BeSHG Interuniversity Course in Genetics

14.20-15.00 Inherited colon cancer and other inherited cancer predispositions

DAY 5: UCLouvain
Friday 11 February 2022
Dr Anne De Leener
Centre de Génétique Humaine

Cliniques universitaires SAINT-LUC UCL BRUXELLES

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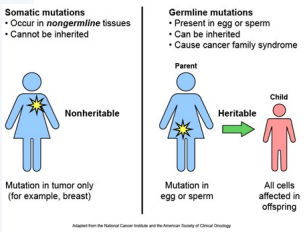
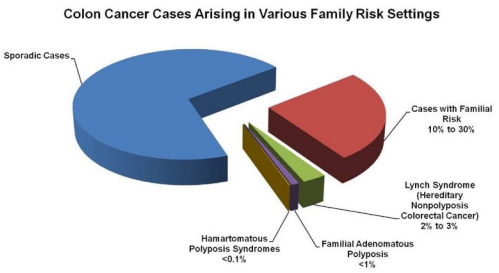
Inherited colorectal cancer

- **Rare :** 10% of all the CRC
- **High risk:** cumulative risk of CRC:
  - 40 - 50 % at 70 yo for Lynch and hamartomatous polyposis
  - 100% at 40 yo for FAP linked to APC
- **Need of medical care**
- **Possibility of predictive testing**

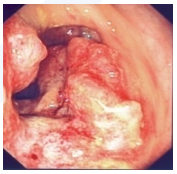




"Polyposis"

FAP
Attenuated polyposis
Other polyposis

"Non polyposis"



LYNCH Syndrome:
5% CRC

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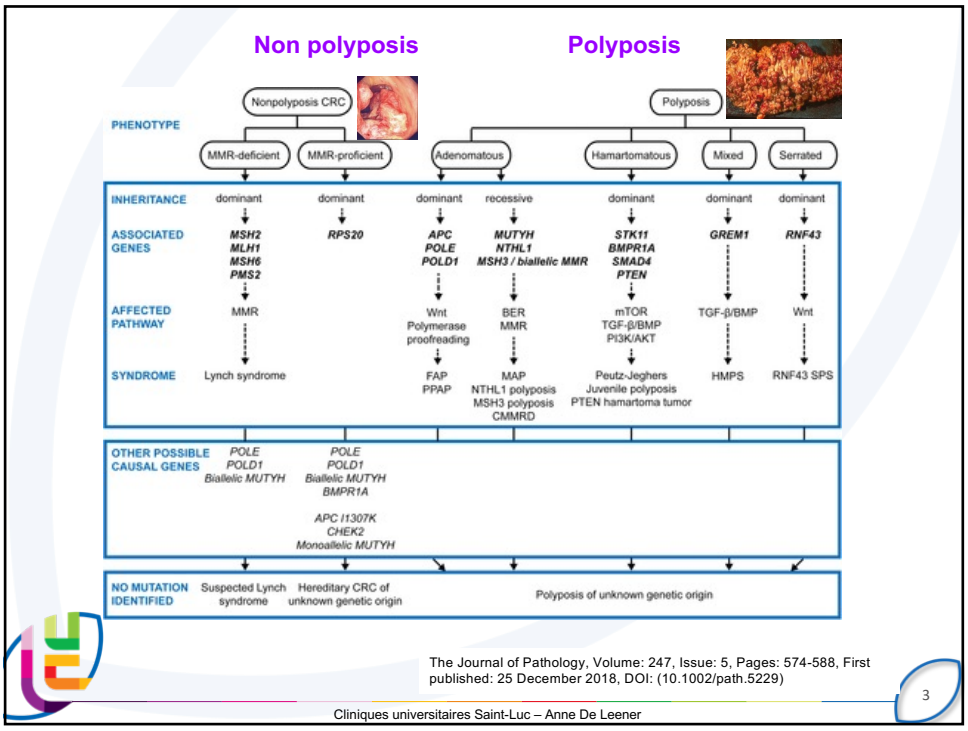

The Journal of Pathology, Volume: 247, Issue: 5, Pages: 574-588, First published: 25 December 2018, DOI: (10.1002/path.5229)

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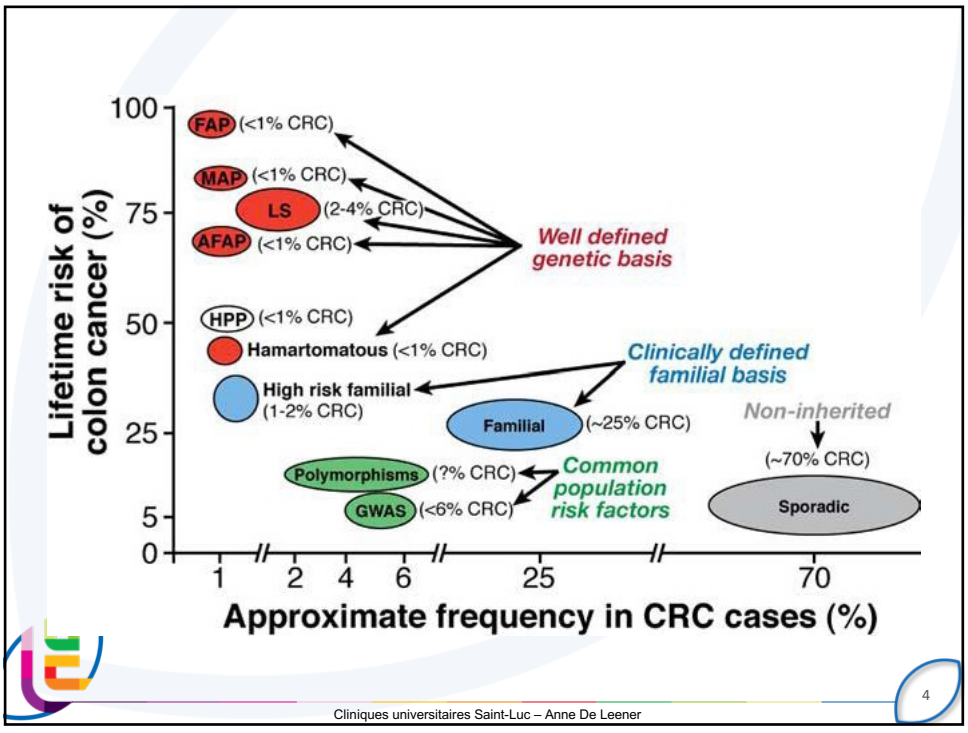

