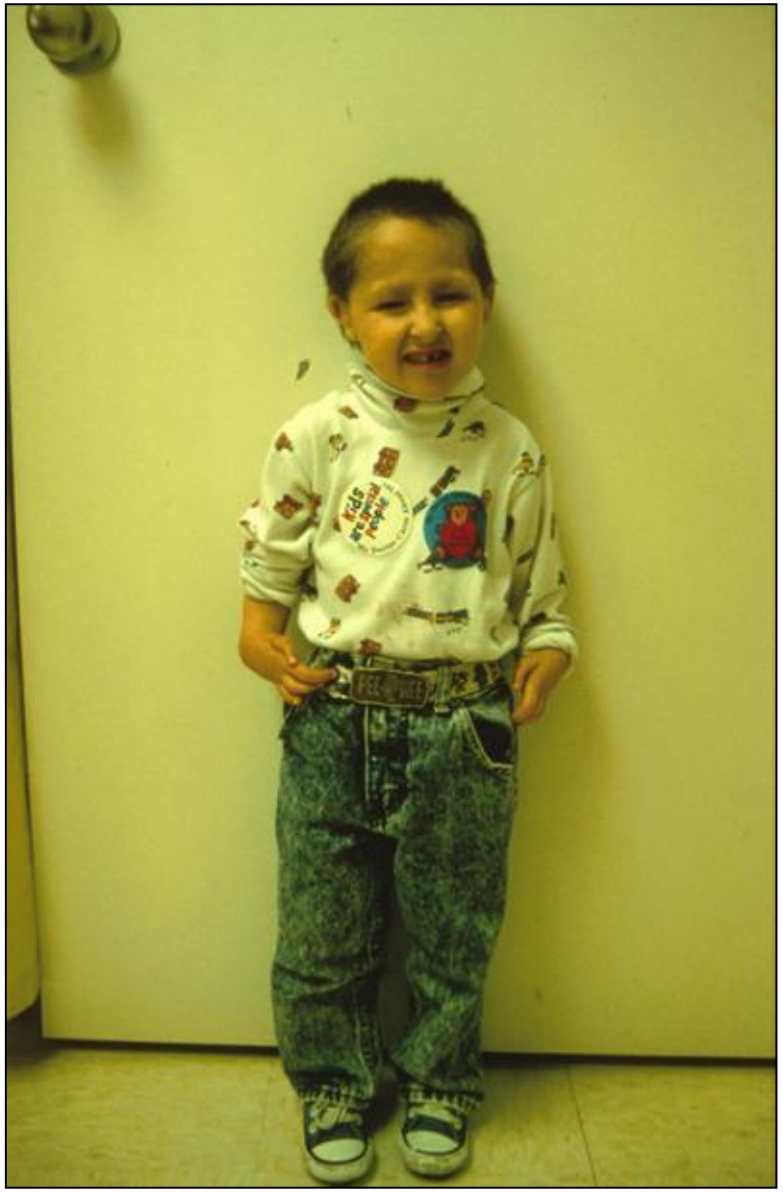
Nepal et al. 2017 Trends in Cancer

Implications:

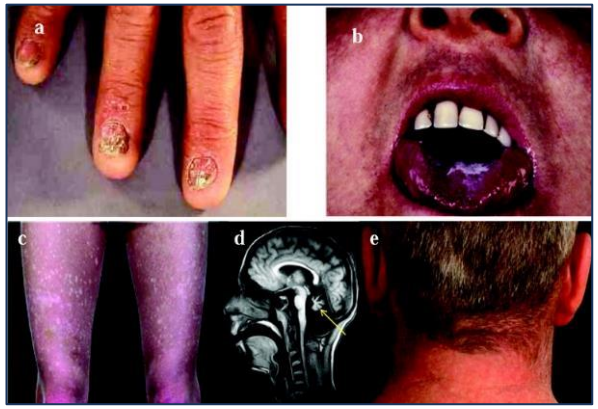
- Not surprisingly, heterozygous carrier state of FA can sort of be thought of as "*BRCA3.*"
- Individuals with heterozygous *BRCA1/2* mutations are carriers of FA.
- Illustrates principle that homozygous state of DNA repair deficiency syndromes (involving TS genes) leads to severe, early onset cancer—because no second hit is required!

