[Journée scientifique de printemps_ARL_07.03.2024]

Syndrome de Lynch : de la clinique à la biologie … et retour !

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I. Prédispositions génétiques au cancer colorectal

II. Syndrome de Lynch

1. Historique
2. Bases moléculaires
3. Critères diagnostiques
4. Dépistage universel
5. En pratique
6. Surveillance et prévention
7. Pronostic et traitement
8. CMMRD syndrome
9. Perspectives et conclusion

PRÉDISPOSITIONS GÉNÉTIQUES AU CANCER COLORECTAL

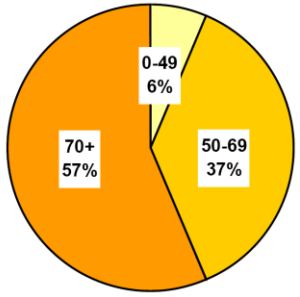
Cancer colorectal : épidémiologie

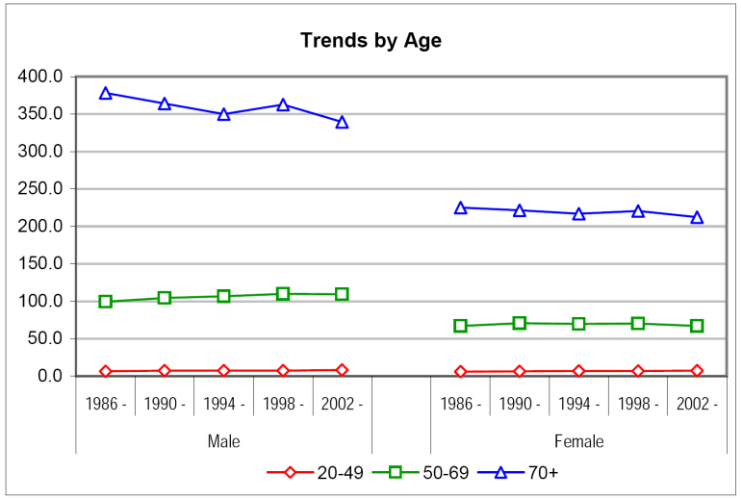
Suisse	♂	♀
Nouveaux cas/an	**2’400**	**1’900**
- côlon	1’550	1’250
- rectum	850	650
Risque cumulatif	**6.3 %**	**4.7 %**
Décès/an	950	750

[Office féderal de la statistique 2016; Swiss Cancer Screening.org]

Cancer colorectal : épidémiologie

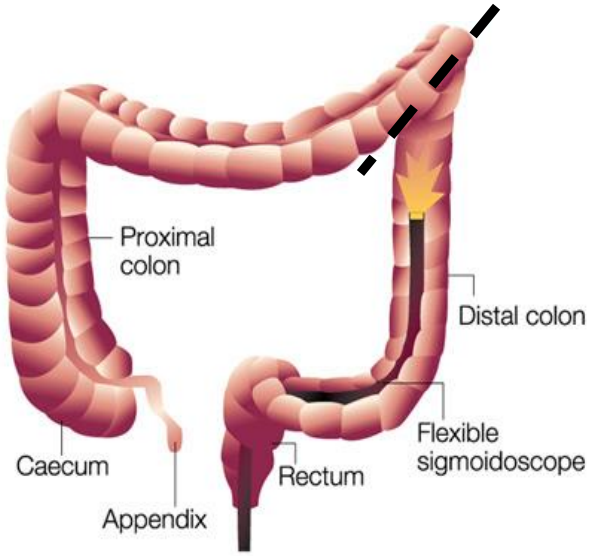
Incidence





[www.asrt.ch]

Localisation



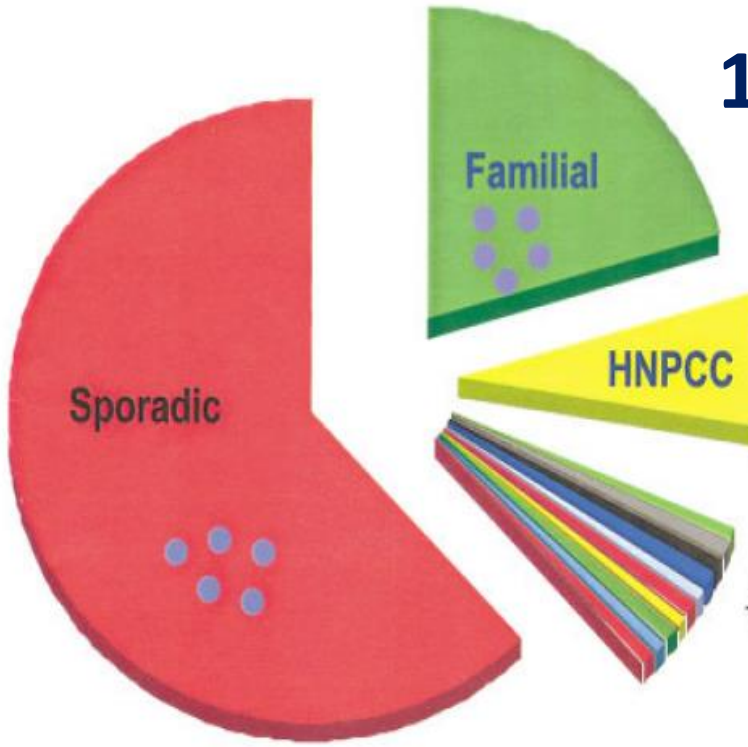
Nature Reviews | Cancer

PROXIMAL ~ 35 % (↑)

DISTAL ~ 65 % (↓)

- **Age moyen au diagnostic : ~ 72 ans**

CANCERS COLORECTAUX



10-20 %

75 %

Syndrome de LYNCH

2-4 %

FAP; AFAP
Mixed Polyposis Syndrome
Ashkenazi I1307K
MYH (MAP)

PJS
FJP
CD
BRRS

Hamartomatous Polyposis Syndromes

= as yet undiscovered hereditary cancer variants
- Serrated Polyposis Syndrome
- Familial Colorectal Cancer Type X

Polyposes
≤ 1 %

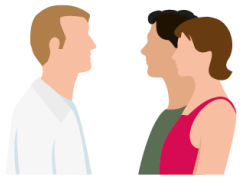
[adapté de Lynch HT. Cancer 2004]

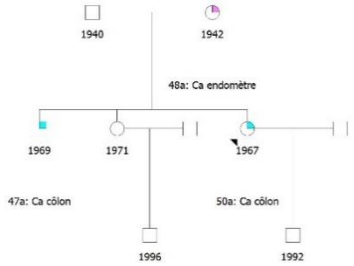
Cancer colorectal : prédispositions héréditaires

Syndromes mendéléiens	Gènes	Mode de transmission	Mutations identifiables
Lynch	*MLH1, MSH2* *MSH6, PMS2*	AD	30-80 %
Polypose adénomateuse familiale	*APC*	AD	>90 %
Polypose associée à *MUTYH*	*MUTYH*	AR	2-20 %
Peutz-Jeghers	*LKB1 (STK11)*	AD	>90 %
Polypose juvénile	*SMAD4*	AD	20-40 %
Cowden	*BMPR1A*	AD	5-20 %
	PTEN	AD	80 %
Syndrome de polypose festonnée	*RNF43*	AD/AR ?	<3 %
Polypes multiples/cancer colorectal	*POLE, POLD1*	AD	
	NTHL1	AR	
	MSH3	AR	

+ GREM1, RNF43, AXIN2, MBD4, TP53, CHEK2, …

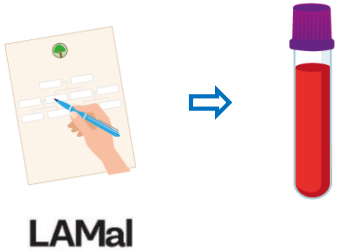
La consultation d'oncogénétique





PREMIÈRE CONSULTATION

CONSENSUS PLURIDISCIPLINAIRE



DEUXIÈME CONSULTATION

CONSEIL GÉNÉTIQUE

Risque **élevé**

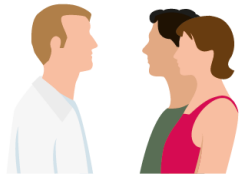
Dépistage génétique disponible

DÉPISTAGE GÉNÉTIQUE

Dépistage refusé

Mesures de **surveillance** et de **prévention**

TROISIÈME CONSULTATION

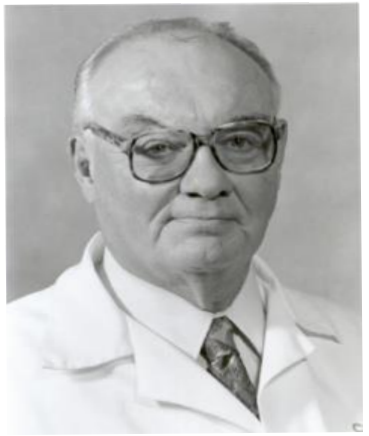


Dépistage génétique en oncologie

BÉNÉFICES
Évaluation précise du risque
Impact thérapeutique
Concentrer les mesures de surveillance/prévention chez les porteurs (meilleure compliance)
Rassurer les non-porteurs
Risque de transmission à la descendance précisé
Levée de l'incertitude (*"right to know"*)

Dépistage génétique en oncologie

BÉNÉFICES	INCONVÉNIENTS
Évaluation précise du risque	Impact psychologique potentiellement négatif (anxiété, dépression)
Impact thérapeutique	Sentiment de culpabilité chez les (non-)porteurs
Concentrer les mesures de surveillance/prévention chez les porteurs (meilleure compliance)	Risques de discrimination
Rassurer les non-porteurs	Perturbation des liens familiaux
Risque de transmission à la descendance précisé	
Levée de l'incertitude (*"right to know"*)	



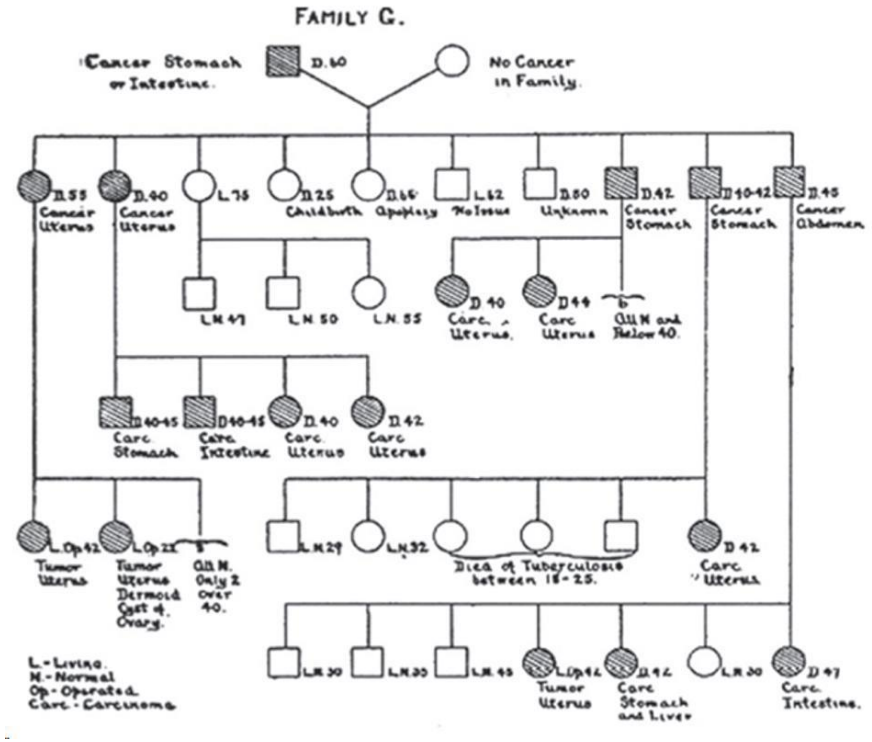
HT. LYNCH
1928-2019

Syndrome de LYNCH

[Syndrome du cancer colorectal héréditaire sans polypose
ou syndrome HNPCC]

