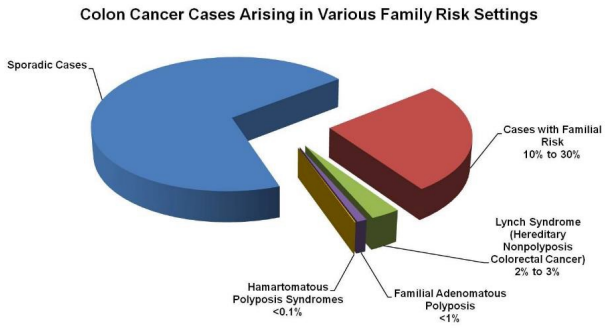
Inherited colon cancer
and other inherited cancer predispositions

Pr. A. De Leener

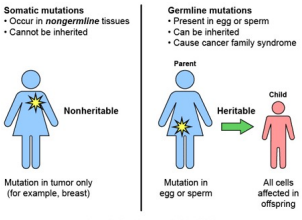
09/02/2024

1

Hereditary predisposition to colorectal cancer:

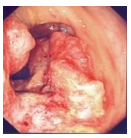


- Rare conditions: +/- 10% CRC
- Major tumor risks
- Need for specific management with proven efficacy
- Possibility of screening in at risk relatives



"Polyposis"

"Non polyposis"



Membre du réseau Lid van het netwerk Huni | 2

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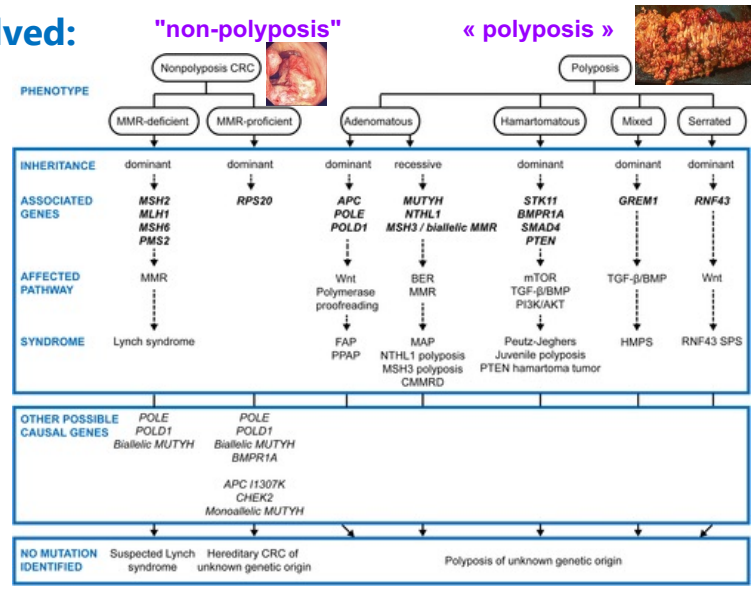
Genes involved:

"non-polyposis" « polyposis »



The Journal of Pathology, Volume: 247, Issue: 5, Pages: 574-588, First published: 25 December 2018, DOI: (10.1002/path.5229)

Membre du réseau Lid van het netwerk Huni | 3

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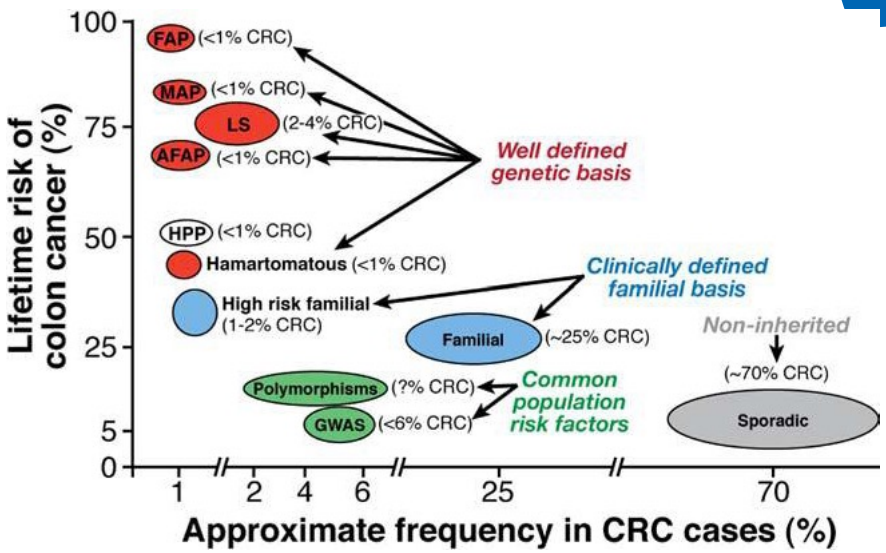

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Terminology:

MMR = *MisMatch Repair*

MMRD = *Mismatch Repair Deficient*

MLH1, MSH2, MSH6, PMS2, EPCAM = 5 main genes involved in the MMR process

RER phenotype *(Replication ERror)* = mutator phenotype cause by MMRD

MSI-H cancer *(MicroSatellite Instability-High)* = cancer with RER mutator phenotype = MMRD cancer

MSS = *MicroSatellite Stable*

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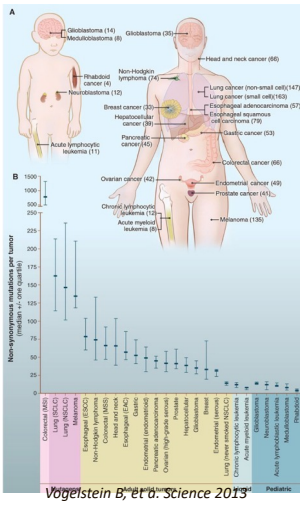
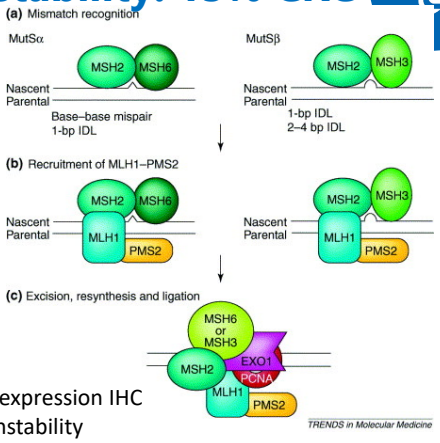
MMR system deficiency and instability: 15% CRC