Fanconi Anemia (FA)

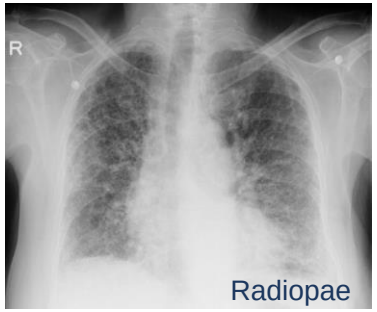
- Autosomal recessive, genetically heterogenous.
- Short stature, radial ray limb defects, abnormal pigmentation, developmental delay.
- Bone marrow failure.
- Increased risk of leukemia and solid tumors (esp. squamous cell cancers of the head and neck), developing at an average age of 23yo.
- Chromosome breakage studies are gold standard



Telomere Biology Disorders

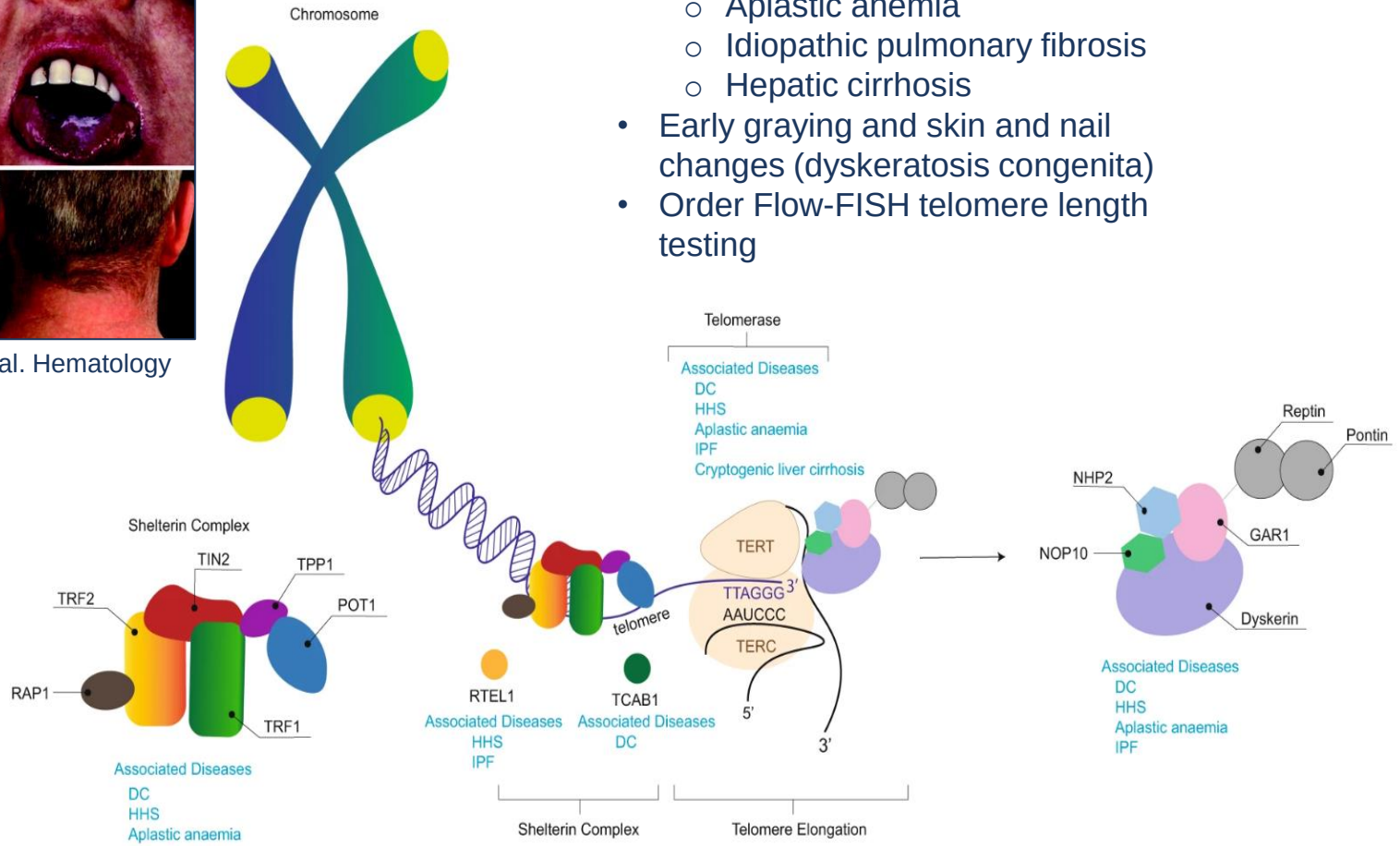