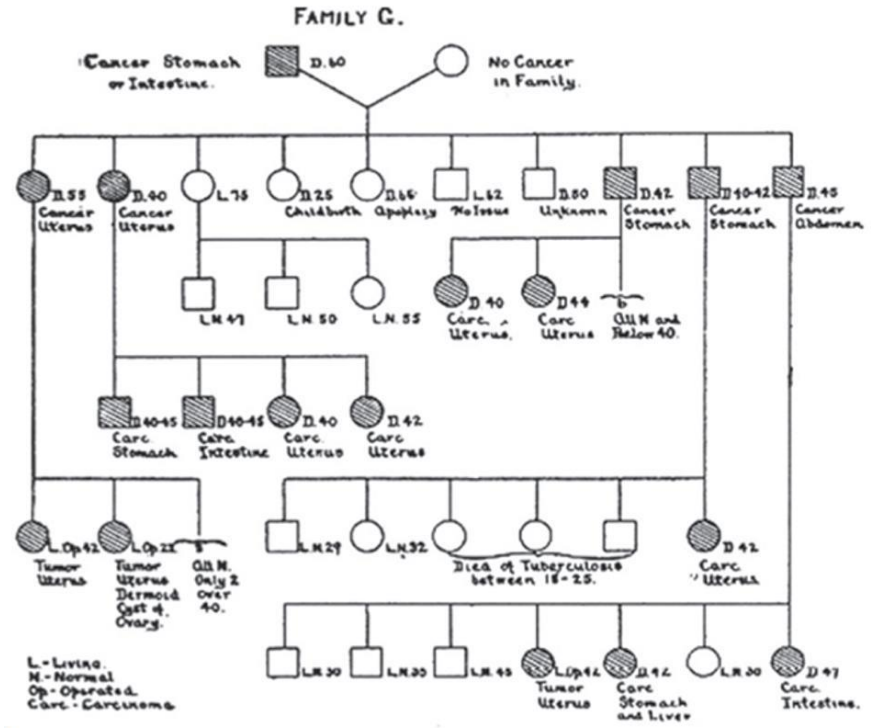
HISTORIQUE

Aldred S. WARTHIN, MD, PhD



[Warthin AS.
Arch Intern Med **1913**]

Aldred S. WARTHIN, MD, PhD



[Warthin AS.
Arch Intern Med 1913]

History and Molecular Genetics of Lynch Syndrome in Family G

A Century Later

[Douglas et al. JAMA **2005**]

Table 1. Demographic Characteristics of Family G by Generation

Generation	Birth Years	No. of Members	No. of Deaths	Current Age, Mean (SD), y*
II	1827-1846	9	9	
III	1845-1891	65	65	
IV	1874-1929	149	120	90 (8)
V	1902-1959	188	62	66 (12)
VI	1927-1988	319	7	44 (11)
VII	1952-1998	188	1	25 (12)
VIII	1983-1999	11	0	9 (5)
Total	1827-1999	**929**	**264**	45 (21)

*Age current as of March 2000.

Table 2. Colorectal and Lynch Syndrome–Associated Cancers in Family G*

Site	No. of Cases	Age at Diagnosis, Mean (SD) [Range]†	Generations
Colorectum	56	55 (16) [23-93]	II, III, IV, V
Endometrium	16	53 (12) [39-78]	II, III, IV, V
Stomach	8	62 (12) [44-76]	II, III, IV, V
Brain	4	44 (16) [23-59]	III, IV, V
Ovary	1	44	V
Total	**85***		

*Includes 74 individuals; 8 were diagnosed with multiple (2-5) primary cancers.
†Actual age is given for cancer of the ovary.

→ variant pathogénique *MSH2*

(T>G splice acceptor site exon 4)

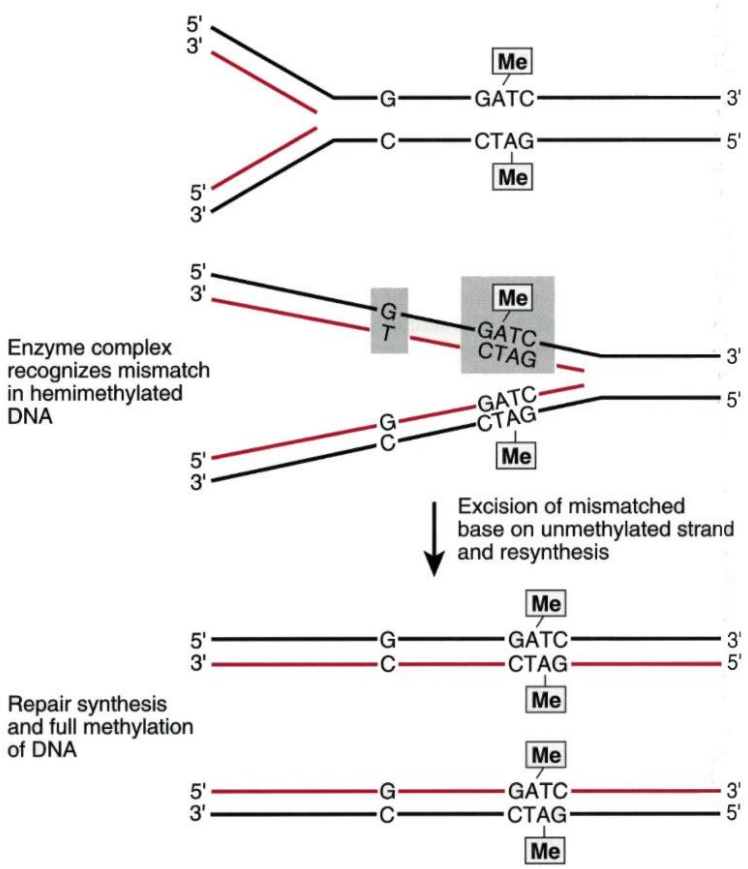
BASES MOLÉCULAIRES

Mismatch Repair (MMR)

- **Système de réparation de l'ADN**
- Découvert chez les procaryotes dans les années 1970-80
- Détecte les **erreurs de réplication** durant la phase S
- Mécanisme ubiquitaire ; **conservé** durant l'évolution
- Correction des erreurs de réplication :

  - 1 base mismatch (ex : G-T, A-A, …)
  - petite boucle sur des séq. répétitives (4-5 nt)
  - « slippage » au niv. de microsatellites

Mismatch Repair c/o procaryotes



[Friedberg, Walker & Siede
In: DNA Repair and Mutagenesis]

PROTEIN	FUNCTION
MutS	Damage recognition
MutL	Binds to MutS
MutH	5’ endonuclease cuts on unmethylated strand at GATC
UvrD	Helicase
DNA polymerase III	DNA resynthesis

+ other required components: exonuclease I, exonuclease VII
RecJ exonuclease, DNA ligase, ATP, NAD, dNTPs

Mismatch Repair c/o mammifères

Table 1 | **Human MutS and MutL homologue complexes that are involved in mismatch repair**

Complex	Components	Function
MutSα	MSH2, MSH6	Recognition of base–base mismatches and small IDLs
MutSβ	MSH2, MSH3	Recognition of IDLs
MutLα	MLH1, PMS2	Forms a ternary complex with mismatch DNA and MutSα; increases discrimination between heteroduplexes and homoduplexes; also functions in meiotic recombination
MutLβ	MLH1, PMS1	Unknown
MutLγ	MLH1, MLH3	Primary function in meiotic recombination; backup for MutLα in the repair of base–base mismatches and small IDLs

IDL, insertion/deletion loop; MLH, MutL homologue; MSH, MutS homologue; PMS, post-meiotic segregation protein.

[Jiricny. Nature Rev Mol Cell Biol 2006]

Fonctionnement en **hétérodimères**

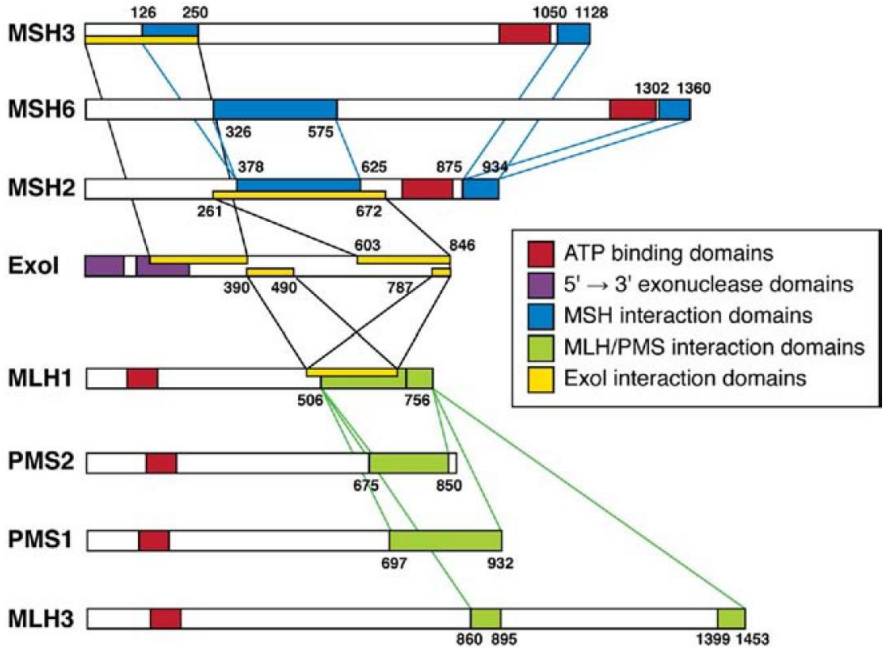
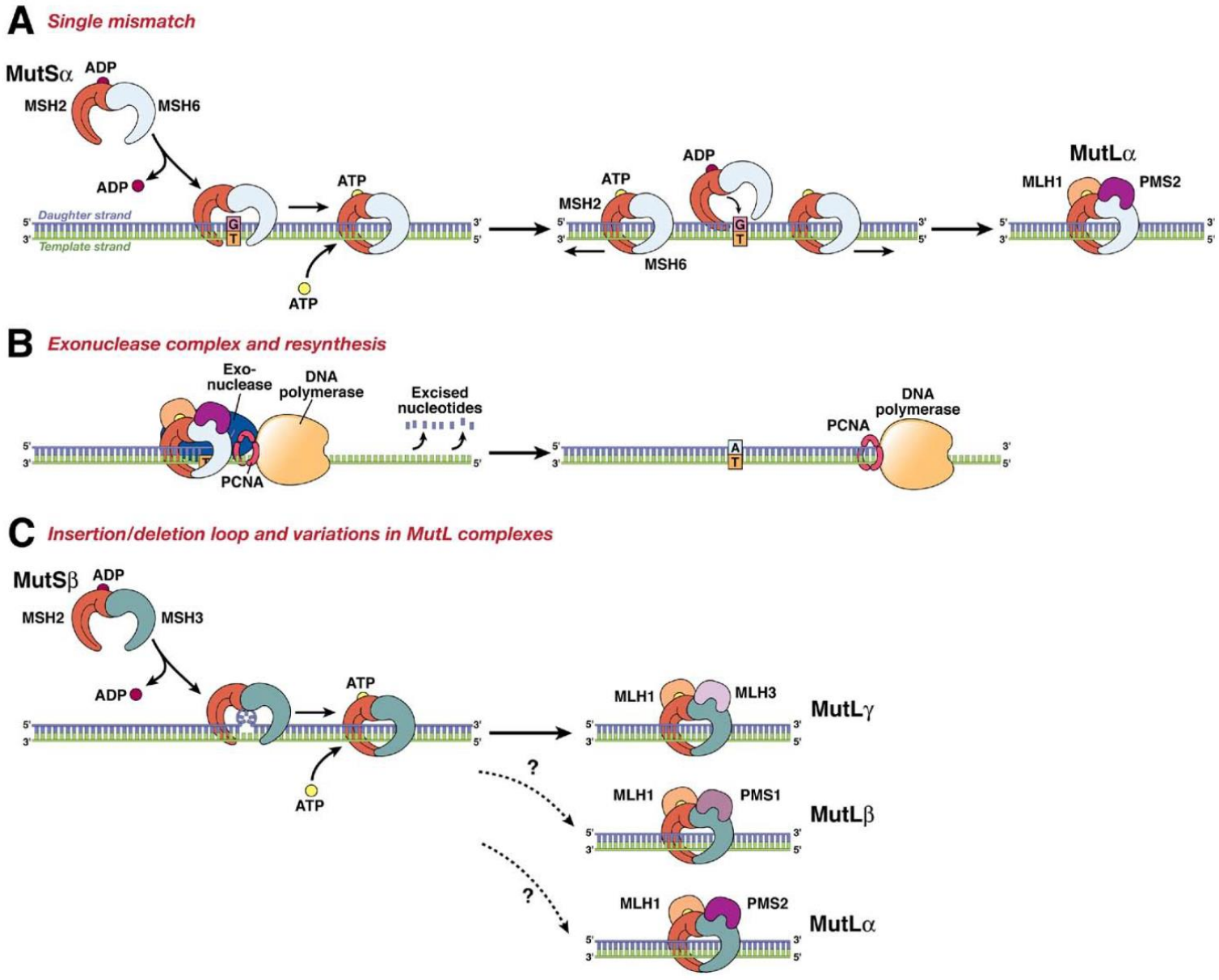