Somatic biallelic mutation

Tumor development

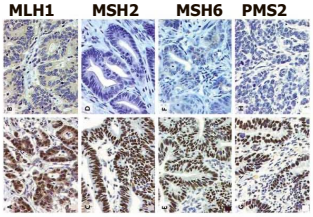


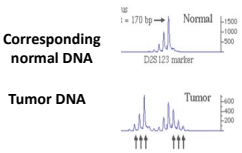
Vogelstein B, et al. Science 2013



Loss of protein expression IHC

Microsatellite instability





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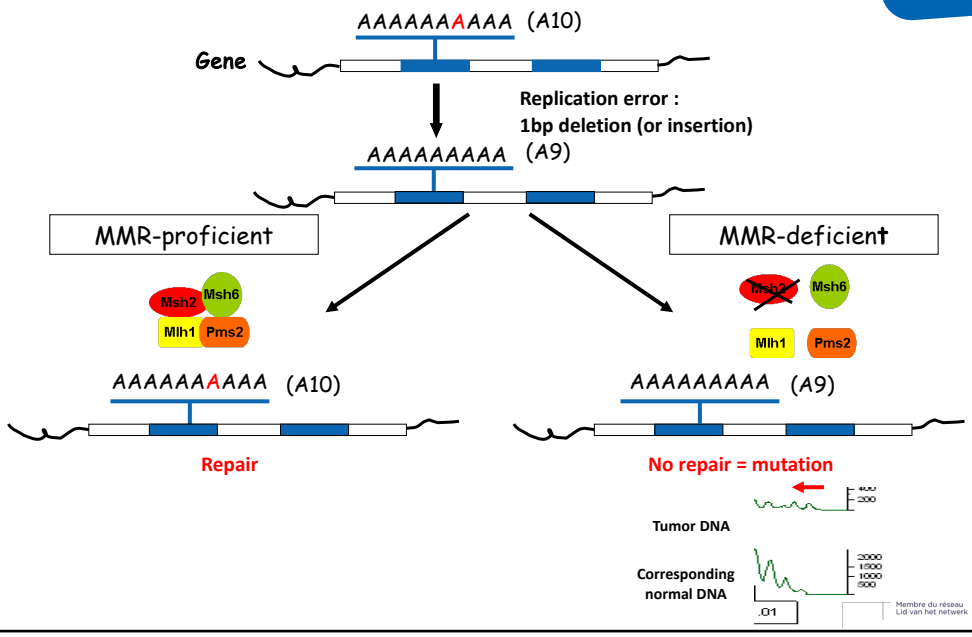
MMR system deficiency and instability



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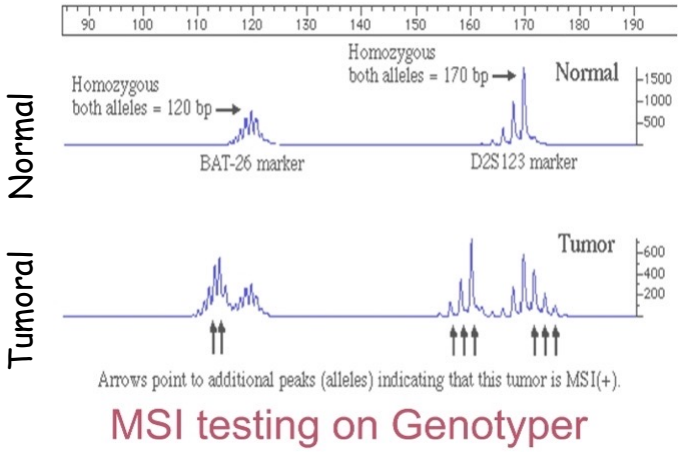
Microsatellites instability (MSI): 15% of CRC

Detection by fluorescent PCR and analysis on automatic sequencer



MSI testing on Genotyper

Selection of at least 5 monomorphic microsatellites : no variation in the population

Lynch, N Engl J Med 2003

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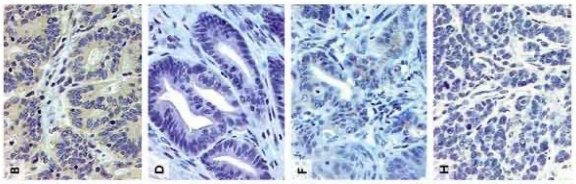
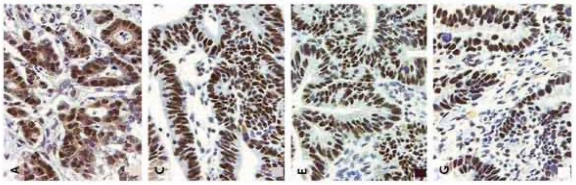
Immunohistochemistry of MMR proteins in CRCs

Tested protein:	MLH1	MSH2	MSH6	PMS2
MSI-H CRCs → (One or more than one protein absent)				
MSS CRCs → (All the MMR proteins are present)				

Hampel, H. et al. N Engl J Med 2005;352:1851-1860

The NEW ENGLAND JOURNAL of MEDICINE

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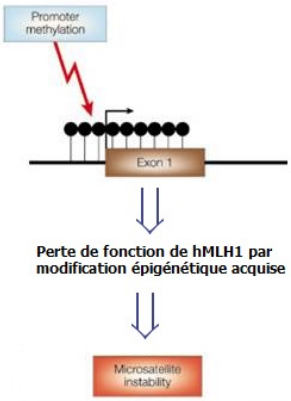
Sporadic MSI-H CRC: epigenetic MLH1 inactivation/Methylation

Hypermethylation of MLH1 = the mechanism of MMR loss of function for sporadic MSI-H CRCs

When considering a MLH1-negative CRC, 2 biological parameters are in favor of a sporadic disease

1. Hypermethylation of MLH1
2. Presence of BRAF V600E acquired mutation



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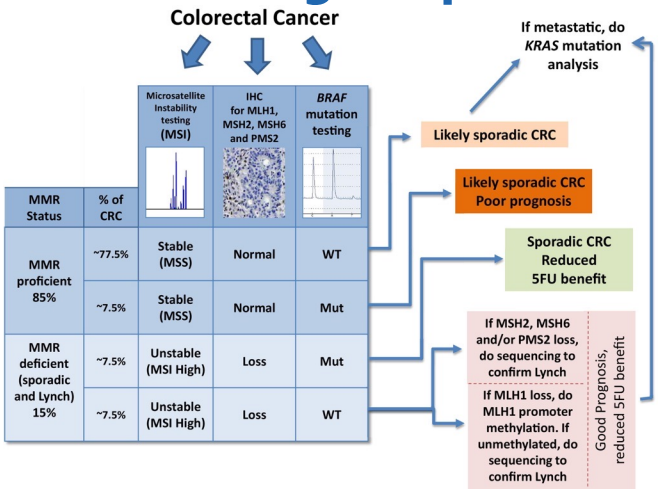
Lynch Syndrome vs Methylation of MLH1 gene promotor



The Journal of Molecular Diagnostics
Volume 14, Issue 2, Pages 91-103 (March 2012)

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LYNCH Syndrome:
AD predisposition to MMR deficiency cancers

Risk of colon cancer +/- 80%(?) H> 50% F → Follow up by coloscopy: 1x/1-2y
- ✓ predominantly MLH1 & MSH2: 46-61%-33-52%
- ✓ MSH6: 10-44%
- ✓ PMS2: 8-20%

and Gastric (intestinal type) +/- 6-13 % (Japan)
Endometrium +/- 34-54
Ovaries +:- 4-20
Urothelial +/- 1-7%
Other tumor risks:
- ✓ Small intestine (3-6%), hepatobiliary,
- ✓ Brain tumor (1-3%, glioblastoma): "Turcot syndrome"
- ✓ Pancreas (1-6%)

Skin lesions (1-9%):
- ✓ Sebaceous carcinoma ("Muir-Torre syndrome"), keratoacanthoma, epithelioma

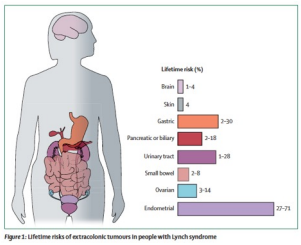

Figure 1: Lifetime risks of extracolonic tumours in people with Lynch syndrome

Incidence: 1/600 - 1/2000
- ✓ Probably more frequent and lower penetrance -> 1/279 in the general population (?)