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Introduction to Lynch Syndrome : Terminology

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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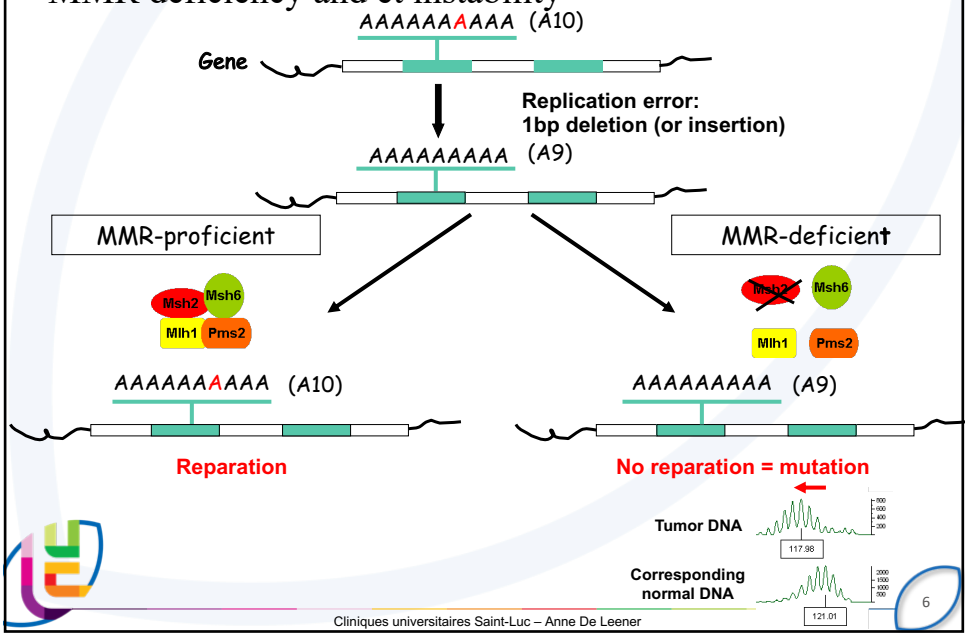
Introduction to LYNCH syndrome :
MMR deficiency and et instability



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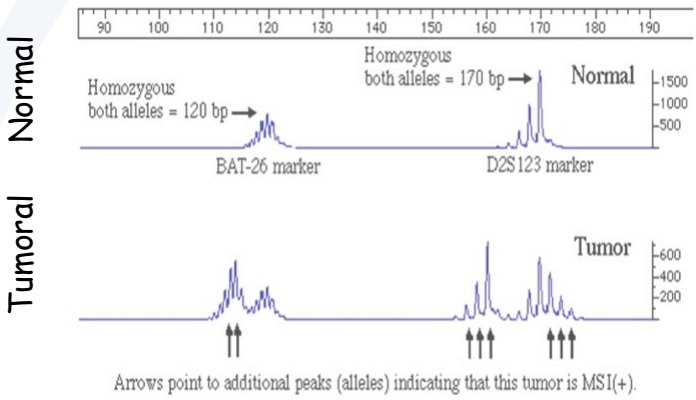
Microsatellites instability (MSI): 15% of CRC



MSI testing on Genotyper

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

Lynch, N Engl J Med 2003

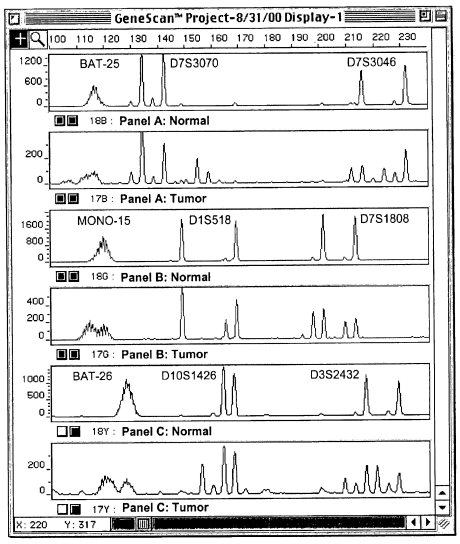
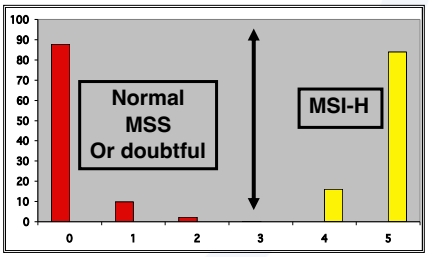


FIG. 12



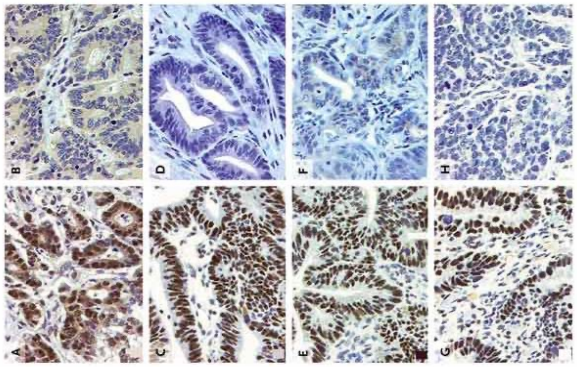
Number of unstable markers

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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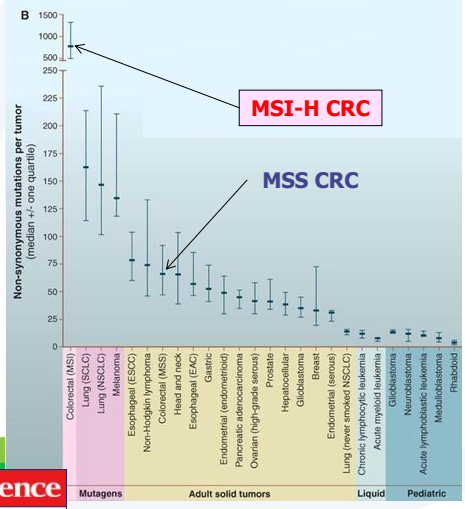
Number of mutations accumulated : MSS vs MSI-H CRC