Figure 4. The regions of protein–protein interactions among the members of the MMR system. Mutations in the regions of protein interactions

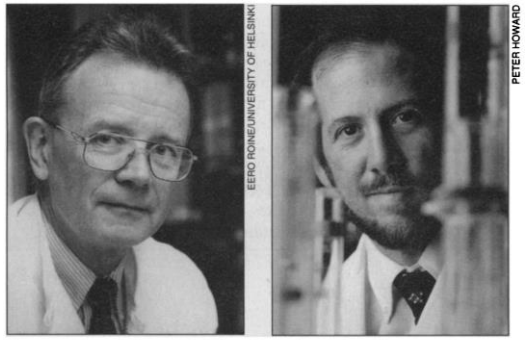
[Boland & Goel. Gastroenterol 2010]

Mismatch Repair c/o mammifères



[Boland & Goel. Gastroenterol 2010]

1993-1994



Gene trackers. Albert de la Chapelle *(left)* and Bert Vogelstein have genetic evidence for a new type of colon cancer susceptibility gene.

Genetic mapping of a second locus predisposing to hereditary non-polyposis colon cancer

nature *genetics* volume 5 november 1993

Mutation in the DNA mismatch repair gene homologue *hMLH1* is associated with hereditary non-polyposis colon cancer

NATURE · VOL 368 · 17 MARCH 1994

Genetic Mapping of a Locus Predisposing to Human Colorectal Cancer

SCIENCE • VOL. 260 • 7 MAY 1993

The Human Mutator Gene Homolog *MSH2* and Its Association with Hereditary Nonpolyposis Colon Cancer

Cell, Vol. 75, 1027–1038, December 3, 1993

Mutation of a *mutL* Homolog in Hereditary Colon Cancer

SCIENCE • VOL. 263 • 18 MARCH 1994

Clues to the Pathogenesis of Familial Colorectal Cancer

SCIENCE • VOL. 260 • 7 MAY 1993

Mutations of a *mutS* Homolog in Hereditary Nonpolyposis Colorectal Cancer

Cell, Vol. 75, 1215–1225, December 17, 1993

Mutations of two *PMS* homologues in hereditary nonpolyposis colon cancer

NATURE · VOL 371 · 1 SEPTEMBER 1994

Mismatch Repair Genes on Chromosomes 2p and 3p Account for a Major Share of Hereditary Nonpolyposis Colorectal Cancer Families Evaluable by Linkage

Am. J. Hum. Genet. 55:659–665, 1994

Microsatellite Instability in Cancer of the Proximal Colon

SCIENCE • VOL. 260 • 7 MAY 1993

Hypermutability and Mismatch Repair Deficiency in RER$^+$ Tumor Cells

Cell, Vol. 75, 1227–1236, December 17, 1993

Loss of the wild type *MLH1* gene is a feature of hereditary nonpolyposis colorectal cancer

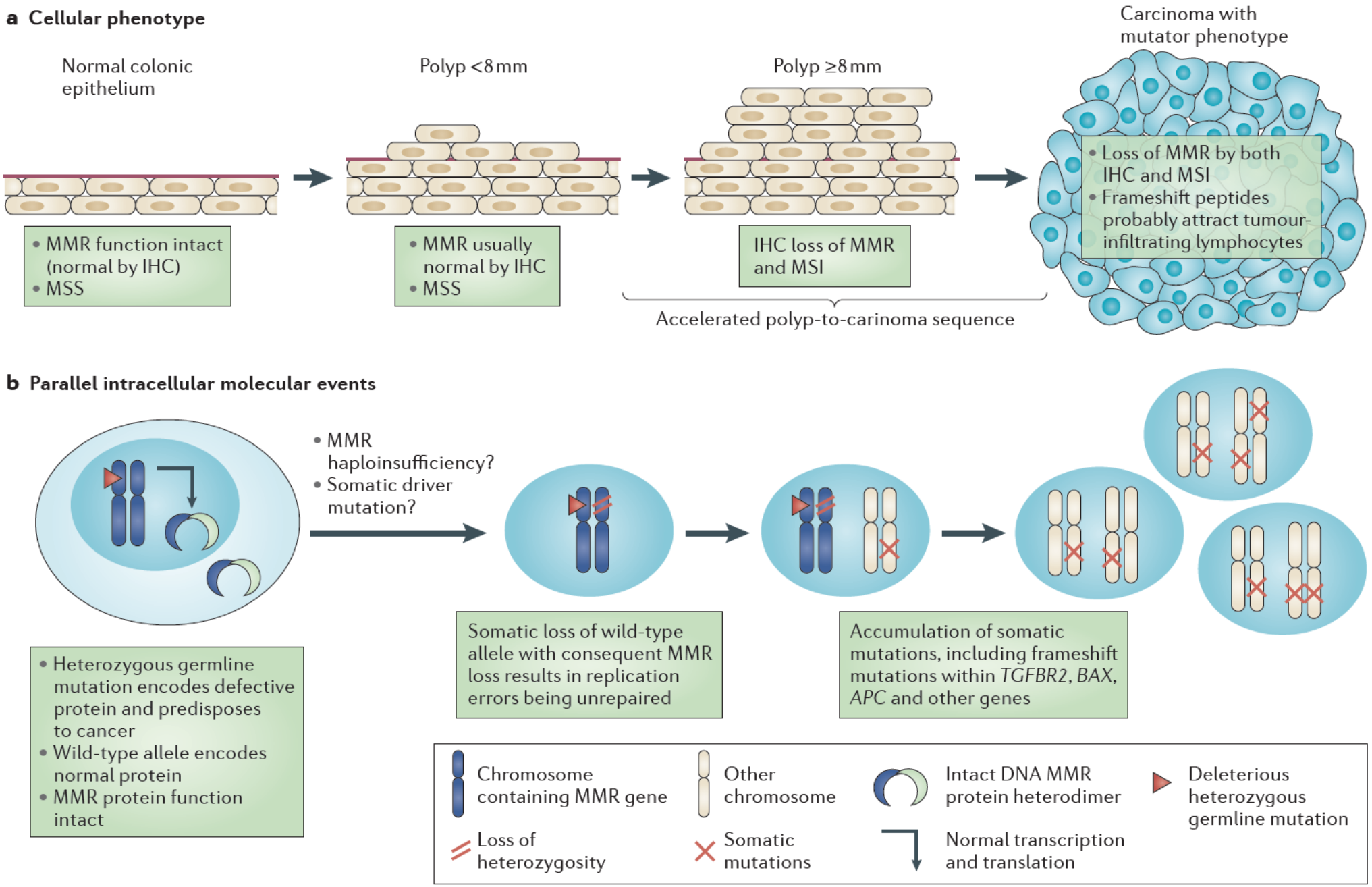
Nature Genetics volume 8 december 1994

Replication Errors in Benign and Malignant Tumors from Hereditary Nonpolyposis Colorectal Cancer Patients[1]

[CANCER RESEARCH 54, 1645–1648, April 1, 1994]

1993-94 : Lien entre MMR et syndrome de Lynch

- Identification des gènes *MSH2*, *MLH1*, *PMS2*, *PMS1*
- Syndrome de Lynch : mutations hétérozygotes dans *MSH2*, *MLH1*, *PMS2*, ou *PMS1*
- Taux de mutations est 100-1000x + élevé si MMR deficient
- Instabilité génétique (séquences microsatellites) dans tout le génome des tumeurs HNPCC et dans certains CCR sporadiques (15-25%)
- Séquences microsatellites aussi dans les parties codantes de gènes impliqués dans la carcinogenèse : *TGFβ-RII*, *PTEN*, *Bax*, *BRCA1*, *MSH6*, *ATM*, …



[Lynch et al. Nat Rev Cancer 2015]

Microsatellites

Courtes séquences répétitives distribuées dans tout le génome

- mononucléotide : $(A)_n$ ... AAAAAAAAAAAAA ...
- dinucléotide : $(AG)_n$ ... AGAGAGAGAGAG ....
- trinucléotide : $(GAG)_n$ ... GAGGAGGAGGAG ...

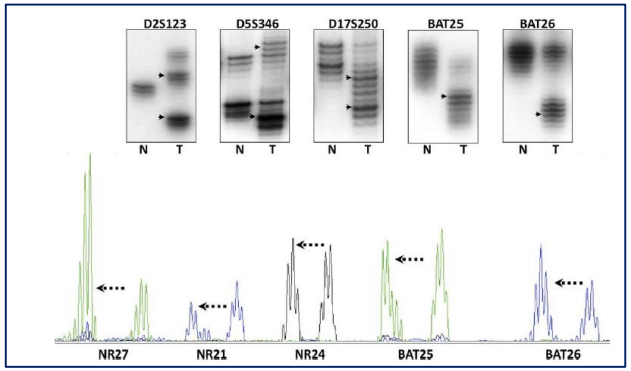
"Simple sequences are not easy to replicate"

- Très abondants dans le génome, polymorphes entre les individus, mais uniformes dans tous les tissus de chaque individu
- Beaucoup utilisés en médecine forensique, en analyse de discrimination d'allèle, en test de paternité, …

= marqueurs génétiques d'un **défaut du *MMR dans la tumeur***

Microsatellites : évaluation (1)

- Technique de référence : **MSI-PCR**
- Analyse de taille de fragments (séq. microsatellites)
- Panel consensus de microsatellites
  - > 20 % de cellules tumorales dans l'échantillon
  - **Panel NCI, 2004 (Pentaplex-PCR)**
    - 5 parmi les 7 marqueurs mononucléotidiques suivants : BAT25, BAT26, BAT40, NR21, NR22, NR24 et NR27
    - microsatellites quasi-monomorphes : sans comparaison avec ADN normal
    - **MSI si au moins 2 marqueurs instables**



[Boland & Goel. Gastroenterol 2010]

[Umar et al. J Natl Cancer Inst 2004]

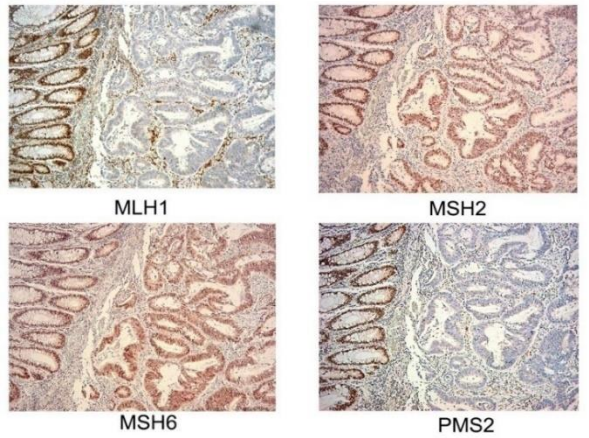
Microsatellites : évaluation (2)