Effect of smoking +++
Role of chemoprevention: awaiting CAPP3 trial
Multidisciplinary follow-up

Relative risk > 8
Effect of tobacco +++

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Lynch syndrome: Diagnosis? Importance of family history

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Prediction programmes : PREMM, MMRpro, MMRpredict

CLINICAL RECOMMENDATIONS

The details of the evidence used to formulate the recommendations below are available in the scientific report and its appendices. The tables below follow the sequence of the chapters of the scientific report.

Lynch syndrome

Recommendations
Family history should be evaluated using a validated prediction model (e.g. PREMM1,2,6) or the revised Bethesda criteria. Individuals considered at risk should be referred for genetic counseling. A first step may be the retrieval and immunohistochemical analysis of stored samples of family members after appropriate consent. This is possibly followed by germline mutation analysis of the referred individual.
Investigation of all colorectal cancers by immunohistochemistry (IHC) of the four mismatch repair (MMR) proteins or by microsatellite instability (MSI) testing is recommended. In case of a positive family history (e.g. based on PREMM1,2,6) or other risk factors, both IHC and MSI should be performed if either MSI of IHC performed alone remains inconclusive.
Immunohistochemistry and MSI tests should only be performed in laboratories that are ISO accredited for these tests.
If the only reason for germline mutation analysis is a positive IHC for MLH1, germline mutation analysis should be accompanied by MLH1 promotor methylation or BRAF mutation analysis.

Table 2. Test Performance in Detection of Lynch Syndrome

Test	Sensitivity, %	Specificity, %	Estimated Lynch probands missed (of 3550), No. (%)
Amsterdam II criteria	42–50	97–98	1780–2060 (50–58)
Revised Bethesda criteria	95	38	180 (5)
Barnetson et al[83]	95	14	180 (5)
Greenson et al[108]	92		280 (8)
MSI	89 (MLH1) 90 (MHS2) 76 (MSH6)		11–355 (0.3–10)
IHC	81 (MLH1) 88 (MHS2) 76 (MSH6)		390–425 (11–12)
Sequencing	99.5	99.9	0 (0)

Oncogenetic testing for Lynch syndrome and familial adenomatous polyposis KCE Report 2015

The Journal of Molecular Diagnostics
Volume 14, Issue 2, Pages 91-103 (March 2012)

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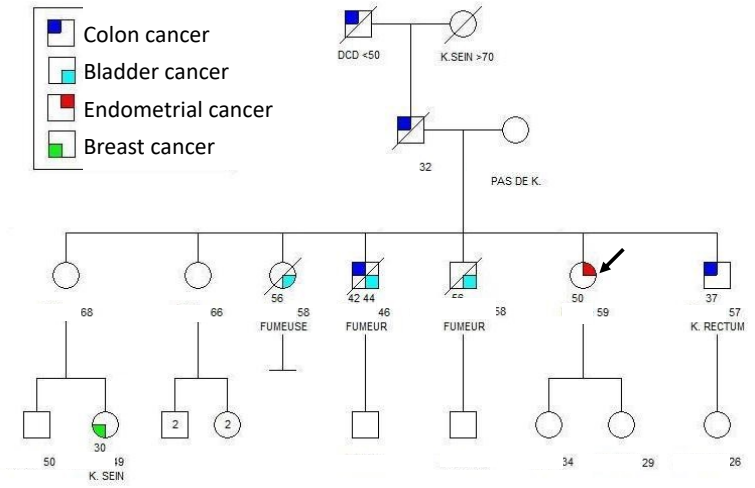
Case 1:



Arbre de la famille dessiné avec l'accord du Dr Janin

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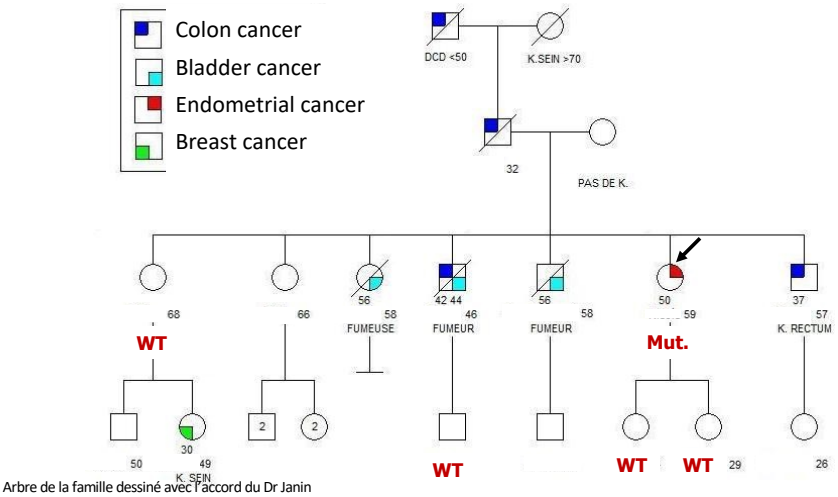
MSH2 mutation found in the family: possibility of predictive testing



Arbre de la famille dessiné avec l'accord du Dr Janin

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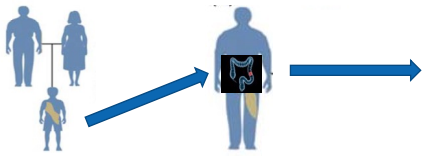
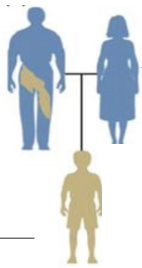
Lynch syndrome: no germline mutation identified

Somatic versus mosaic mutation





Possible risk of transmission if mosaic present in germ cells

Familial Cancer
DOI 10.1007/s10689-012-9568-9

ORIGINAL ARTICLE

Somatic mosaicism and double somatic hits can lead to MSI colorectal tumors

Isabelle Sourrouille · Florence Coulet · Jeremie H. Lefevre · Chrystelle Colas · Mélanie Eyries · Magali Svrcek · Armelle Bardier-Dupas · Yann Parc · Florent Soubrier