Dokal et al. Hematology 2011



Radiopaedia

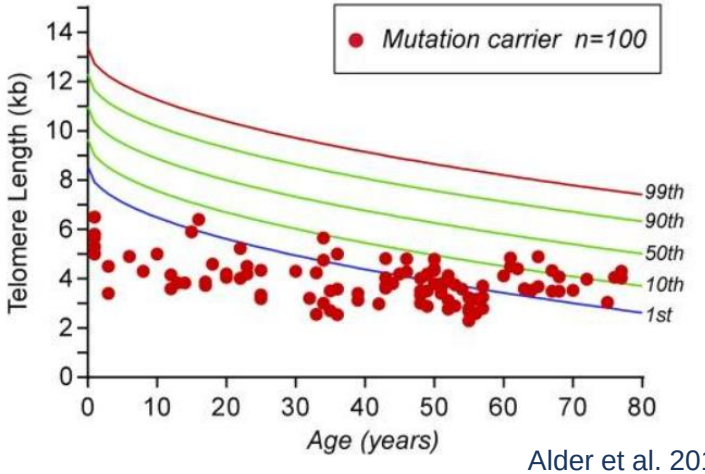
- Genetically heterogeneous
- Can present with
  - Aplastic anemia
  - Idiopathic pulmonary fibrosis
  - Hepatic cirrhosis
- Early graying and skin and nail changes (dyskeratosis congenita)
- Order Flow-FISH telomere length testing



Kam et al. 2021 NPJ Genomic Med

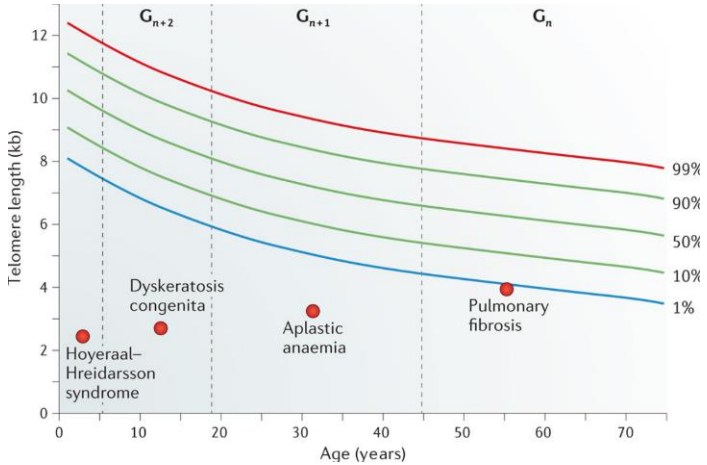
Age-Dependent Presentation & Genetic Anticipation in Telomere Biology Disorders