- Technique de détection immunologique de l'expression des protéines MMR

- **Immunohistochimie (IHC) des protéines MMR** :
  → tumeur dMMR (deficient) / pMMR (proficient)

- **+ :** grande sensibilité, facilité de mise en place, faible coût, rapide, applicable à tout type tumoral
- **- :** différence de fixation induit un signal équivoque, détection possible malgré mutations faux-sens, difficultés si petites biopsies

- Si IHC + pour MLH1-PMS2 : rechercher hyperméthylation du promoteur de *MLH1* et/ou variant *BRAF* V600E (si CCR)



Concordance IHC – MSI

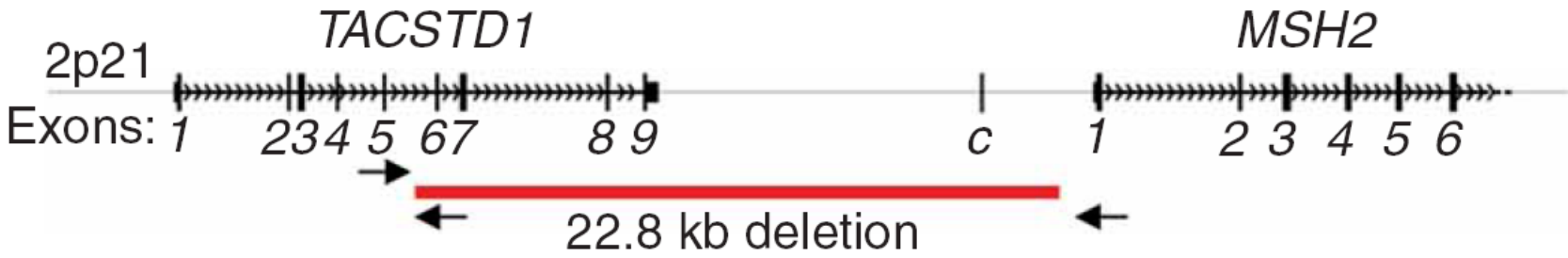
Identifying mismatch repair-deficient colon cancer: near-perfect concordance between immunohistochemistry and microsatellite instability testing in a large, population-based series

Maurice B Loughrey,[1,2,3] Jason McGrath,[4] Helen G Coleman,[2,3] Peter Bankhead,[5] Perry Maxwell,[4] Claire McGready,[4,6] Victoria Bingham,[4] Matthew P Humphries,[4] Stephanie G Craig,[2] Stephen McQuaid,[1,4,6] Manuel Salto-Tellez[1,2,4] & Jacqueline A James[1,2,4,6]

Histopathology 2021, **78**, 401–413

! Pas nécessairement généralisable pour toutes les types de tumeurs

Délétion du gène *EPCAM*
un autre mécanisme de mutation *MSH2*



[Ligtenberg et al., Nat Genet 2009]

- délétion des 2 derniers exons d'*EPCAM/TACSTD1* et du site de polyadénylation (en amont de *MSH2)*
- ⇨ protéine de fusion
- ⇨ **hyperméthylation de *MSH2***
- transmission autosomale dominante
- mutation fondatrice en Hollande
- Dépistage systématique par MLPA

CRITÈRES DIAGNOSTIQUES

Syndrome de Lynch

Critères d'Amsterdam (ICG-HNPCC)

Amsterdam I criteria (1991)

At least three relatives must have histologically verified colorectal cancer:
- One must be a first-degree relative of the other two.
- At least two successive generations must be affected.
- At least one of the relatives with colorectal cancer must have received the diagnosis before the age of 50 years.
- Familial adenomatous polyposis must have been excluded.

Amsterdam II criteria (1999)

At least three relatives must have a cancer associated with hereditary non-polyposis colorectal cancer (colorectal, endometrial, stomach, ovary, ureter or renal-pelvis, brain, small-bowel, hepatobiliary tract, or skin [sebaceous tumors]):
- One must be a first-degree relative of the other two.
- At least two successive generations must be affected.
- At least one of the relatives with cancer associated with hereditary non-polyposis colorectal cancer should have received the diagnosis before the age of 50 years.
- Familial adenomatous polyposis should have been excluded in any relative with colorectal cancer.
- Tumors should be verified whenever possible.

Bethesda guidelines (NCI, 2004)

Tumors from individuals should be tested for MSI in the following situations:
1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors,* regardless of age.
3. Colorectal cancer with the MSI-H† histology‡ diagnosed in a patient who is less than 60 years of age.§
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

[Vasen et al. Dis Colon Rectum 1991]
[Vasen et al. Gastroenterology 1999]
[Umar et al. J Natl Cancer Inst 2004]

❶ Critères diagnostiques validés (Amsterdam, Bethesda)

❷ Outils de dépistage validés

- recherche instabilité des microsatellites
- étude IHC des principales protéines du système MMR

❸ Impact démontré de la surveillance sur la survie

MAIS …

… le syndrome de Lynch est demeuré sous-diagnostiqué

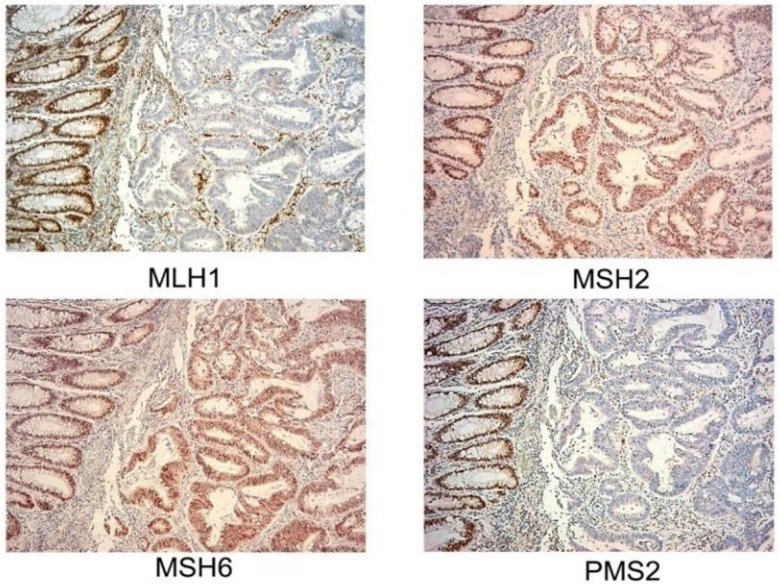
Synd. de Lynch : difficultés diagnostiques

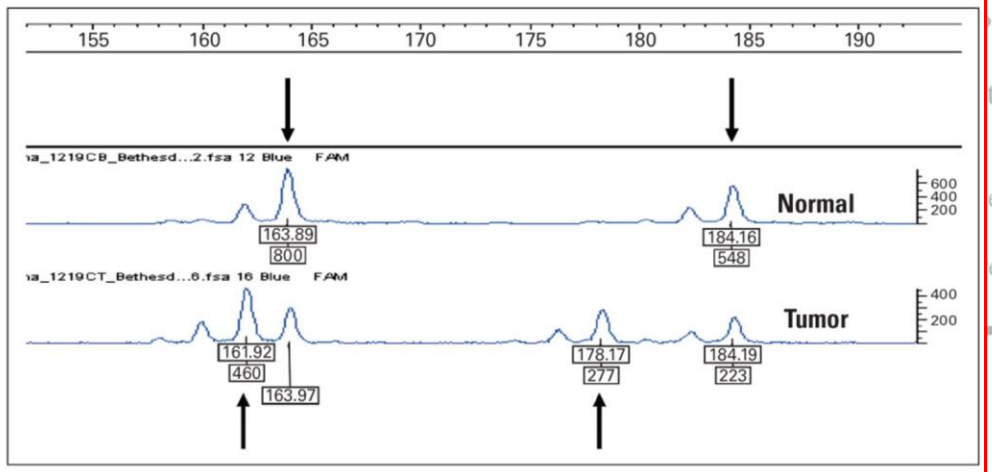
- Phénotype sans particularité
- Pénétrance incomplète ; phénocopie
- Antécédents familiaux non disponibles
  - inconnus du patient
  - non relevés par le médecin
- Arbres généalogiques “restreints” ; fausse paternité ; adoption
- Néomutations

DÉPISTAGE UNIVERSEL (>2010)

Syndrome de Lynch

Universal tumor screening (UTS)



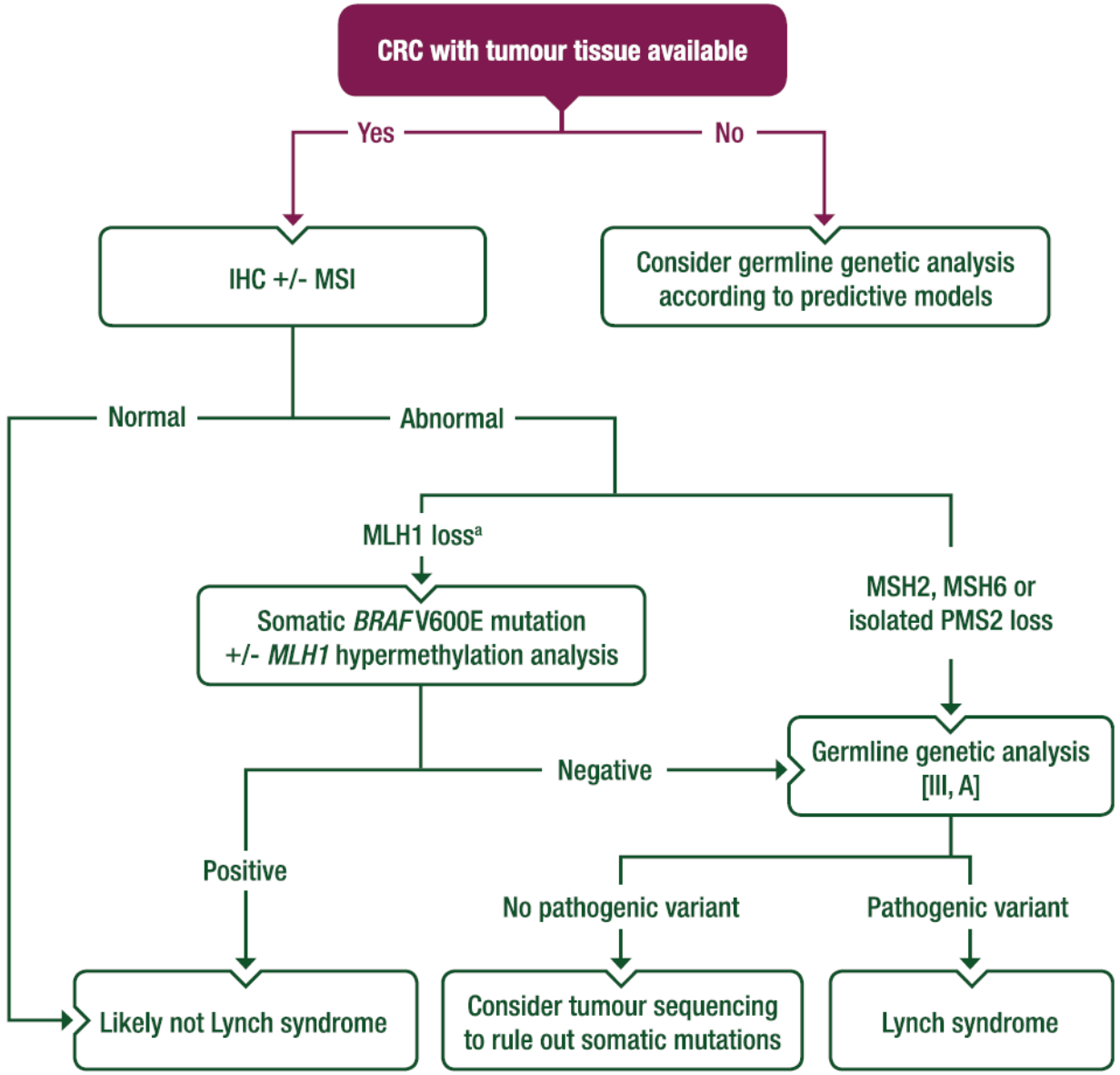


+ hyperméthylation du promoteur *MLH1*
ou mutation *BRAF* V600E

[Weissman SM, et al. J Genet Couns 2012]