Promoter mutation, deep intronic mutations, complex CNV: difficult to interpret
PMS2 gene conversion with PMS2-CL pseudogene

If possible: Analysis to be carried out on frozen tumour tissue
Then search for mosaic on adjacent healthy tissue

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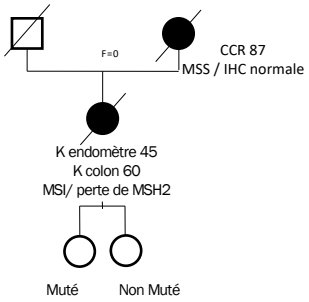
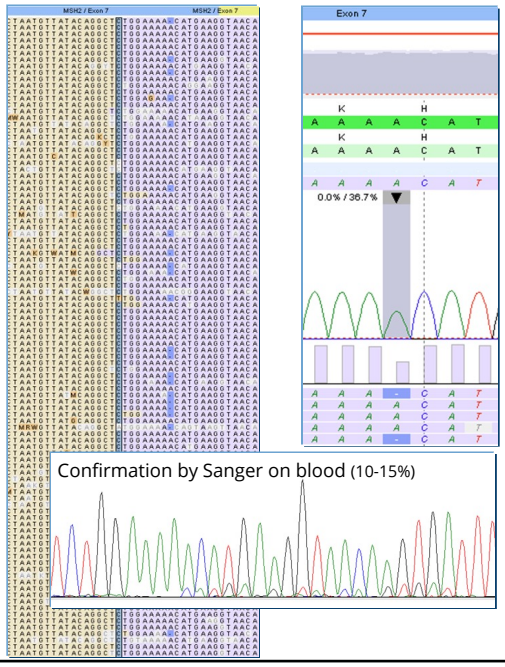


No constitutive mutation in sanger sequencing

Analysis of frozen tumour
c.1269delA,p.Lys423Asnfs*15

De novo mosaic mutation on MSH2



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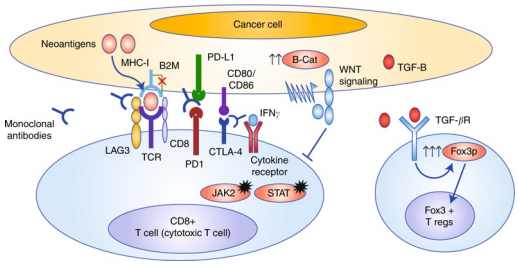
MSI-H cancer treatment

Better prognosis

No response to 5FU

Lower interest of chemotherapy in stage II and III

-> immunotherapy: somatic mutations have the potential to encode "non self" immunogenic antigens -> tumors with a large number of somatic mutations are susceptible to immune checkpoint blockade



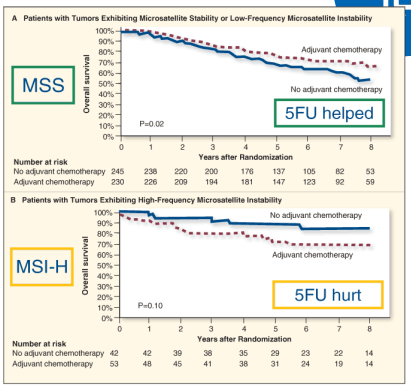


Figure 2. Overall survival stage II (55%) or stage III (45%) colon cancer according to treatment status (570 pts) Ribic C et al: *N Engl J Med* 349:247-257, 2003. Used with permission.

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

British Journal of Cancer **volume 121**, pages809–818(2019)

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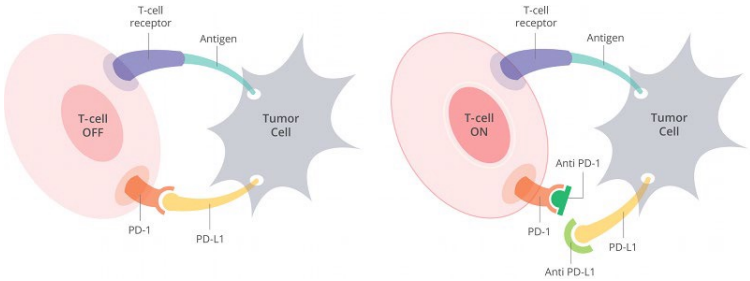
Lynch: **chemoprevention**:
- CAPP2 study: 861 Lynch patients: 600 mg aspirin versus placebo for 4 years. Reduction in the occurrence of CRC with a mean intake of 25 months.
- CAPP3 study: studied the long-term effect of taking aspirin in 3000 Lynch patients by comparing 3 doses: 100, 300, or 600 mg/day.

Role of **immuno-oncology** in hereditary CRC
- FDA: use of pembrolizumab (May 2017), then nivolumab (July 2017), then the combination of ipilimumab (antibody directed against the CTLA-4 receptor) and nivolumab (anti-PD1) (July 2018) in the treatment of stage IV hypermutated/MSI cancers progressing on chemotherapy.



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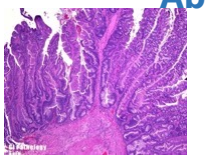
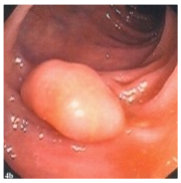
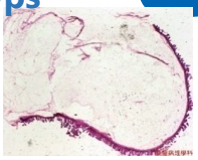
POLYPOSIS

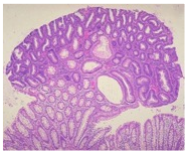
About 95% of CRC arise from polyps

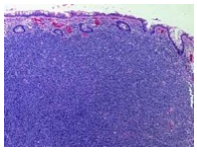
« Polyp »

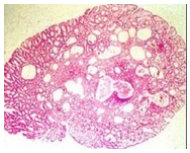

Hyperplasic

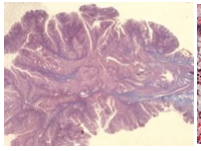


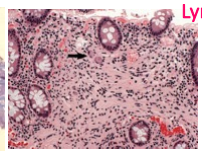

Lipoma


Adenoma


Lymphoma


Juvenile


Peutz-Jeghers


Hamartomas

Hamartomatous P

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Colorectal polyposis « genetically determined »

Adenomatous Polyposis

- **Adenomatous polyposis Linked to *APC***
  Familial Adenomatous Polyposis (mutation ***APC***)

Classic and attenuated forms

- **Adenomatous polyposis linked to *MUTYH*** (bi allelic mut. ***MUTYH***)
  MYH-Associated Polyposis (MAP)

- **Adenomatous polyposis associated with axin** (mutation axin 2)

- **Adenomatous polyposis associated with POL** (mutation ***POLE*** or ***POLD1***)

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Colorectal polyposis « genetically determined »

Hamartomatous polyposis

- **Polyposis of Peutz-Jeghers** (mutation ***STK11/LKB1***) -> see Pr Duhoux
- **Juvenile polyposis** (mutation ***SMAD4*** or ***BMPR1A***), associated manifestations
- Cowden* (mutation ***PTEN***) -> see Pr Duhoux
- Ganglioneuromatosis*

  ** Not associated with an increase of RR of CRC*

Hyperplasic polyposis (gene?)