- median number of non-synonymous mutations per tumor with genome wide tools
- MSI-H tumors have by far the greatest numbers of mutations

B Vogelstein et al. *Science* 2013;339:1546-1558

Science AAAS

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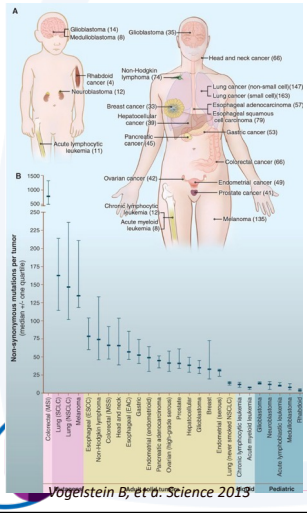
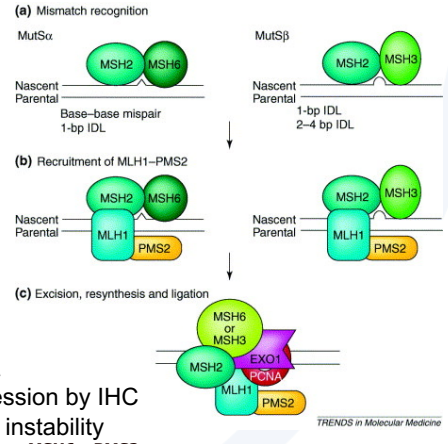
MMR deficiency and instability : 15% of CRC

Biallelic somatic mutation

Tumor development

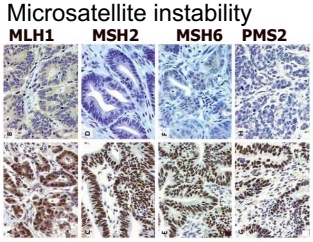


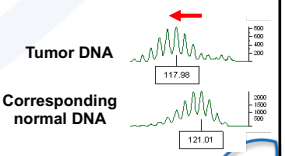
Vogelstein B, et al. Science 2013



Loss of expression by IHC

Microsatellite instability



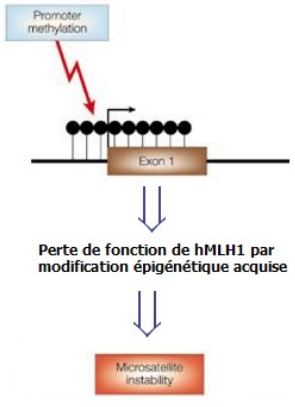


Sporadic MSI-H CRC: epigenetic MLH1 inactivation/Methylation

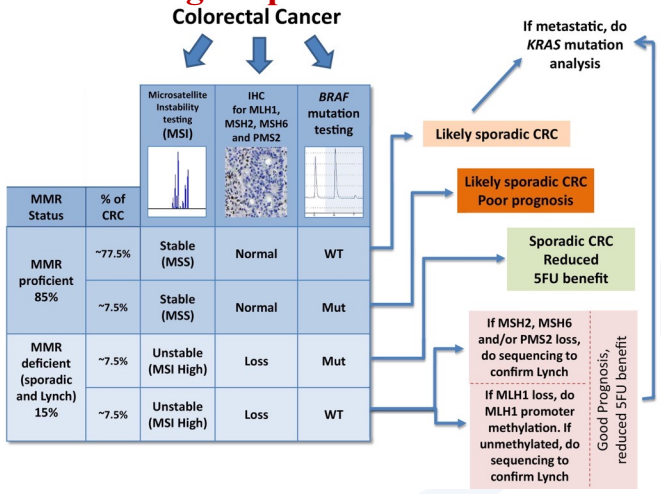
Hypermethylation of MLH1 = **the** mechanism of MMR loss of function for sporadic MSI-H CRCs

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



Syndrome de Lynch vs Methylation of MLH1 gene promotor



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Lynch syndrome: germline testing ? Importance of familial history

Prediction model: 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)

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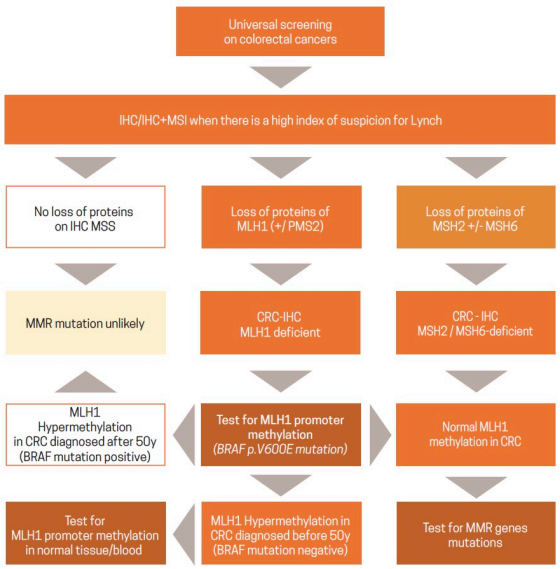
For the diagnostic approach in Belgium, we propose the following strategy

(Ferber M, Mao R, Samowitz W, et al. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). Genetics in Medicine 2014;16(1):101-16, Hébrant A, Jouret-Mourin A, Froyen G, et al. Molecular test algorithms for digestive tumours. Belgian Journal of Medical Oncology 2019,13:4-10).

Figure 3: Diagnostic approach in Belgium



https://belgianfapa.be/

- Immunohistochemical testing for DNA mismatch repair (MMR) protein expression (ie, MLH1, MSH2, MSH6, and PMS2 expression) is performed on formalin-fixed, paraffin embedded tissue on colorectal biopsy rather than resection specimen and can be considered if Lynch Syndrome-related tumors[2] . Rigorous technical processing with appropriate quality assessement and training for interpretation of immunohistochemical staining, is indicated. (https://kce.fgov.be/sites/default/files/atoms/files/KCE_220_Oncogenetic%20testing.pdf).