Algorithme pour le diagnostic moléculaire

! *BRAF* V600E seulement pour CCR



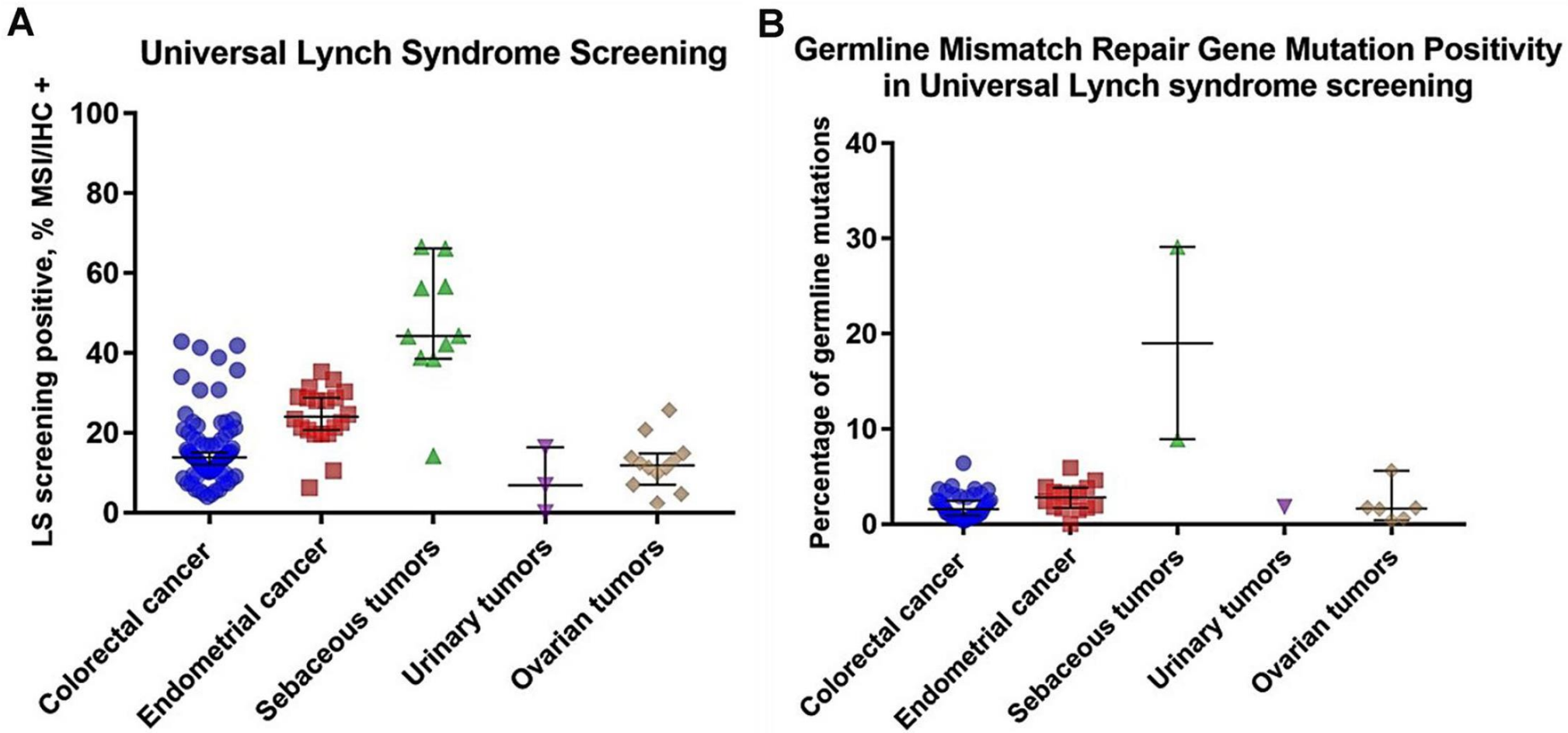
[Stjepanovic et al. Ann Oncol 2019]

Familial Cancer (2022) 21:57–67
https://doi.org/10.1007/s10689-020-00226-w

ORIGINAL ARTICLE

Comparison of universal screening in major lynch-associated tumors: a systematic review of literature

George Kunnackal John[1] · Vipin Das Villgran[2] · Christine Caufield-Noll[3] · Francis M. Giardiello[4]



Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer

Alicia Latham, MD[1]; Preethi Srinivasan, MS[1]; Yelena Kemel, ScM[1]; Jinru Shia, MD[1]; Chaitanya Bandlamudi, PhD[1]; Diana Mandelker, MD, PhD[1]; Sumit Middha, PhD[1]; Jaclyn Hechtman, MD[1]; Ahmet Zehir, MD, PhD[1]; Marianne Dubard-Gault, MD, MS[1]; Christina Tran[1]; Carolyn Stewart[1]; Margaret Sheehan, MS[1]; Alexander Penson, PhD[1]; Deborah DeLair, MD[1]; Rona Yaeger, MD[1,2]; Joseph Vijai, PhD[1]; Semanti Mukherjee, PhD[1]; Jesse Galle[1]; Mark A. Dickson, MD[1,2]; Yelena Janjigian, MD[1,2]; Eileen M. O'Reilly, MD[1,2]; Neil Segal, MD, PhD[1,2]; Leonard B. Saltz, MD[1,2]; Diane Reidy-Lagunes, MD, MS[1,2]; Anna M. Varghese, MD[1,2]; Dean Bajorin, MD[1,2]; Maria I. Carlo, MD[1,2]; Karen Cadoo, MD[1,2]; Michael F. Walsh, MD[1,2]; Martin Weiser, MD[1,2]; Julio Garcia Aguilar, MD, PhD[1,2]; David S. Klimstra, MD[1]; Luis A. Diaz Jr, MD[1,2]; Jose Baselga, MD, PhD[1,2]; Liying Zhang, MD, PhD[1]; Marc Ladanyi, MD[1]; David M. Hyman, MD[1,2]; David B. Solit, MD[1,2]; Mark E. Robson, MD[1,2]; Barry S. Taylor, PhD[1]; Kenneth Offit, MD, MPH[1]; Michael F. Berger, PhD[1,2]; and Zsofia K. Stadler, MD[1,2]

J Clin Oncol 37:286-295. © 2018

15'045 patients; 50 cancer types
MSISensor score
Lynch syndrome identified in:
- 53/326 (16.3%) of MSI-H
- 13/699 (1.9%) in MSI-indeterminate
- 37/14'020 (0.3%) in MSS

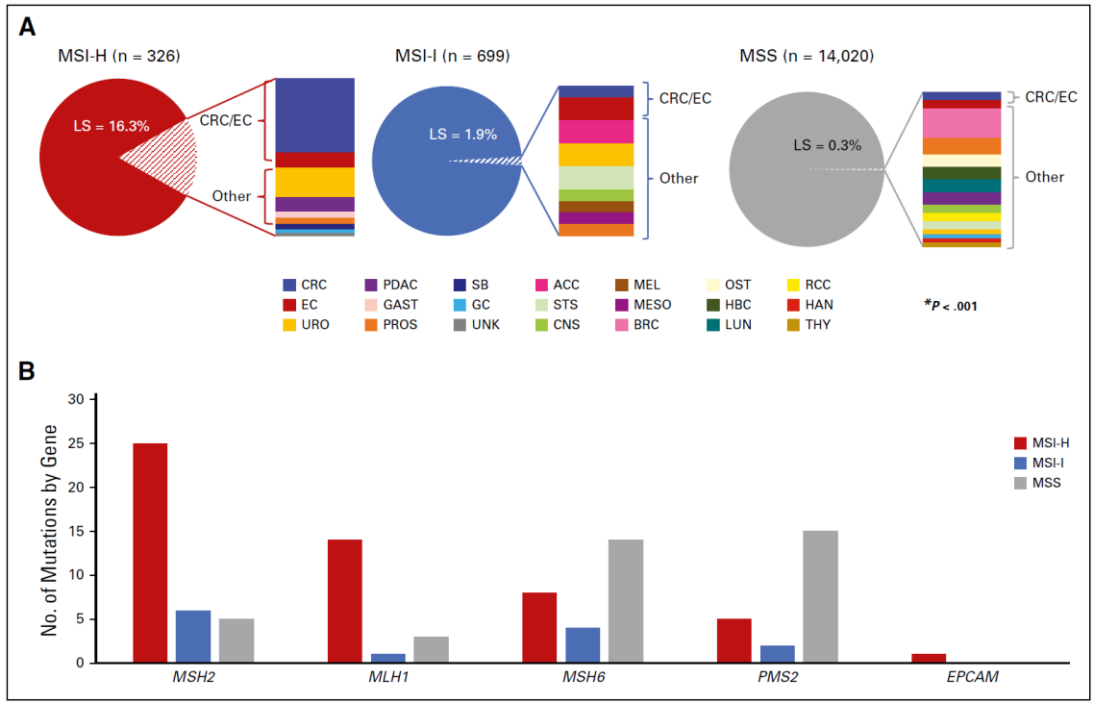
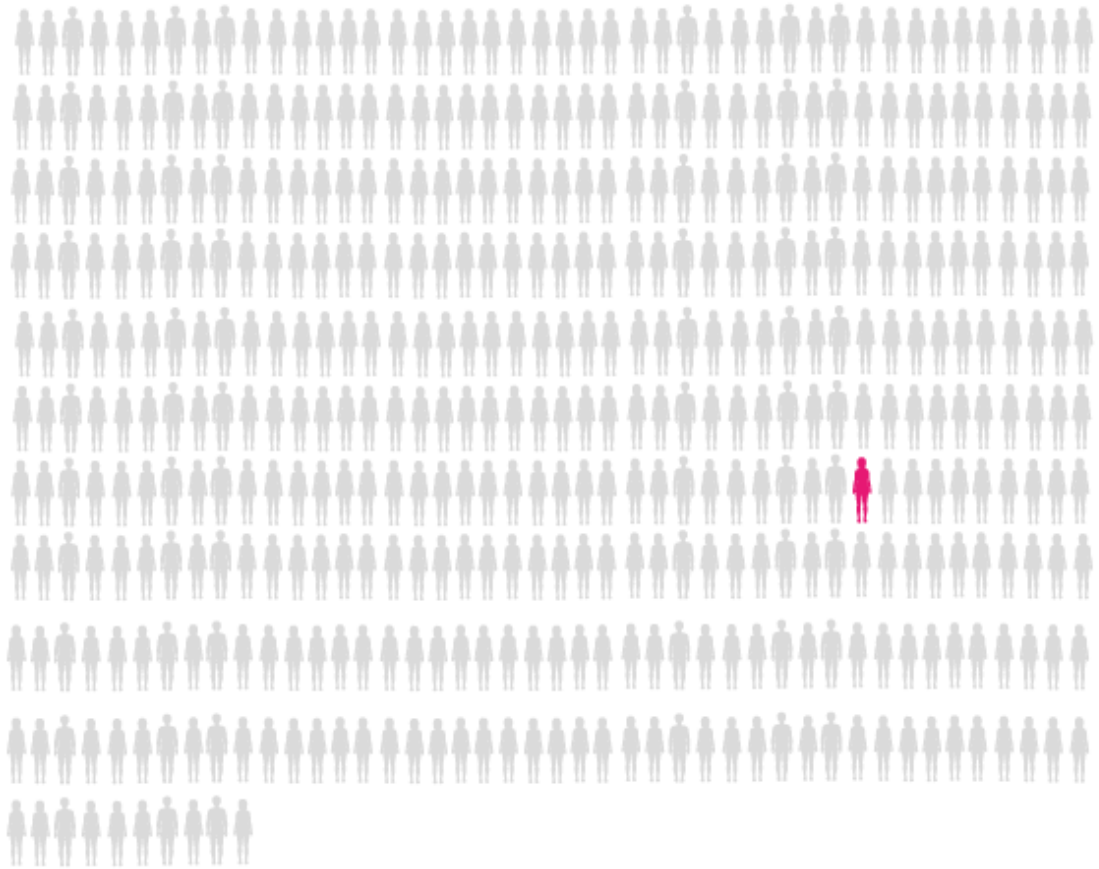