Age-dependent diagnostic thresholds



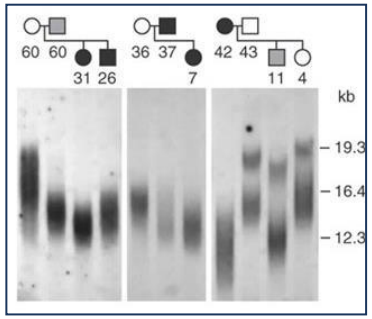
Alder et al. 2018 PNAS

Age-dependent manifestations with anticipation



Armanios et al. 2012 Nat Rev Genetics

Genetic anticipation

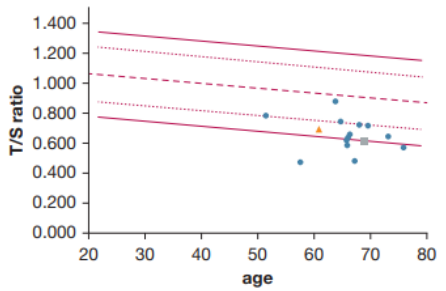


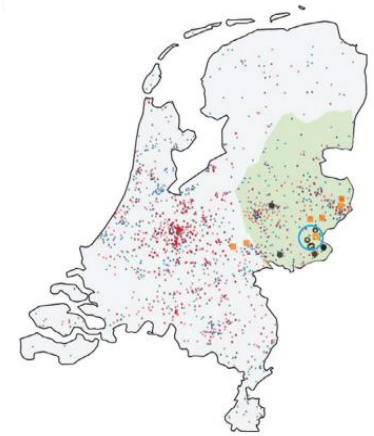
Vulliamy et al. 2004 Nat Genet

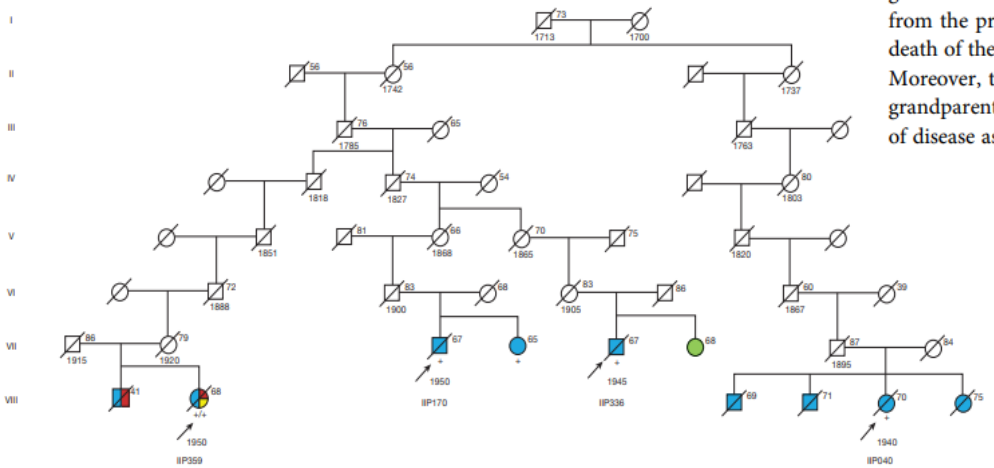
CHEST [158#2 CHEST AUGUST 2020]

Pulmonary Fibrosis and a *TERT* Founder Mutation With a Latency Period of 300 Years

Joanne J. van der Vis, BSc; Jasper J. van der Smagt, MD; Frederic A. M. Hennekam; Jan C. Grutters, MD, PhD; and Coline H. M. van Moorsel, PhD



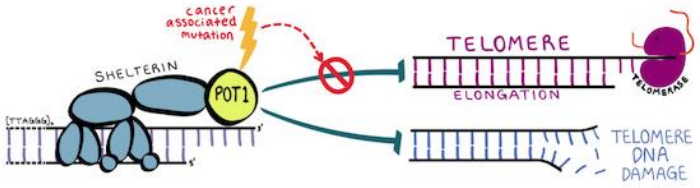




The self-reported data on family history of disease in our study suggest that up to eight generations may pass before PF appears as first manifestation of STSs. None of the c.2005T carriers reported STS associated disease in their ancestors. Albeit this does not prove genetic anticipation and we do not have medical records from the preceding generations, the available ages at death of the ancestors do not suggest decreased survival. Moreover, the parents died at an older age than the grandparents did, a convincing finding against presence of disease associated with STSs in earlier generations