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LYNCH Syndrome: AD predisposition to MMR deficiency cancers

- Prevalence: 1/600 (?)
- 70-80% lifetime risk of **CRC**

→ Follow up by coloscopy: 1x/1-2y

MLH1 – MSH2: highest risk (44 yo)

- 11-19% risk of intestinal type **gastric tumor** (higher in at risk population: Japan)

Woman:

- risk of **endometrial** cancer: 30-60% (46–62 y)
  - 5-9% of endometrial cancer < 50yo
- Risk of ovarian cancer: 9-12% (42y), all types but not borderline tumor

Skin lesions: sebaceous carcinomas (Torre-Muir syndrome), keratoacanthomas, epithelioma

Other:

- **Bowel**, hepatobiliary, **urinary tract** (typically transitional carcinomas of the ureter and renal pelvis)
- Brain tumor (glioblastomas): Turcot syndrome
- Pancreas

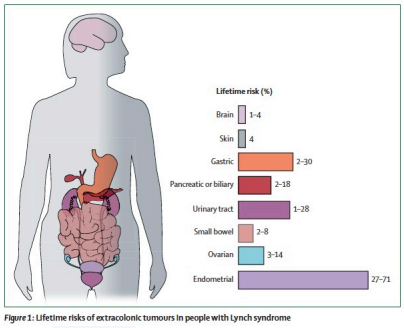

Figure 1: Lifetime risks of extracolonic tumours in people with Lynch syndrome

Relative risk > 8
Effect of tobacco +++

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LYNCH Syndrome

Table 1: Cumulative incidence at age 75 (%)

	MLH1	MSH2	MSH6	PMS2	Population risk
Colorectal cancer	60-80	60-80	10-20	10-20	4-5
Endometrial cancer	35	50	40	10-15	1.5
Ovarian cancer	10	17	10[b]	3[b]	0.8
Upper GI cancer	10-20	10-20	4-8	4	
Ureter-bladder-kidney	10-12	25-30	6-9	/	
Prostate cancer	10-20	20-30	/	/	10

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Surveillance guidelines (FAPA)

Table 2: Surveillance guidelines

Disorder		Lower age limit (y)	Examination	Interval(y)
Lynch Syndrome & Presumed LS	Colorectal cancer	(20-)25[A] or 5y younger than the youngest age at diagnosis of CRC in family if diagnosed before 25y	Colonoscopy Essential to visualize the complete colon and the terminal ileum	1-2
	Gastric cancer	(30-)35	Baseline Gastroduodenoscopy with gastric biopsy of the antrum Treating Helicobacter pylori infection when found Subsequent surveillance can be considered every 3–5y based on individual patient risk factors (MLH1/MSH2 mutations) and/or family history of gastric and duodenal cancer[B]	3-5
	Gynecological cancer	(30-)35	Pelvic examination Transvaginal ultrasound and endometrial biopsy [C] Prevention options (use of oral contraceptives) [D]	1
		Age 40 or after completion of Childbearing	Hysterectomy and bilateral salpingo-oophorectomy should be discussed with women who are known to be MLH1/MSH2 carriers	
	Urinary tract cancer[E]	(30-)35	Urinalysis for microscopic hematuria Urine cytology based on individual patient risk factor (MSH2 mutation) and/or family history	1
Revised Bethesda no MMR deficiency		20-40	Colonoscopy (interval need to be discussed in view of fam. history)	
Familial CRC 2 FDR With CRC or one FDR diagnosed < 50 years		40	Colonoscopy	5
Familial CRC One FDR with CRC > 50 years		40	Average risk method	

Other tumors are managed as in the general population.

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Lynch : chemoprevention:

• CAPP2 study: 861 Patients Lynch: 600 mg aspirine versus placebo during 4 years. Reduction of CCR occurrence with an average take of 25 month.

• CAPP3 study: studies the long-term effect of taking aspirin in 3000 Lynch patients by comparing 3 doses : 100, 300, or 600 mg/day.

www.thelancet.com Vol 395 June 13, 2020

Role of **immuno-oncology** in inherited CRC

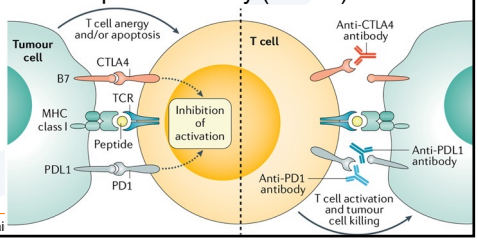
MSI-H tumor: Better prognosis

But: No response to 5FU

-> Lower interest of chemotherapy in stage II and III

-> immunotherapy:

• Immunotherapy is class of treatments that **take advantage of a person's own immune system to help kill cancer cells**. There are several FDA-approved immunotherapy options for colorectal cancer, including for tumors with high microsatellite instability (MSI-H) or DNA mismatch repair deficiency (dMMR).



British Journal of Cancer **volume 121**, pages809–818(2019)
Nat Rev Gastroenterol Hepatol. 2019 Jun; 16(6): 361–375.

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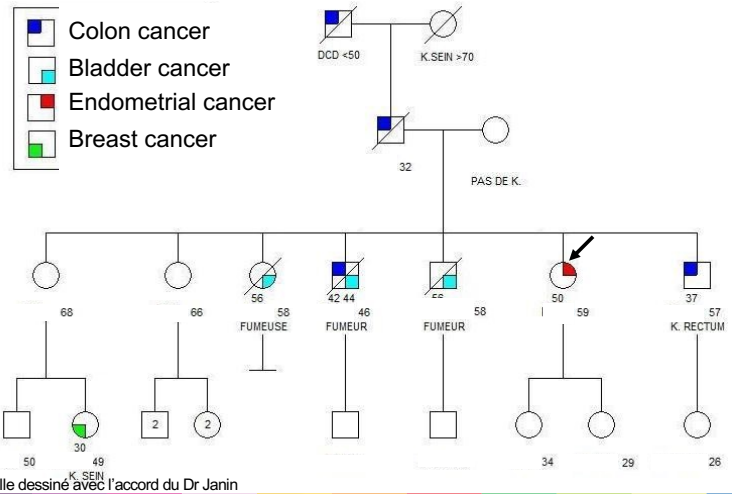
Case 1:



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

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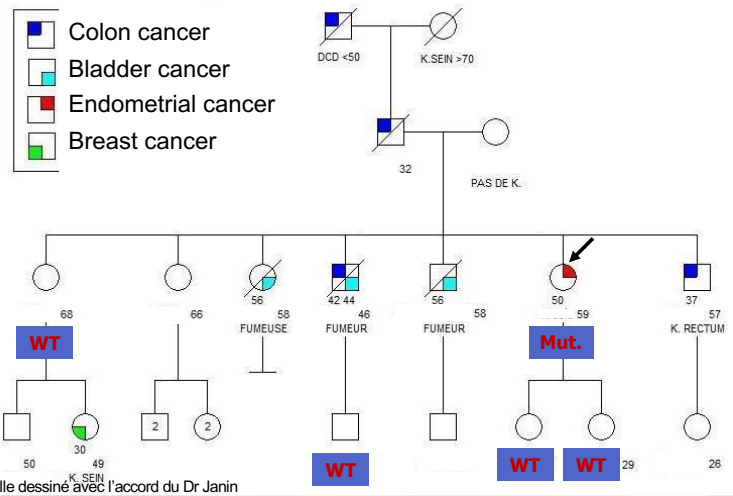
MSH2 mutation found in the family: possibility of predictive testing



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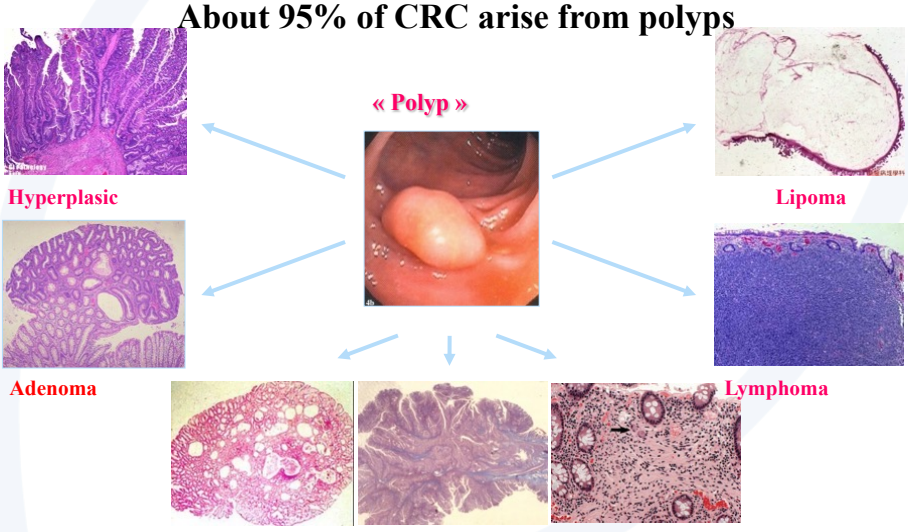
B. POLYPOSIS

About 95% of CRC arise from polyps



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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 Dr Duhoux
- **Juvenile polyposis** (mutation ***SMAD4*** or ***BMPR1A***), associated manifestations
- Cowden* (mutation ***PTEN***) -> see Dr Duhoux
- Ganglioneuromatosis*

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

Hyperplasic polyposis (gene?)

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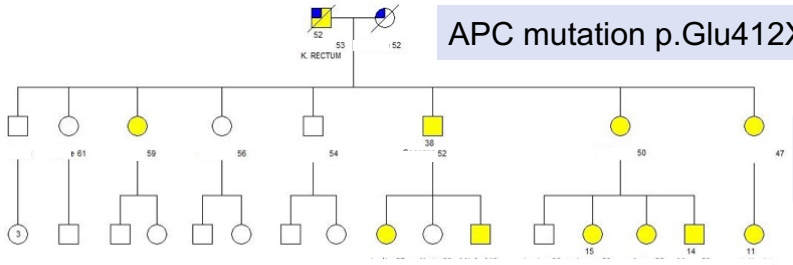
Familial Adenomatous Polyposis : clear autosomal dominant transmission



APC mutation p.Glu412X

Easy diagnostic in beginning of the seventies

Standard care of family → No death.

Responsible APC mutation discovered in 2011

Interest of testing: 1. Avoid colonoscopies
2. Avoid transmission

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

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Familial Adenomatous Polyposis Genotype Phenotype correlation

Colorectal polyposis +++

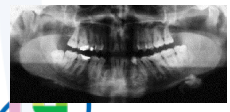
Cancer risk: 100% at 40 yo

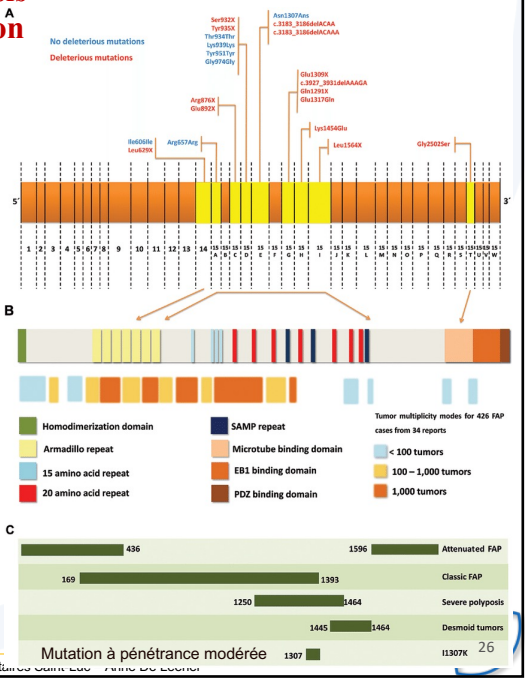
Extradigestive:

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

Manifestations extra-digestives

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





Mutation à pénétrance modérée

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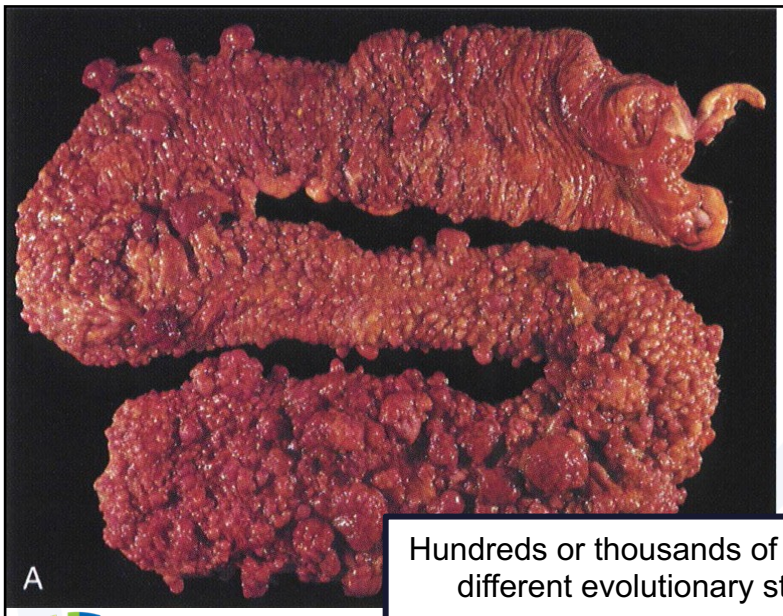

Hundreds or thousands of polyps at different evolutionary stages.