TABLE 2. Prevalence of Lynch Syndrome by Tumor Type and MSI Status

Tumor Type	Total Count	MSI-H/I	% MSI-H/I Lynch	95% CI
Colorectal	826	137	19 (26/137)	12.8 to 26.6
Endometrial	525	119	5.9 (7/119)	2.4 to 11.7
Small bowel	57	17	11.8 (2/17)	1.5 to 36.4
Gastric	211	13	15.4 (2/13)	1.9 to 45.5
Esophageal	205	16	0 (0/16)	0.0 to 20.6
Bladder/urothelial	551	32	37.5 (12/32)	21.1 to 56.3
Adrenocortical	44	19	10.5 (2/19)	1.3 to 33.1
Prostate	1,048	54	5.6 (3/54)	1.2 to 15.4
Germ cell	368	33	3 (1/33)	0.1 to 15.8
Soft tissue sarcoma	785	45	4.4 (2/45)	0.5 to 15.1
Pancreatic	824	34	14.7 (5/34)	5.0 to 31.1
Mesothelioma	165	6	1.7 (1/6)	0.4 to 64.1
CNS tumors	923	30	3.3 (1/30)	0.1 to 17.2
Ovarian	343	46	0 (0/46)	0.0 to 7.7
Lung	1,952	94	0 (0/94)	0.0 to 3.8
Renal	458	11	0 (0/11)	0.0 to 28.5
Breast	2,371	150	0 (0/150)	0.0 to 2.4
Melanoma	573	25	4 (1/25)	0.1 to 20.4
Other tumor type*	2,816	144	0 (1/144)*	0.0 to 3.8

EN PRATIQUE

Syndrome de Lynch dans la population



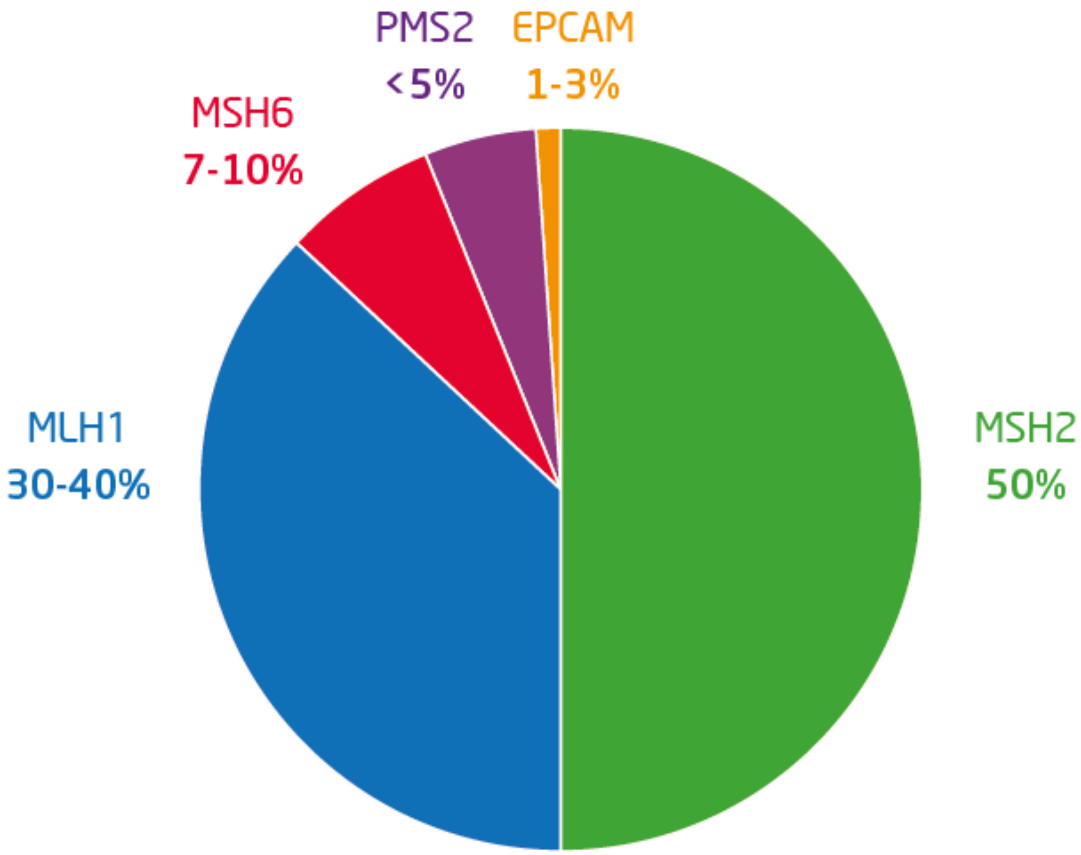
- Rare : 1:270-1:440 dans la population générale
- ~3% des patients atteints d'un cancer du colon
- ~5% des patientes atteintes d'un cancer de l'utérus
- Syndrome le plus fréquent dans les cas de tumeur colique et de l'utérus
- Transmission AD, pénétrance variable

SAKK
WE BRING PROGRESS TO CANCER CARE

Quand soupçonner une origine héréditaire?

- Âge < 50 ans, localisation droite
- Multiples cancers colorectaux
- Cancer colique et autres cancers du spectre du S. de Lynch :
  - Utérus
  - Ovaire
  - Estomac
  - Intestin grêle
  - Pancréas
  - Uretère/de la vessie
  - Etc
- Cancer de l'utérus à < 60 ans
- Instabilité micro-satellitaire établie ou perte d'expression dans les tissus tumoraux
- Plusieurs cas de tumeurs dans une famille attribuable au syndrome de Lynch

Mutations génétiques dans le Syndrome de Lynch



Mutation dans un gène de réparation de l'ADN (MLH1, MSH2/EPCAM, MSH6, PSM2)

[www.insight-group.org/]

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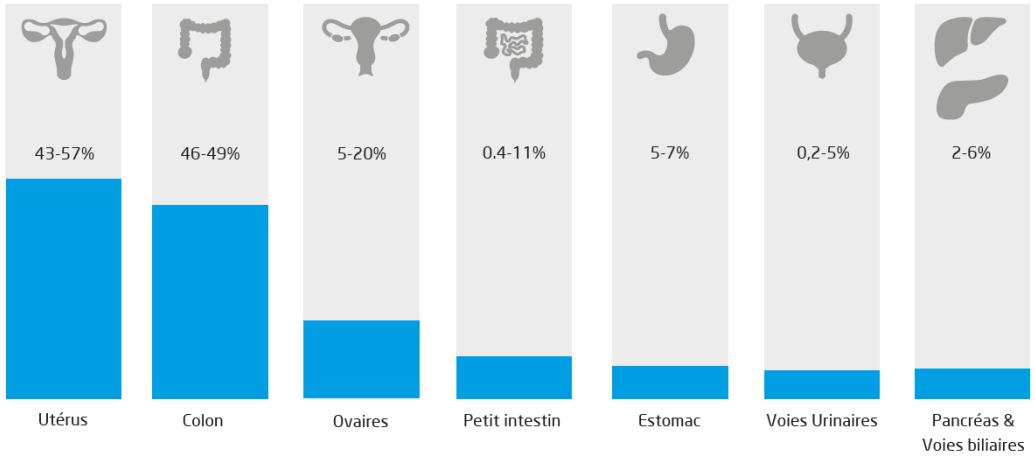
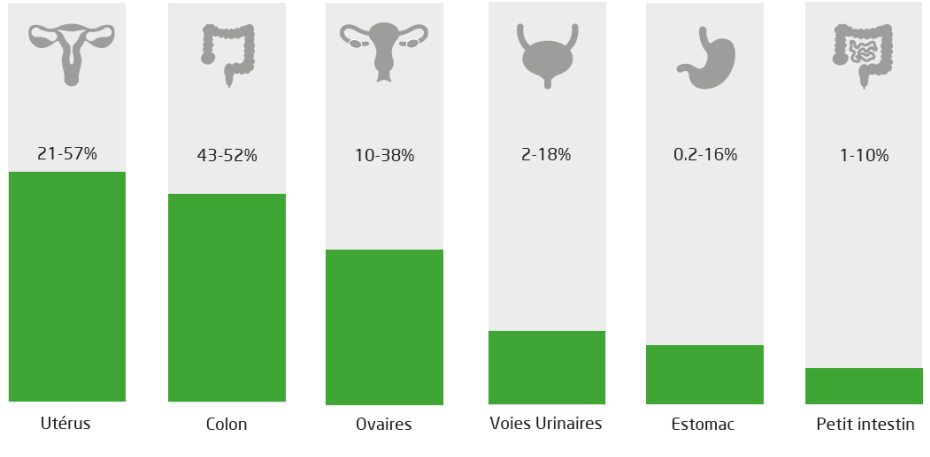
WE BRING PROGRESS TO CANCER CARE

Pénétrance (à 75 ans)

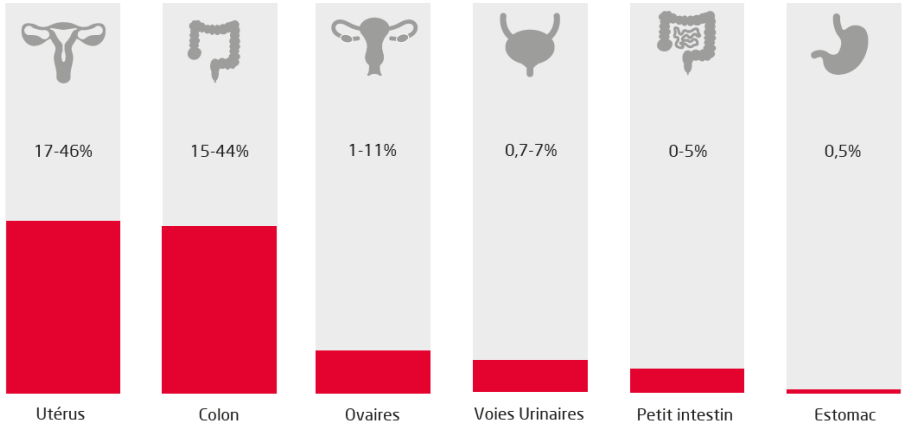
MLH1



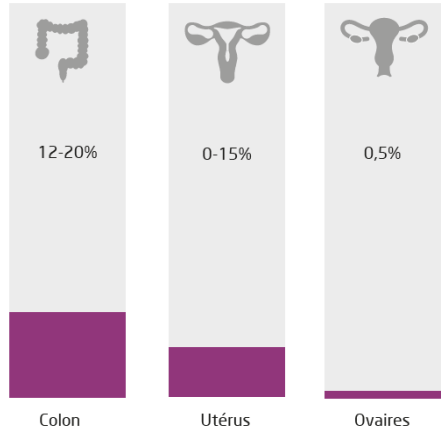
MSH2



MSH6



PMS2



[Vasen et al. J Med Genet 2007; Bonadona et al. JAMA 2011; Möller et al. Gut 2018 NCCN.org; v2.2023]

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WE BRING PROGRESS TO CANCER CARE

Calcul du risque individuel

PLSD
Prospective Lynch Syndrome Database

Prospective Lynch Syndrome Database (PLSD) - cumulative risk for cancer by age, genetic variant, and gender in carriers subject to colonoscopy

Any cancer | Carrier without previous cancer | Carrier with previous cancer | About

Calculation of cumulative risk for cancer in selected organ(s) irrespective of cancer(s) in any other organ