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Familial adenomatous polyposis or FAP

- Incidence: 1 per 7000 to 1 per 14000 births
- Prevalence: 26 (± 4) patients per 1,000,000
- Causes 1% of colorectal cancers

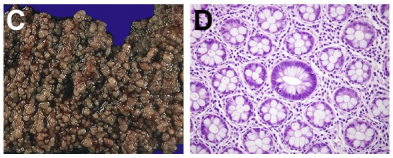
- Germline mutation of the *APC* gene (5q21-22)

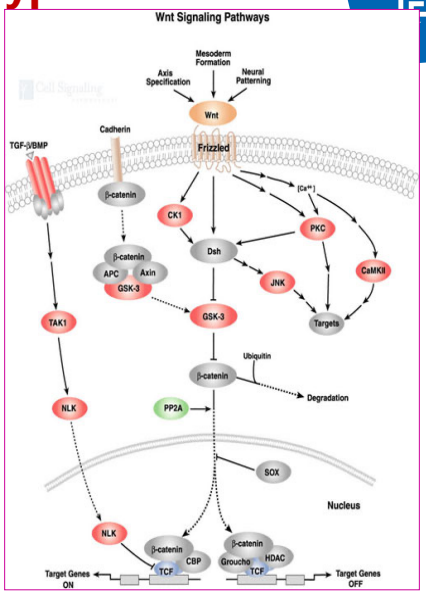
Tumour suppressor gene: maintenance of b-catenin (CTNNB1) outside the cell nucleus

Activation of the Wnt/b-catenin-APC pathway

Autosomal dominant transmission

- Very high penetrance (but not always)





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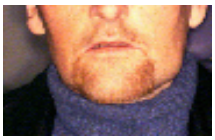
Familial Adenomatous Polyposis Genotype Phenotype correlation

Colorectal polyposis +++

Cancer risk: 100% at 40 yo

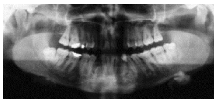
Extra-coloreal digestive disease

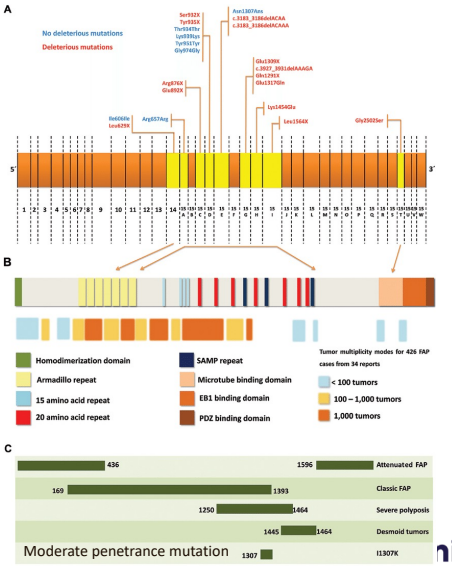
- **duodenale polyposis**
- glandulokystic polyposis
- gastric adenomas



Extra-digestive manifestations

- **desmoid tumor**
- Dermatological lesions
- Osteoma; dental anomalies -> gardner syndrome
- Other cancer types





Cancer Cytopathol 120: 2081-2088, 2013

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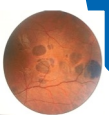
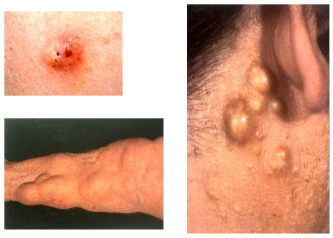
Familial Adenomatous Polyposis



- ✓ Congenital hypertrophy of the retinal pigment epithelium
- ✓ Dermatological lesions: epidermoid cysts, lipomas, etc.
- ✓ Pancreatic adenocarcinoma: RR:4.46 TIPMP (?); acinar cell carcinoma; papillary and cystic tumours; endocrine tumours; pancreatoblastoma
- ✓ Brain tumours: Medulloblastoma > Glial tumours
- ✓ Thyroid carcinoma: RR:7.6. Papillary carcinoma ++; "cribriform morular" architecture
- ✓ Hepatoblastoma ++ hepatocellular carcinoma; intrahepatic cholangiocarcinoma

Suggested analysis if
>20 adenomas
>10 polyps and / or family history / suggestive lesion



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FAP: follow up

Child carrier of the germline mutation or from a suspected FAP family without mutation identified

- ► Annual Recto-sigmoidoscopy from 10-12 yo
- ► Coloscopy when polyps are detected
- ► Prophylactic surgery at de 15-25 yo
  - • colectomy with ileorectal anastomosis, or
  - • coloproctectomy with ileo-anal anastomosis and ileal
- ► Supervision of rectum or reservoir
- ► Supervision of the upper digestive tract

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Adenomatous polyposis associated with MUTYH (MAP)

Molecular genetics:

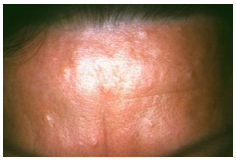
- Bi allelic mutation of the *MYH* gene (*MUTYH*): recessive
  - ✓ Failure of the BER (Base Exision Repair) system to repair oxidative damage to DNA
  - ✓ Accumulation of somatic mutations in the form of transversions: G:C -> T:A

Prevalence:

- 16 to 40% of attenuated adenomatous polyposis (15< polyps <100) APC negative
- 7.5 to 12% of classic adenomatous polyposis (polyps >100) APC negative
- Incidence: 1/5000 to 1/40000
- Frequency of heterozygotes? 1 to 2% general population?

Clinical Manifestations?

- Mostly attenuated polyposis (<100), colon and duodenum.
- Dermatological lesions (sebaceous adenomas) other?



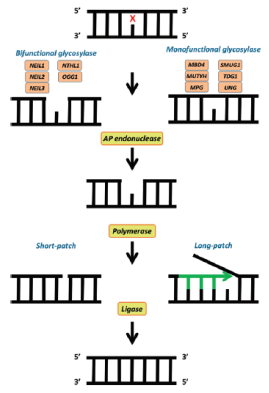


Figure 1. The BER pathway. The damaged nucleotide (X) is removed by a monofunctional or bifunctional DNA glycosylase, and the gap is processed by an AP endonuclease. One nucleotide (short-patch) or multiple nucleotides (long-patch, green) are incorporated by a polymerase, and a ligase seals the remaining nick to complete the DNA repair process. For a comprehensive review of the mammalian BER pathway, see [57] or [59].