Evolutionary potential to cancer identical to sporadic MSS polyps

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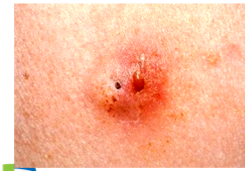
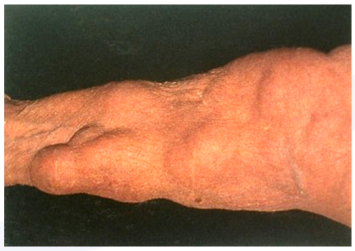
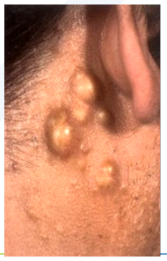
Germline APC mutations and predisposition to other tumors

APC loss-of-function mutations can participate to the development of other tumors that can also occur in FAP:

1. Malignant tumors: thyroid cancer (RR: 7,6), pancreas cancer (RR: 4,46), hepatoblastoma, medulloblastoma (Turcot Syndrome)
2. Benign tumors: adenomatous polyps of the upper digestive tract, desmoid tumors, osteomas, epidermoid cysts, benign hypertrophy of retina pigment epithelium

Skin lesions can occurs very early, before CRC

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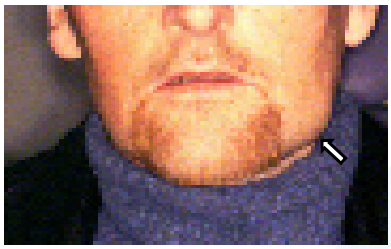
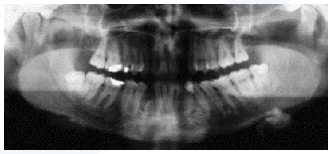
FAP with osteomas (Gardner syndrome)

- Bone deformation of the mandibular left angle



- Radiography → osteoma



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Familial adenomatous polyposis (FAP)

Recommendations
It is preferable that first-degree family members of patients with classic adenomatous polyposis and a pathogenic APC (adenomatous polyposis coli) mutation are referred for genetic counseling at the age of 10-12 years. If a clinical picture characteristic of attenuated familial adenomatous polyposis (AFAP) is seen with multiple family members, this may take place at a later age (young adult age). If a pathogenic APC mutation is found in the index patient, genetic testing is recommended as it may provide a decisive answer for all family members in relation to risk of the disorder. Children of mutation carriers have a 50% chance of the genetic predisposition to (A)FAP.
In the case of a person with MAP (biallelic MUTYH mutations), all brothers and sisters of this person should be referred for genetic evaluation given they have a 25% chance of a genetic predisposition. The a priori chance of MAP in a child of a patient with MAP is <1%, given the other parent has a small risk (± 2%) of being a carrier of a MUTYH mutation as well. To determine the risk for potential children of a patient with MAP, it is advised that MUTYH mutation testing is performed on the other parent. If the other parent is shown to be a mutation carrier, the children have a 50% chance of biallelic MUTYH mutations.
All patients under the age of 60 years with >10 adenomas cumulatively, should be referred for genetic counseling. Exceptionally, referral for genetic analysis should also be considered for young persons with <10 adenomas (high grade dysplasia). In persons ≥60 years of age with more than 10 adenomas cumulatively genetic testing should be considered in case of a positive family history of multiple adenomas.
Periodic endoscopic examination is recommended in the following patients: • Patients with FAP, AFAP, MAP or 'adenomatous polyposis of unknown origin.' • Persons with a pathogenic APC mutation • Persons with biallelic pathogenic MUTYH mutations • Risk carriers: first-degree family members of patients with adenomatous polyposis where the disorder cannot be confirmed by mutation analysis because a pathogenic mutation has not been found in the index patient • Risk carriers: first-degree family members of mutation carriers, who have not (yet) been tested themselves. Classic FAP: in mutation carriers or risk carriers of classic FAP; yearly surveillance using sigmoidoscopy is recommended from the age of 10-12 AFAP or MAP: in mutation carriers or risk carriers of AFAP or MAP, surveillance using colonoscopy is recommended once a year or every two years from the age of 18.
Participation of patients in the FAPA registry[b] is recommended and should be offered to patients concerned.
APC mutation carriers should be screened for extracolonic manifestations.

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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)

Prevalence

• **30%** of « *APC* negatives » adenomatous polyposis with attenuated form **(15< polyps <100)**

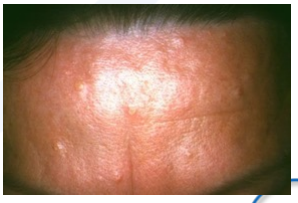
• **10%** of « *APC* negatives » adenomatous polyposis with classical form **(polyps >100)**

Molecular genetic

- Bi allelic mutation of the ***MYH* gene (*MUTYH*): recessive**
- Gene involved in the Base Excision Repair system: accumulation of somatic mutations (transversions)

Clinical characteristics?