Organ

Any organ

Genetic variant

path_MLH1

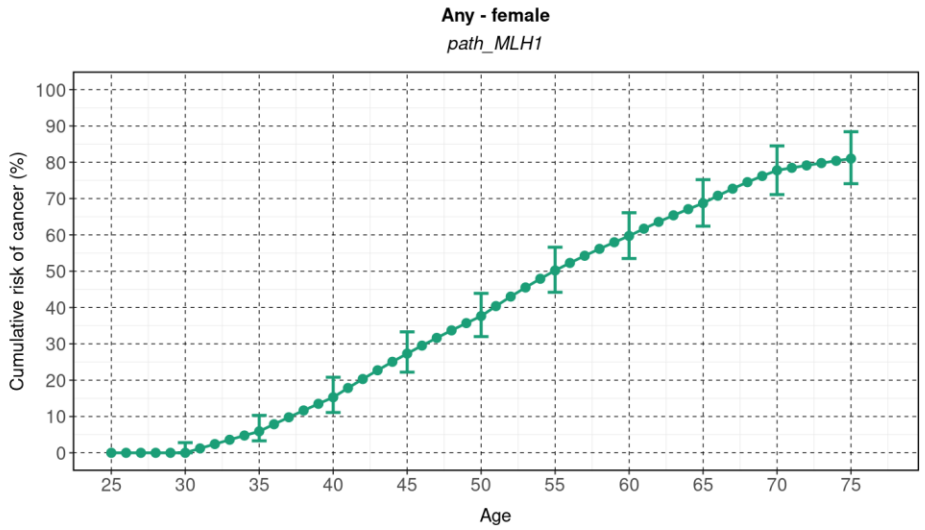
Current age

25 — 70

25 30 35 40 45 50 55 60 65 70

Gender

Female



Age	Risk (%)	95% Confidence interval
25	0.00	[0 - 0]
40	15.30	[11.1 - 20.8]
50	37.70	[32 - 43.9]
60	59.70	[53.5 - 66.1]
70	77.80	[71.1 - 84.5]
75	81.00	[74.1 - 88.4]

[www.plsd.eu]

Cadre légal en Suisse

Chapitre 3 Mesures de prévention

Art. 12*d*[132] Mesures en vue du dépistage précoce de maladies chez certains groupes à risques

[1] L'assurance prend en charge les coûts des mesures suivantes en vue du dépistage précoce de maladies chez certains groupes à risques aux conditions ci-après:

- dès quel âge ?
- intervalle ?

b.	Coloscopie	En cas de cancer du côlon familial (au moins trois parents du premier degré atteints ou un avant l'âge de 30 ans).
f.[141]	Conseil génétique, pose d'indication pour des analyses génétiques et prescription des analyses de laboratoire associées conformément à la liste des analyses (LA) en cas de suspicion de prédisposition à un cancer héréditaire	Chez les patients et leurs parents au premier degré présentant: – un syndrome héréditaire de cancer du sein ou de l'ovaire – une polypose colique ou une forme atténuée de polypose colique – un syndrome héréditaire de cancer colorectal sans polypose (syndrome HNPCC, hereditary non polypotic colon cancer) – un rétinoblastome.

Liste des Analyses

- *APC*
- *MLH1, MSH2, MSH6, PMS2*

SURVEILLANCE & PRÉVENTION

Table 2. LS surveillance recommendations

Site	Technique	Age (years)	Interval (years)
Colorectum	Colonoscopy	• *MLH1/MSH2*: 25[a,b] • *MSH6/PMS2*: 35	1–2
Uterus	TV US Endometrial biopsy	30–35	1
Ovaries	CA 125 + TV US	30–35	1
Stomach	UGI endoscopy[c] Consider testing *Helicobacter pylori*	30–35	1–3
Other LS-associated cancers	None[d]		

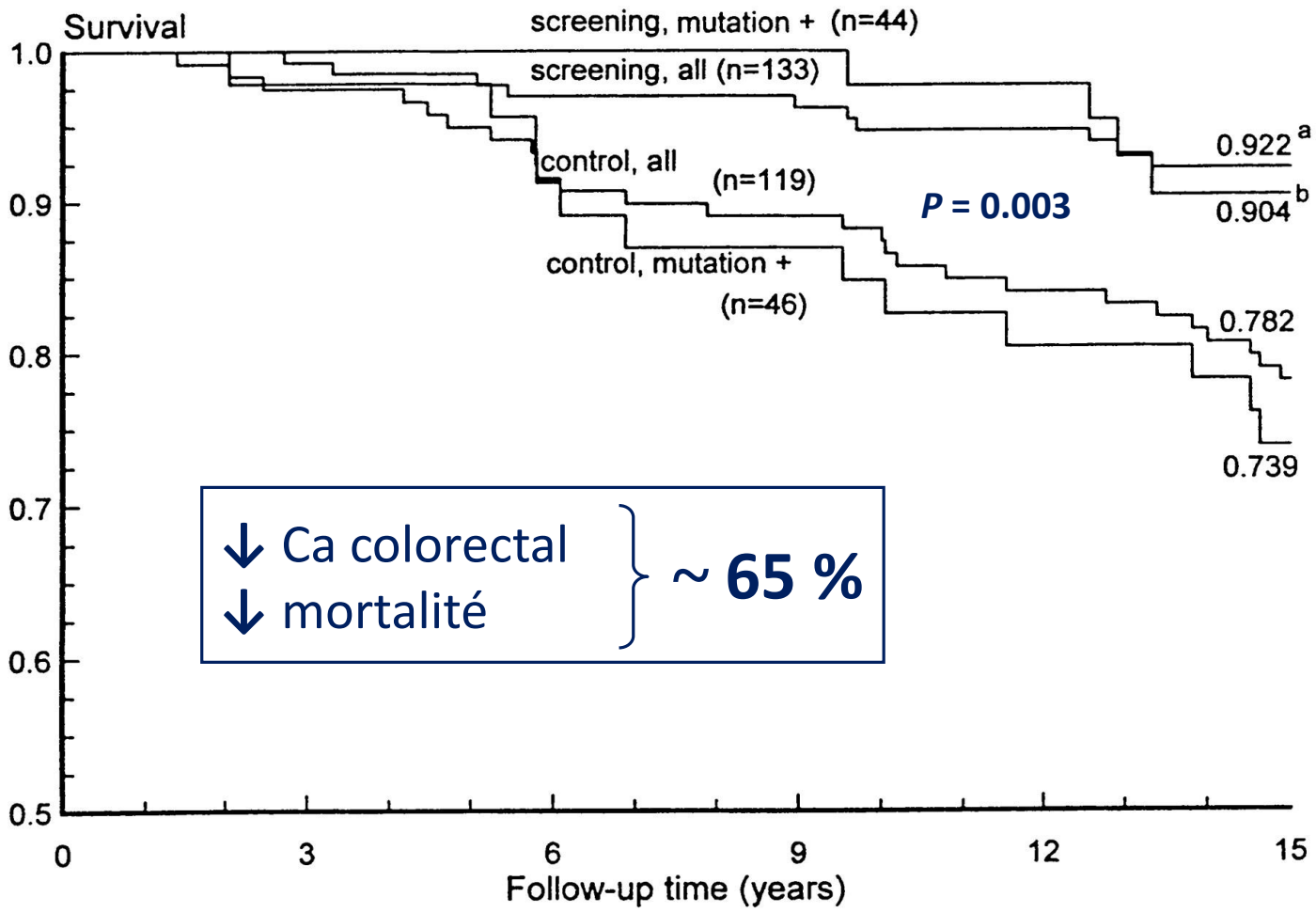
[a]Or 5 years before the earliest CRC, if diagnosis <25 years.
[b]Consider later age for *MSH6* carriers.
[c]Consider in high-incidence countries or family history of gastric cancer.
[d]Consider pancreatic/urinary tract cancer surveillance if family history.
CA 125, cancer antigen 125; CRC, colorectal cancer; LS, Lynch syndrome; TV, transvaginal; UGI, upper gastrointestinal; US, ultrasound.

Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

N. Stjepanovic[1], L. Moreira[2], F. Carneiro[3,4,5,6], F. Balaguer[2], A. Cervantes[7], J. Balmaña[1] & E. Martinelli[8], on behalf of the ESMO Guidelines Committee*

Annals of Oncology 30: 1558–1571, 2019

Impact de la surveillance par coloscopie



[Järvinen et al. Gastroentology 2000]

Prophylactic Surgery to Reduce the Risk of Gynecologic Cancers in the Lynch Syndrome

Kathleen M. Schmeler, M.D., Henry T. Lynch, M.D., Lee-may Chen, M.D., Mark F. Munsell, M.S., Pamela T. Soliman, M.D., Mary Beth Clark, M.S.W., Molly S. Daniels, M.S., Kristin G. White, B.S., Stephanie G. Boyd-Rogers, R.N., Peggy G. Conrad, M.S., Kathleen Y. Yang, M.D., Mary M. Rubin, Ph.D., Charlotte C. Sun, Dr.P.H., Brian M. Slomovitz, M.D., David M. Gershenson, M.D., and Karen H. Lu, M.D.

N Engl J Med 2006;354:261-9

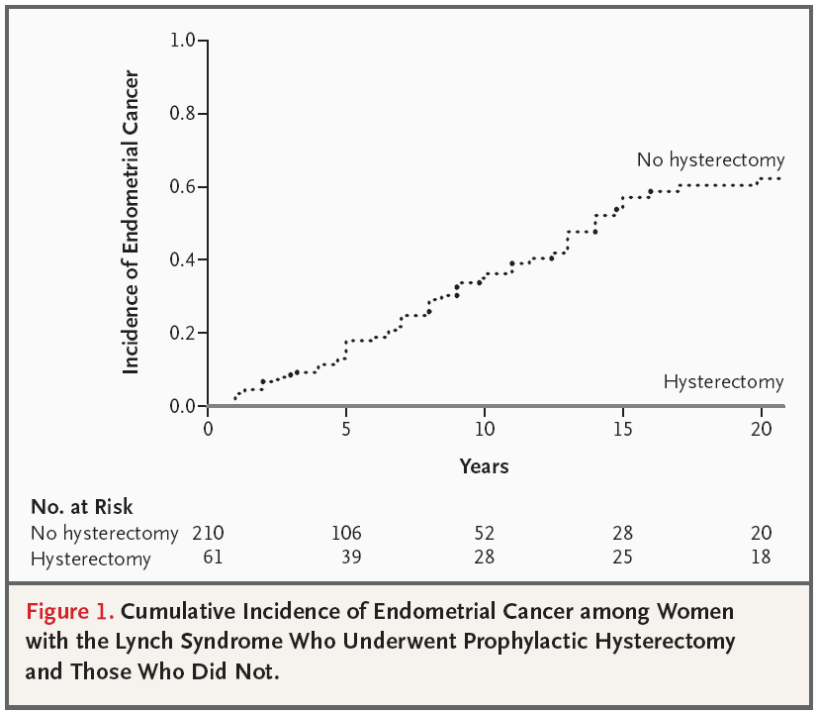


Figure 1. Cumulative Incidence of Endometrial Cancer among Women with the Lynch Syndrome Who Underwent Prophylactic Hysterectomy and Those Who Did Not.

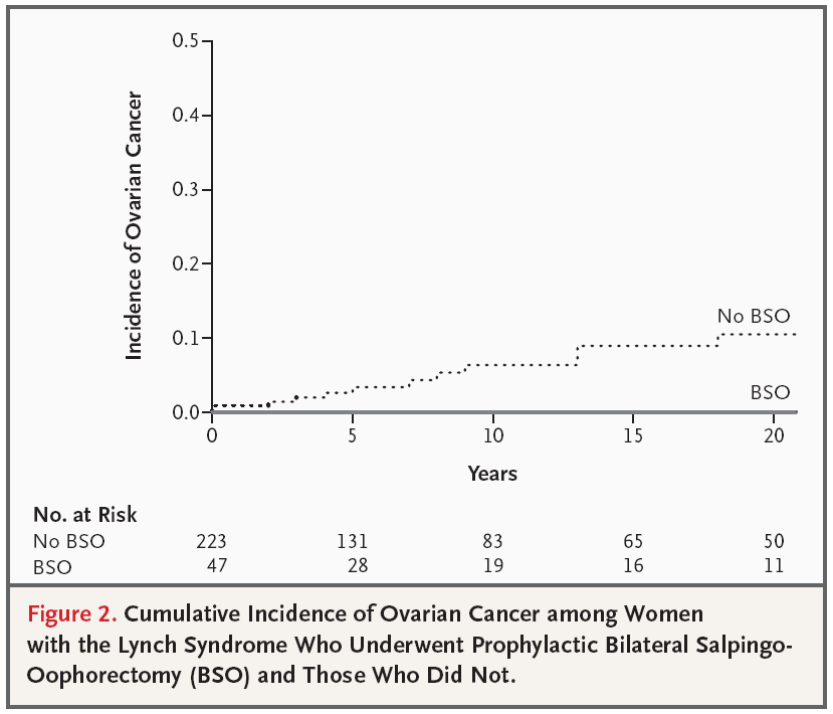


Figure 2. Cumulative Incidence of Ovarian Cancer among Women with the Lynch Syndrome Who Underwent Prophylactic Bilateral Salpingo-Oophorectomy (BSO) and Those Who Did Not.