J Pathol 2018; 244: 135–142

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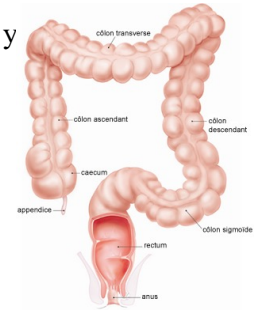
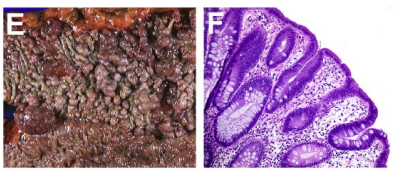
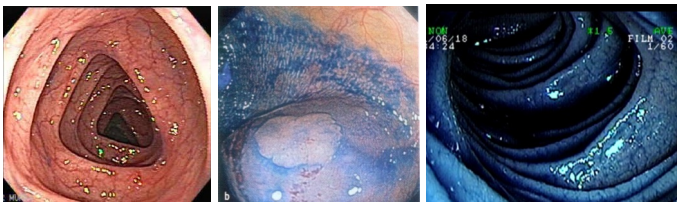
MUTYH: follow up of the index case

- **CRC:** (Video) coloscopy at 20, 25, 30 yo -> each 2 y
- **Duodenal:** surveillance: fibroscopy OGD idem
- Initial consultation in **dermatology**





Average age at diagnosis: 45 yo



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MUTYH: follow up of the family

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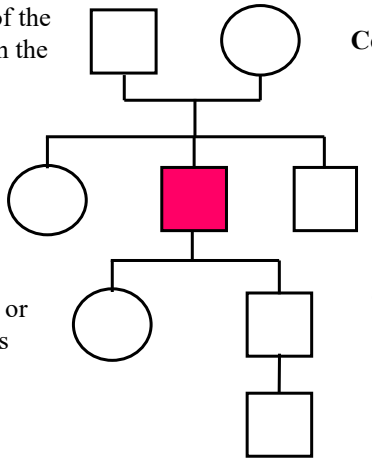
Indication of MUTYH analysis

Medical follow up

Targeted analysis of the 2 mutations found in the index case

Coloscopy > 40y each 5y



Targeted analysis of the 2 mutations found in the index case

Coloscopy regarding test:
Bialleic: idem IC
Monoallec: Colo / 5 y
Ø MUT: Ø Coloscopy

Targeted analysis or complete analysis

Coloscopy regarding genotype
(Mono or bi-allelic)

No analysis

No follow up

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MUTYH associated polyposis (MAP)

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Monoallelic heterozygous *MUTYH* mutations, occurs in 1–2% of the Caucasian population

Various studies have reported an increased risk of gastric, liver and endometrial and breast cancer for monoallelic mutation carriers while other studies did not find statistical evidence for an increased risk of breast or liver cancer.

Site of cancer	HR (95% CI)*	Cumulative risk % (95% CI)**	
		Males	Females
Biallelic carriers			
Urinary bladder	19 (3.7–97)	25 (5.4–77)	7.6 (1.5–33)
Ovary	17 (2.4–115)		14 (2.2–65)
Monoallelic carriers			
Stomach	9.3 (6.7–13)	5.0 (3.6–6.9)	2.3 (1.7–3.3)
Hepatobiliary tract	4.5 (2.7–7.5)	2.9 (1.7–4.7)	1.4 (0.8–2.3)
Endometrium	2.1 (1.1–3.9)		3.3 (1.8–6.2)
Breast	1.4 (1.0–2.0)		11 (8.3–16)
Ovary	0.4 (0.1–2.6)		
Prostate	0.5 (0.3–1.0)		
Brain	2.1 (0.9–4.9)		
Renal pelvis/Kidney	2.3 (0.1–3.1)		
Pancreas	2.3 (0.2–4.1)		

NCCN Guidelines 2023: There are no specific data available to determine screening recommendations for a patient with a heterozygous MUTYH mutation and a second-degree relative affected with CRC.

Int J Cancer. 2016 October 1; 139(7): 1557–1563

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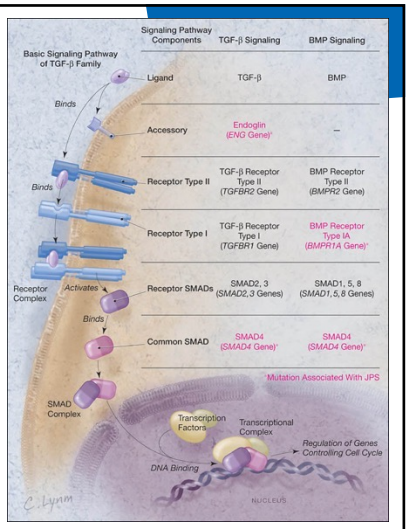
Juvenile polyposis:

- Germline mutation of the *MADH4* gene = *SMAD4* (20% of cases) or of the *BMPR1A* gene (20% of cases) >> *ENG*
- Autosomal dominant transmission
- Incidence: 1/100,000
- Very high penetrance



Phenotype/genotype correlations described

Colorectal or disseminated digestive polyposis

- ✓ > 3-5 juvenile polyps in the colon
- ✓ often < 20 years of age

Extradigestive manifestations:

- ✓ Macrocephaly; mental retardation; hypertelorism
- ✓ CIA; CIV
- ✓ Pulmonary stenosis
- ✓ Cryptorchidism
- ✓ Intestinal malrotation (15%)

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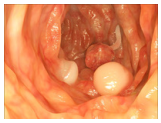
Juvenile polyposis:



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Risk of colorectal cancer (40-50%) > Gastric (if polyps: 21%) > pancreatic > small intestine

- ✓ Pure gastric forms (SMAD4)
- ✓ Rendu Osler syndrome (SMAD4)
  - ✓ Telangiectasias, epistaxis and arteriovenous malformations (skin, mucous membranes, lung, liver, brain)
- ✓ Infantile forms
  - ✓ deletion 10q23 carrying BMPR1A and PTEN
  - ✓ More severe, but not always associated with juvenile polyposis

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Follow-up of patients with a predisposition to CRC:

Familial setting	RR	95% CI
One first-degree relative with CRC	2.25	2.00 to 2.53
< 45 y	3.87	2.40 to 6.22
45–59 y	2.25	1.85 to 2.72
> 59 y	1.82	1.47 to 2.25
Two or more first-degree relatives with CRC	4.25	3.01 to 6.02
Only two first-degree relatives	3.76	2.56 to 5.51
One second- or third-degree relative with CRC	1.50	
Two second-degree relatives with CRC	2.30	
One first-degree relative with an adenoma < 60 y	1.99	1.55 to 2.55

Table 2. Colonoscopy surveillance recommendations for individuals with germline pathogenic variants (high-penetrance syndromes) [14]