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



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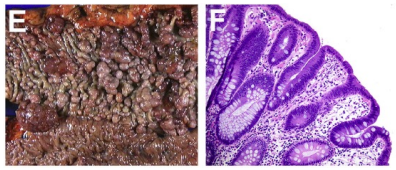
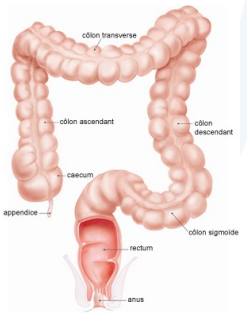
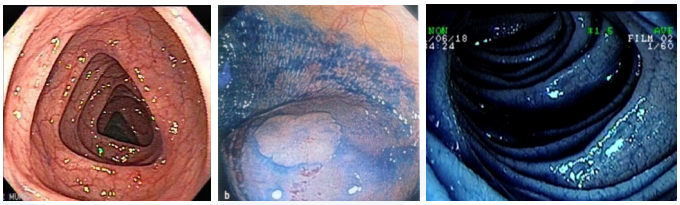
MUTYH: follow up of the index case

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





Average age at diagnosis: 45 yo



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MUTYH: follow up of the family

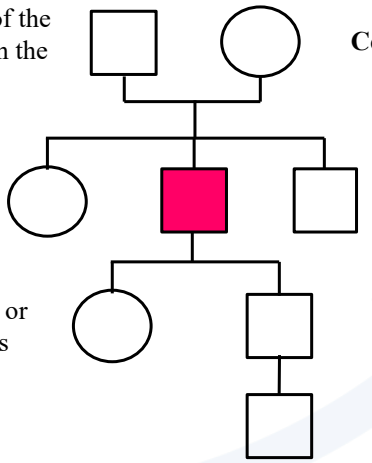
Indication of MUTYH analysis

Targeted analysis of the 2 mutations found in the index case

Targeted analysis of the 2 mutations found in the index case

Targeted analysis or complete analysis

No analysis



Medical follow up

Coloscopy > 40y each 5y

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

Coloscopy regarding genotype
(Mono or bi-allelic)

No follow up

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MUTYH associated polyposis (MAP)

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 2021: 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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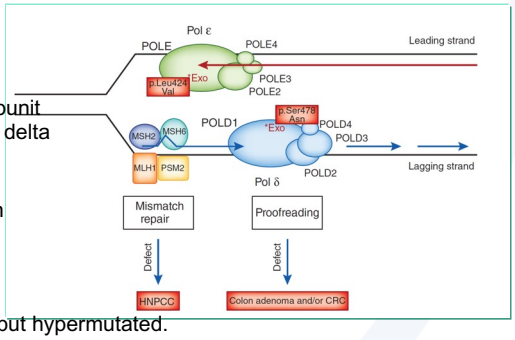
POL oligopolyposis associated

Polymerase proofreading associated polyposis syndrome (PPAP)

POLE DNA polymerase epsilon, catalytic subunit
POLD1 catalytic subunit of DNA polymerase delta

3'-5' proofreading exonuclease activity that corrects errors arising during DNA replication



Variable phenotype:
AD; from attenuated polyposis to HNPCC
CRC MSS without loss of expression MMR but hypermutated.
POLD1: increased risk of endometrial cancer

Rare cases of other features:
POLE homozygous splice site mutation -> FILS Syndrome (facial dysmorphism, immunodeficiency, livedo, and short stature) OMIM: 615139
POLE compounds heterozygous mutations: intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, genital anomalies, and immunodeficiency (IMAGEI) OMIM 618336

POLD1 in-frame deletion of residue ser605 (AD) causes Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (MDPL) OMIM: 615381

Palles *et al.* Nature Genet 2013; 45: 136-144
The American Journal of Human Genetics 103, 1038–1044, December 6, 2018
Genetics in medicine | Volume 18 | Number 4 | April 2016

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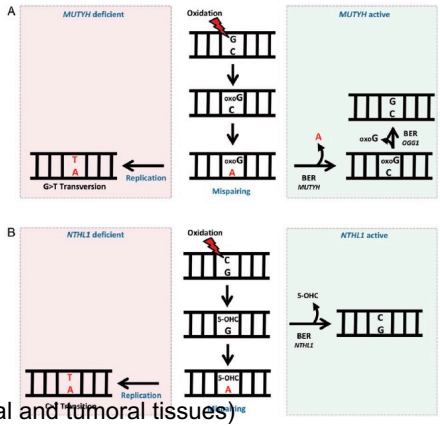
Rare AR forms of adenomatous polyposis

NTHL1

J Pathol 2018; 244: 135–142



DNA N-glycosylase of the endonuclease III family catalyzes the first step in base excision repair BER
Transversion **G:C** -> **A:T**

- Rare
- 11 families
- Other cancer types not described

MSH3

MMR associated protein

- Rare
- Loss of expression of MSH3 (in both normal and tumoral tissues)
- Tumeur MSI-H

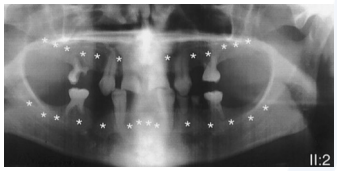
PMS2 (CMMRD)

IHC : no expression in both normal and tumor tissues
Increased risk of CRC, cerebral tumor, malignant hemopathy. Cafe au lait spot

The American Journal of Human Genetics 99, 337–351, August 4, 2016

Other rare Adenomatous Polyposis

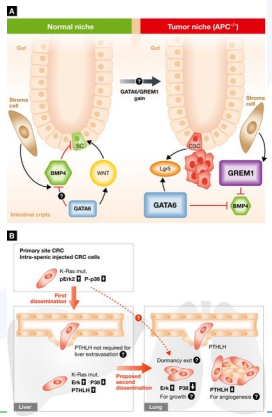
Germline mutation of ***AXIN2*** (R656X)
Finland families
Attenuated adenomatous polyposis
Oligodontia (dental agenesis)
Wnt/β-catenin.



Lammi L *et al*. Am J Hum Genet 74: 1043-1050.