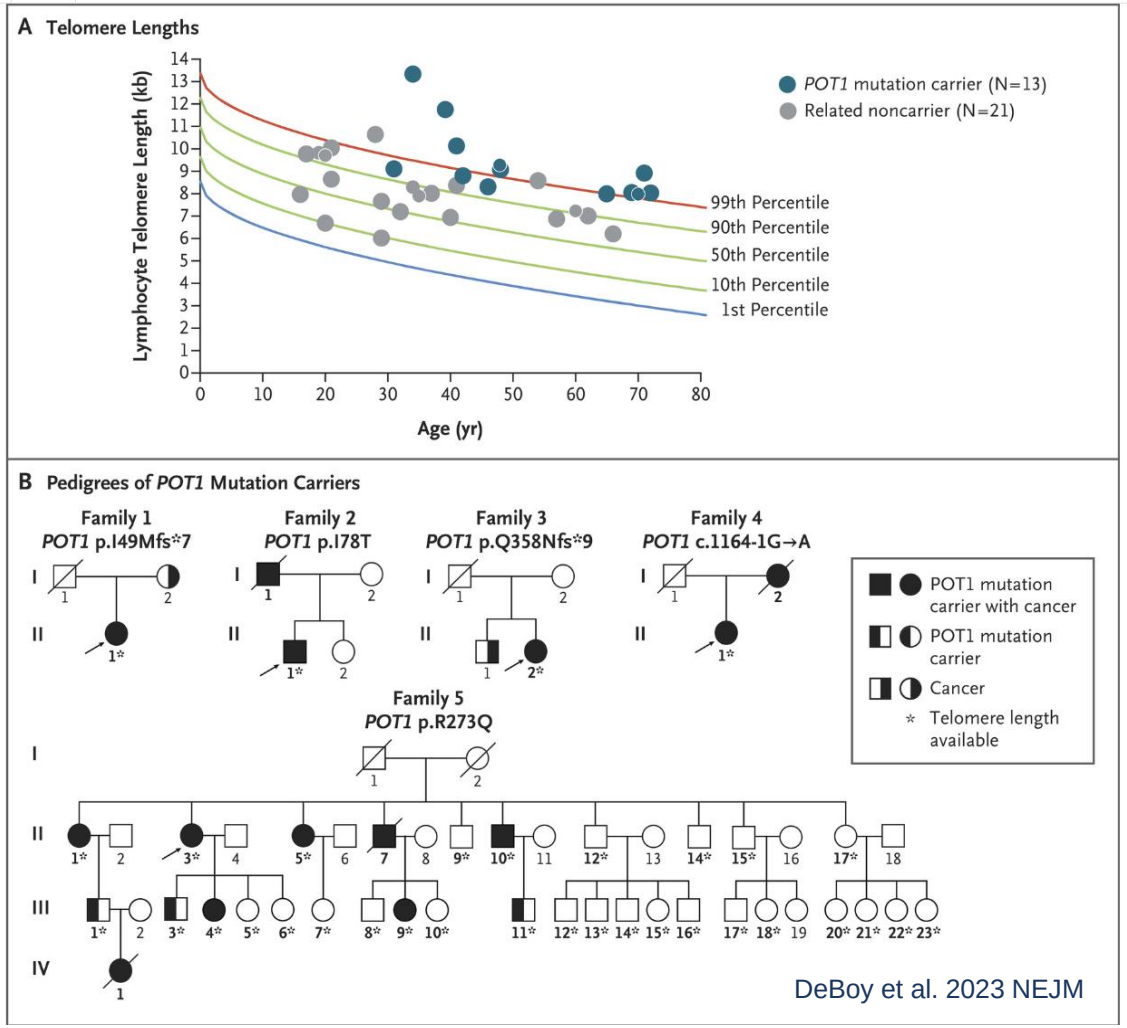
The family tree suggests that it takes up to eight generations, spanning three centuries, before PF presents in 50- to 70-year-old individuals as first manifestation of an STS. This suggests that the c.2005T mutation minimally affects telomere length maintenance per generation.

POT1 Germline Mutations: Too-Long Telomeres



Kim et al. 2021
EMBO J

- Melanoma
- CLL
- Angiosarcoma (esp. cardiac)
- Gliomas
- Others (Li-Fraumeni syndrome-like)



DeBoy et al. 2023 NEJM

Fred Hutch Cancer Center

Thank you

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