Syndrome (gene)	Family history of CRC	Age at CRC screening initiation	Screening interval if no adenomas
No mutation*	No	50	10 years
	Yes (≥ 1 FDR)	40†	5–10 years
FAP (*APC*)	N/A	10–15	1 year, colectomy if polyps too numerous
Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*)	N/A	20–25	1–2 years until age 40, then every year
MAP (*MUTYH* biallelic)	N/A	25–30	1–3 years depending on polyp burden
Juvenile polyposis (*SMAD4*, *BMPR1A*)	N/A	15	1–3 years depending on polyp burden
Peutz–Jeghers (*STK11*)	N/A	15	2–3 years depending on polyp burden
Li–Fraumeni (*TP53*)	N/A	20–25	3 years
Hereditary breast ovarian cancer (*BRCA1*/*BRCA2*)	No	50	10 years
	Yes	50 or per family history	5 years

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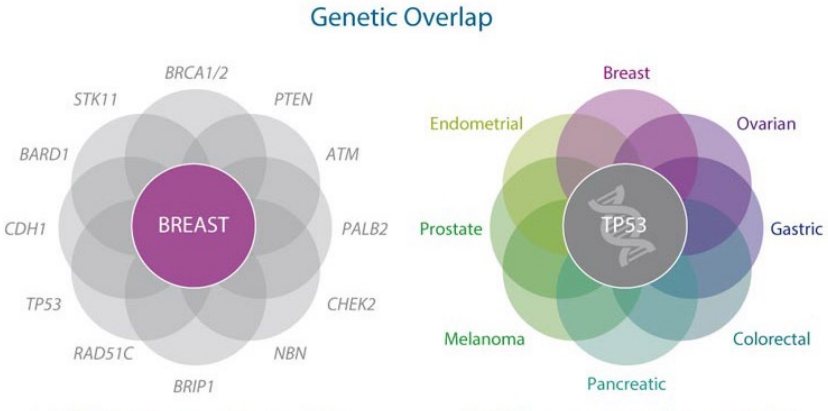
Other inherited cancer predispositions

Breast (ovary, prostate): see Pr Duhoux



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Heredity of pancreatic cancer:

5-10% of pancreatic cancers

Surveillance?

Familial: at least two relatives and no mutation identified

Hereditary pancreatitis: 40% risk Pancreatic Cancer (RRX69):
SPINK1 (AR), *PRSS1* (AD), *CFTR*

Non-syndromic :
BRCA2: if FDR+. 6% families >> *BRCA1*
CDKN2A (p16): if FDR+ cofactor = tobacco (RRX47)
PALB2 if FDR+.

Syndromic :
Peutz Jeghers Syndrome: TIPMP: 20% Pa. Ca. risk (RRX132)
LYNCH: rare (RRX8.6) but medullary and MSI-H, KRAS wt
FAP (*APC*) rare: pancreatoblastoma
ATM +/-
? *TP53* (LFS)

Gut 2020;69:7–17.

Table 1 Definition of high-risk individuals eligible for pancreatic cancer surveillance.

Gene mutation	PDAC family history criteria	Agreement	Grade
LKB1/STK11 (Peutz-Jeghers syndrome)	Regardless of family history	99%	1
CDKN2A p16* (FAMMM)	With at least one affected FDR	99%	1
CDKN2A p16* (FAMMM)	Regardless of family history	77%	1
BRCA2	If at least one affected FDR, or at least two affected relatives† of any degree	93%	2
PALB2	If at least one affected FDR	83%	2
MLH1/MSH2/MSH6 (Lynch)	If at least one affected FDR	84%	2
ATM	If at least one affected FDR	88%	2
BRCA1	If at least one affected FDR	69.6%‡	3
Regardless of gene mutation status	If at least three affected relatives† on the same side of the family, of whom at least one is an FDR to the individual considered for surveillance	97%	2
Regardless of gene mutation status	If at least two affected relatives† who are FDR to each other, of whom at least one is an FDR to the individual considered for surveillance	93%	2
Regardless of gene mutation status	If at least two affected relatives† on the same side of the family, of whom at least one is an FDR to the individual considered for surveillance	88%	2

*Only encompassing *CDKN2A* mutations leading to changes in the p16 protein.
†Wherever relative is stated, this indicates blood relatives only.
‡An additional 20.3% somewhat agreed with surveillance (total 89.9%).
ATM, ataxia telangiectasia mutated; *BRCA2*, breast cancer 2; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; FAMMM, familial atypical multiple mole melanoma; FDR, first-degree relative; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; HBOC, hereditary breast and ovarian cancer; LKB1/STK11, liver kinase B1/serine/threonine kinase 11; Lynch syndrome, *MLH1*, mutL homolog 1; *MSH2*, mutS homolog 2; *MSH6*, mutS homolog 6; PALB2, partner and localizer of BRCA2; PDAC, pancreatic ductal adenocarcinoma.

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Predisposition to the development of gastric cancer

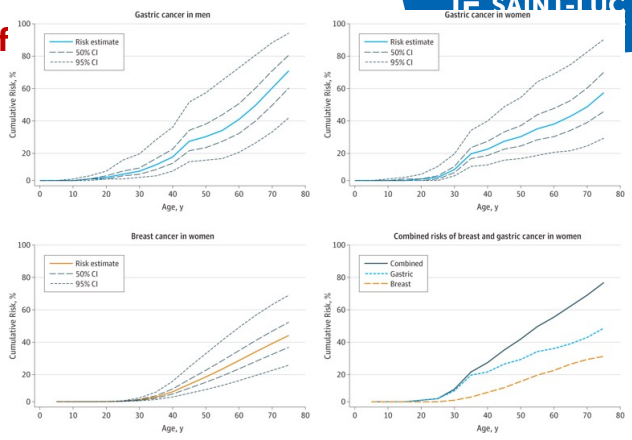
CDH1 (tumour suppressor gene) : Epithelial cadherin
Somatic alteration: loss of expression of e-cadherin
association :

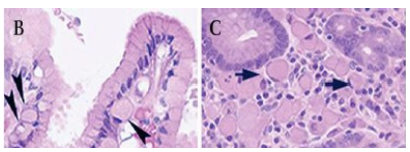
- ✓ Diffuse gastric cancer
- ✓ Lobular breast cancer (60% risk at 80a), bilateral
- ✓ Clefts (CLP)

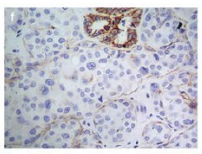
CTNNA1

Code for a e-catenin: same complex as CDH1
Penetrance to be determined in larger studies
No risk of breast cancer or CLP described

MAP3K6 and MYD88 (AR): to be clarified







Young J Choi, Modern Pathology (2008) 21, 1224–1237

J Med Genet. 2015 Jun; 52(6): 361–374.
Weren RDA, et al. J Med Genet 2018;0:1–6. doi:10.1136

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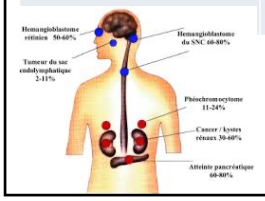
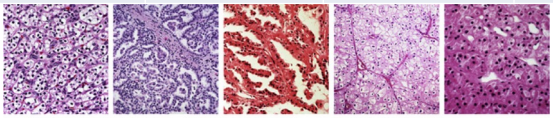
Kidney: genes involved in sporadic forms of kidney carcinomas.