Germline mutation in ***GREM1***
Attenuated form
Ashkenazi Jewish families segregating autosomal dominant hereditary mixed polyposis syndrome due to duplication of the regulatory region
Has to be confirmed by larger studies

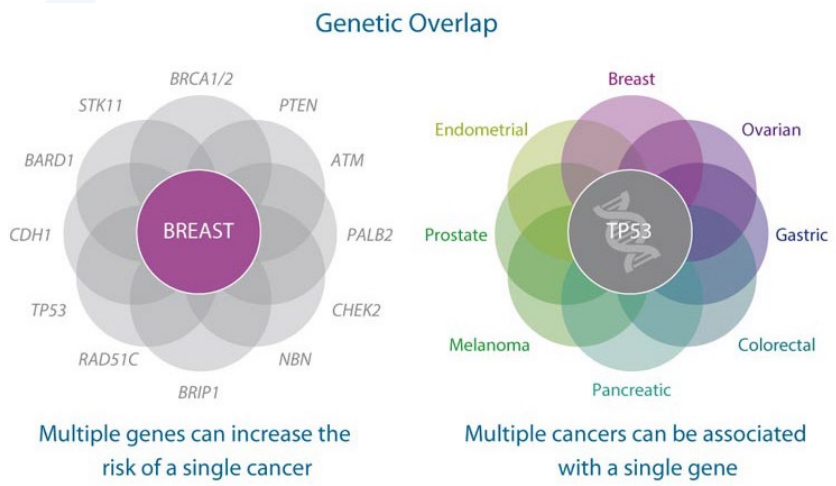
Gastroenterology. 2017 Jun;152(8):1876-1880



The EMBO Journal (2014) 33, 1737-1739

Other inherited cancer predispositions:

Breast: see Dr Duhoux



Pancreatic cancer:

5-10% of the the PC
Familial PC: > 2 relatives and no germline mutation

Surveillance?
Pancreatitis: increased risk of PC up to 40% (RRX69):
SPINK1 (AR), PRSS1 (AD), CFTR

Non syndromic :
BRCA2 : if familial history: 6% >> BRCA1
CDKN2A (p16): if FH + (RRX47)
PALB2: if FH +

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

Gut 2020;69:7–17.

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

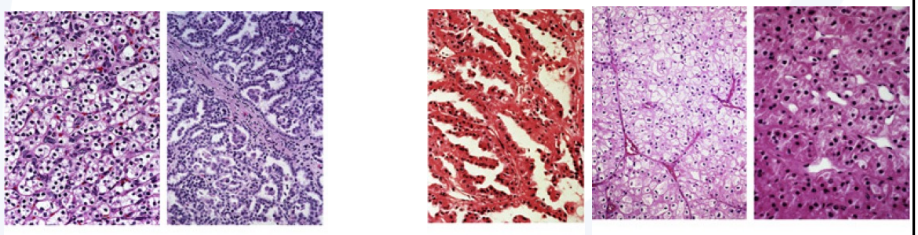
Gene mutation	PDAC family history criteria	Agreement	Grade
LKB1/STK11 (Peutz-Jeghers syndrome)	Regardless of family history	99%	1
CDKN2A p16* (FAMMM)	With at least one affected FDR	99%	1
CDKN2A p16* (FAMMM)	Regardless of family history	77%	1
BRCA2	If at least one affected FDR, or at least two affected 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.

Other inherited cancer predispositions

Kidney: genes involved in sporadic forms of kidney carcinomas. 2-3% inherited

VHL	MET	FH	FLCN
Von Hippel Lindau Disease	HPRC	Leiomyomatosis	Birt Hogg Dube
TSG	Oncogene	TSG Uterine Cutaneous	TSG Cutaneous Pneumothorax / Cyst
Clear cell	Papillary type 1	Papillary type 2	Various



Clear Cell 75% | Papillary Type 1 5% | Papillary Type 2 5% | Chromophobe 5% | Oncocytoma 5%

Linehan et al., Semin Cancer Biol 2013

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Other inherited cancer predispositions

Kidney:

Von Hippel Lindau (80% of inherited cases)

1st cause of hereditary renal and pheo. cancers

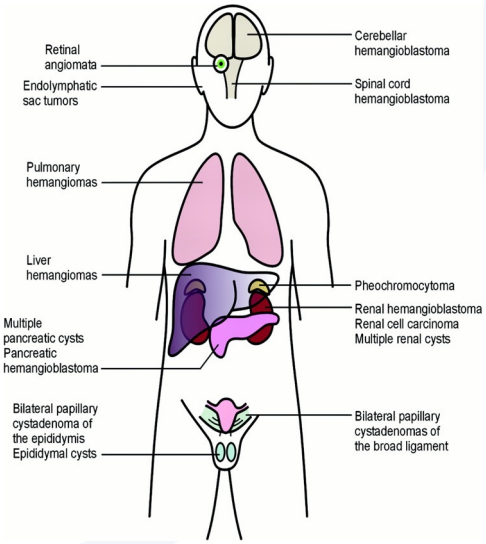
1/36000

Mutation in VHL gene (> 300), also in 75% of the sporadic cancers (somatic)

Hemangioblastoma (of the retina)

Pheochromocytoma and PGL:

See Dr Persu



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Next Generation Sequencing : Use of gene panel in clinical practice ?

Mixed investigation without a priori

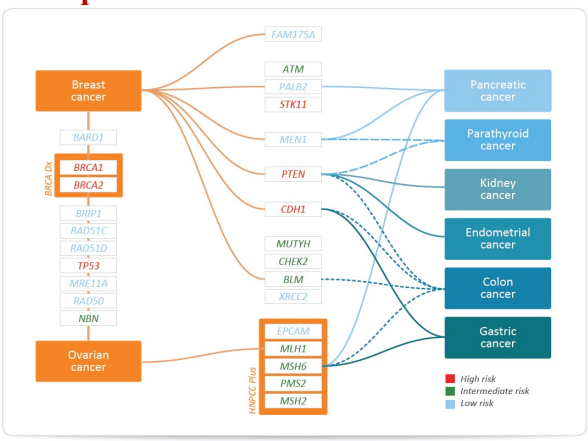
Time saving

Cheaper

Possibility of several germline mutations in a same individual

To take into acount

- Number of genes limited by panel
- Coverage
- VUS
- Incidental findings
- link with pathology



Gene Panel 26 (35 actually) multiplicom

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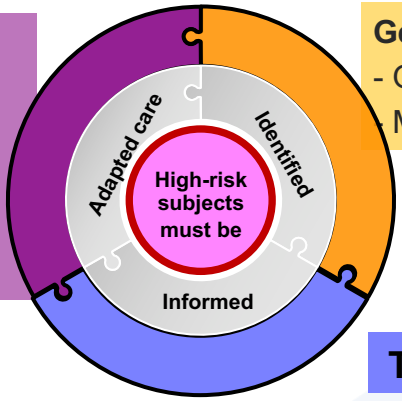
General conclusion: Partners involved in the correct care for high risk subjects

Many doctors:
- 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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