3-9% of kidney cancers are linked to a hereditary predisposition

Von Hippel Lindau	HPRC	HLRCC	Birt Hog Dubbé	Tuberous sclerosis of Bourneville	Cowden Syndrome (PHTS)	Autres SDHdeficient
VHL (80% of hereditary cancers)	MET	FH	FLCN	mTOR, TSC1/2	PTEN	SDHx SMARCB-1
Tumour suppressor genes (TSG)	Oncogène	TSG	TSG	Oncogène, TSG	TSG	TSG
Clear cell carcinoma Renal cysts ! Wait-and-see attitude ! De novo or mosaic mutation	Papillary carcinoma (WHO 2022) (<15%) High RR (100%?) Delayed surgery up to 3cm	Non-classical papillary carcinoma or WHO 2022 FH-deficient (mostly old type 2) ! Risk of M+ !	Chromophobic carcinomas Hybrid tumours Oncocytomas Slow growth	Angiomyolipomas Low potential oncocytic tumour (LOT) ! De novo or mosaic mutation	Macrocephaly! Up to 34% risk of kidney cancer (renal cell cancer)	RCC-SDHB deficient RCC-SMARCB-1 deficient
Hemangioblastomas Pancreatic NET - Pheo/PGL	Rare	Cutaneous leiomyomas Uterine leiomyomas (! Sarcomas)	Fibrofolliculomas Cysts - pneumothorax	1/6000 births Syndromic form with high penetrance	Macrocephaly Ca endometrium, thyroid, colon (hamartomatous polyposis)	Phéo/PGL





: Clear Cell | Papillary Type 1 | Papillary Type 2 | Chromophobe | Oncocytoma

! Importance of the history and clinical examination

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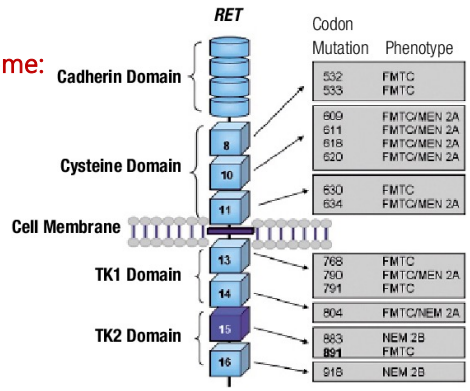
Other inherited cancer predispositions

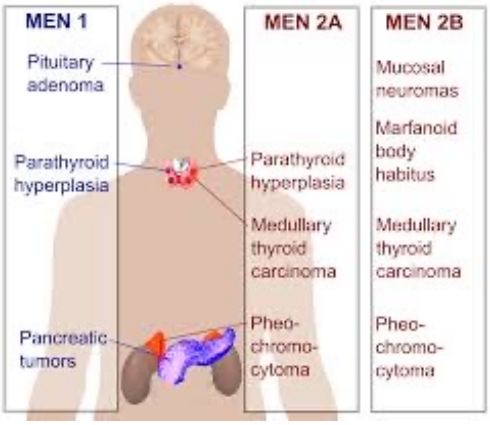
Melanoma: *CDKN2A, CDK4, BAP1, MITF, MC1R*

Endocrine syndrome:

MEN1

MEN2 (*RET*)





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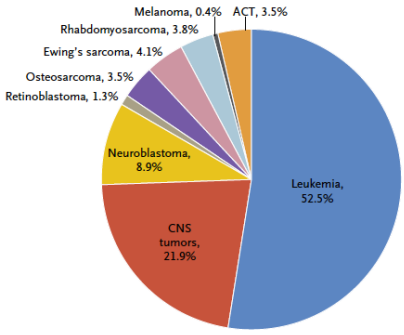
Predisposition to paediatric cancers?

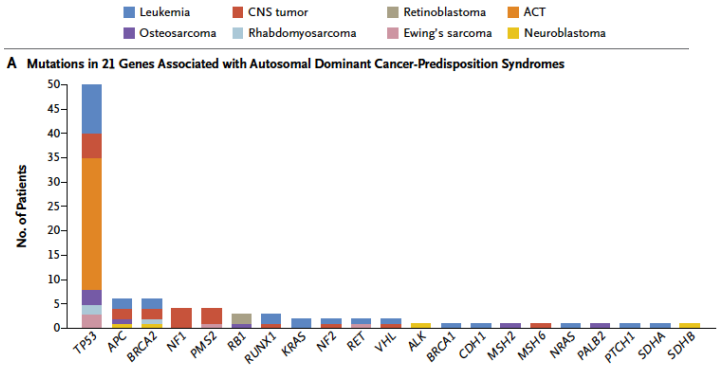
1120 patients aged < 20 years

Screening for 565 cancer predisposition genes

8.5% germline mutation

Positive family history in 40% of cases





N Engl J Med 2015;373:2336-46

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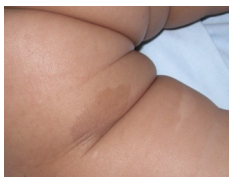
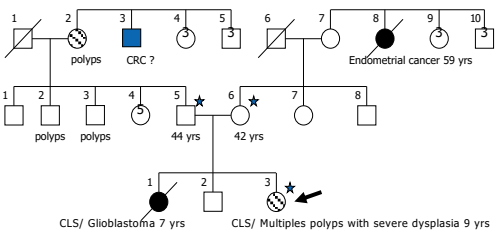
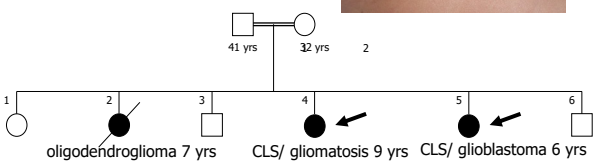
CMMRD: biallelic mutation in an MMR gene

- ✓ Multiple polyps
- ✓ Café au lait spots
- ✓ Haematological cancers (leukaemia, diffuse lymphoma)
- ✓ Brain tumours (gliomas, medulloblastomas)
- ✓ Early onset







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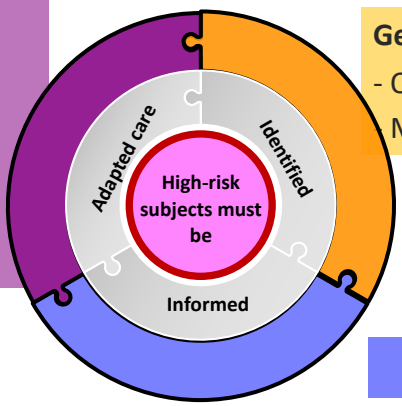
General conclusion:
Partners involved in the correct care for high risk subjects

Multidisciplinary team:
- General Pract.
- Gynecologist
- Radiologist
- Surgeon
- Oncologist…



Geneticists
- Oncogeneticist
- Molecular biologist

THE FAMILY

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Thank you for your attention !

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