HRT : option de prévention à discuter en péri-ménopause

Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial

John Burn, Harsh Sheth, Faye Elliott*, Lynn Reed, Finlay Macrae, Jukka-Pekka Mecklin, Gabriela Möslein, Fiona E McRonald, Lucio Bertario, D Gareth Evans, Anne-Marie Gerdes, Judy W C Ho, Annika Lindblom, Patrick J Morrison, Jem Rashbass, Raj Ramesar, Toni Seppälä, Huw J W Thomas, Kirsi Pylvänäinen, Gillian M Borthwick, John C Mathers, D Timothy Bishop, on behalf of the CAPP2 Investigators*

Lancet 2020; 395: 1855–63

CAPP2 Trial (1999-2005)

- 861 porteurs de mutations MMR
- 43 centres ; étude randomisée double aveugle internationale
- Aspirine 600 mg ± amidon ± placebo (*2x2 factorial design*) pour 4 ans
- Age moyen: 45 ans
- F-up moyen: ≥ 10 ans

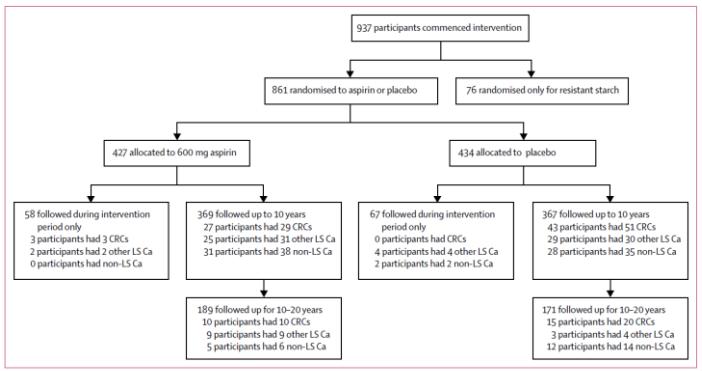


Figure 1: Trial profile

	Hazard ratio† (95% CI)	p value	Incidence rate ratio‡ (95% CI)	p value
Colorectal cancer				
Intention-to-treat analysis (n=861, 98 events for hazard ratio analysis)				
Aspirin *vs* placebo	0·65 (0·43–0·97)	0·035	0·58 (0·39–0·87)	0·0085
Per-protocol analysis§ (n=509, 67 events)				
≥2 years' placebo	1·0	..	1·0	..
≥2 years' aspirin	0·56 (0·34–0·91)	0·019	0·50 (0·31–0·82)	0·0057
Cumulative aspirin dose¶ (n=861, 98 events)				
Units of 100 aspirin	0·98 (0·96–1·00)	0·079	0·98 (0·96–1·00)	0·032
Non-colorectal Lynch syndrome cancers				
Intention-to-treat analysis (n=861, 72 events)				
Aspirin *vs* placebo	0·94 (0·59–1·50)	0·81	1·05 (0·65–1·69)	0·84
Per-protocol analysis§ (n=509, 46 events)				
≥2 years' placebo	1·0	..	1·0	..
≥2 years' aspirin	0·75 (0·42–1·34)	0·33	0·87 (0·48–1·61)	0·67
Cumulative aspirin dose¶ (n=861, 72 events)				
Units of 100 aspirin	0·98 (0·96–1·01)	0·20	0·99 (0·97–1·02)	0·50
All Lynch syndrome cancers				
Intention-to-treat analysis (n=861, 163 events)				
Aspirin *vs* placebo	0·76 (0·56–1·03)	0·081	0·75 (0·56–1·02)	0·065
Per-protocol analysis§ (n=509, 107 events)				
≥2 years' placebo	1·0	..	1·0	..
≥2 years' aspirin	0·63 (0·43–0·92)	0·018	0·65 (0·44–0·94)	0·022
Cumulative aspirin dose¶ (n=861, 163 events)				
Units of 100 aspirin	0·98 (0·97–1·00)	0·033	0·98 (0·97–1·00)	0·040
All non-Lynch syndrome cancers				
Intention-to-treat analysis (n=861, 78 events)				
Aspirin *vs* placebo	0·81 (0·52–1·26)	0·34	0·79 (0·49–1·28)	0·34
Per-protocol analysis§ (n=509, 56 events)				
≥2 years' placebo	1·0	..	1·0	..
≥2 years' aspirin	0·81 (0·48–1·37)	0·43	0·71 (0·41–1·22)	0·21
Cumulative aspirin dose¶ (n=861, 78 events)				
Units of 100 aspirin	0·99 (0·97–1·01)	0·43	0·99 (0·96–1·01)	0·32

*Adjusted for age and gender in all participants up to 10 years and up to 20 years in England, Finland, and Wales, randomly assigned to aspirin or placebo. †Adjusted for age at consent and gender. ‡Incidence rate ratio from negative binomial regression adjusted for age at consent and gender. §The threshold for 2 years' intervention was consumption of more than 1400 aspirin tablets; rounded from a 2-year total of 1461 to allow for early scheduling of the exit colonoscopy or occasional missed dosage. ¶Units of 100 aspirin=total number of aspirin taken divided by 100.

Table 2: Cox proportional hazards and negative binomial regression analyses of cancer incidence*

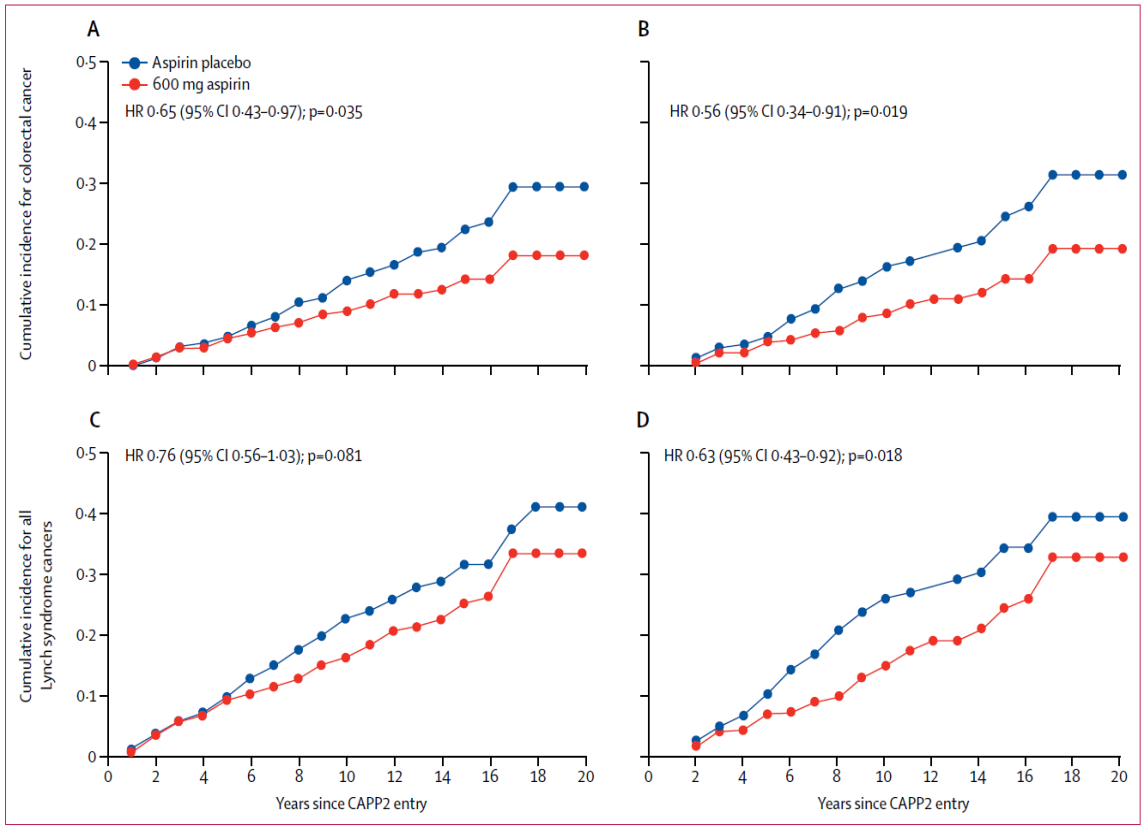


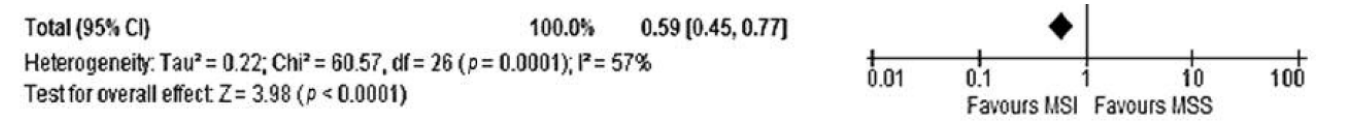
Figure 2: Time to first colorectal cancer and time to any Lynch syndrome cancer in all CAPP2 study participants followed up for 10 years and for 20 years in England, Finland, and Wales

PRONOSTIC & TRAITEMENT

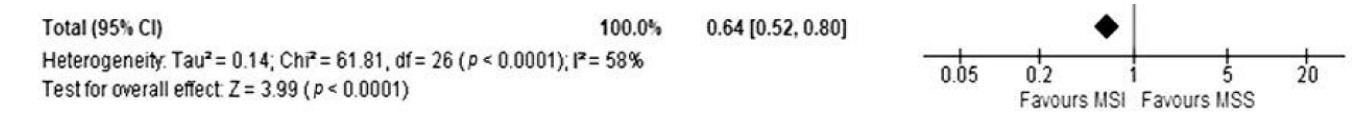
- Meilleur pronostic du CCR comparé au cas sporadiques, en particulier pour les stades précoces

Microsatellite Instability and Survival in Stage II Colorectal Cancer: A Systematic Review and Meta-analysis

FAUSTO PETRELLI[1], MICHELE GHIDINI[2], MARY CABIDDU[1], EZIO PEZZICA[3], DANIELA CORTI[3], LUCA TURATI[4], ANTONIO COSTANZO[4], ANTONIO VARRICCHIO[4], ANTONIO GHIDINI[5], SANDRO BARNI[1] and GIANLUCA TOMASELLO[6]



Meta-analysis of disease-free survival for MSI vs. MSS colorectal cancer.

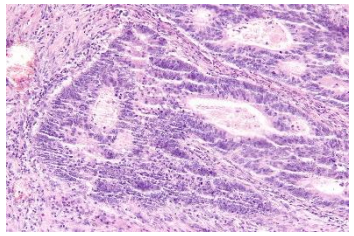


Meta-analysis of overall survival for MSI vs. MSS colorectal cancer.

- Pas de bénéfice du 5-FU en adjuvant pour les stades II/III ; bénéfice de l'oxaliplatine (?)

- Moins bonne réponse à la chimiothérapie pour les CCR avancé ou en rechute ou lors de la chimiothérapie néoadjuvante [Cercek et al. Clin Cancer Res 2020]

Cancers avec MSI : immunothérapie

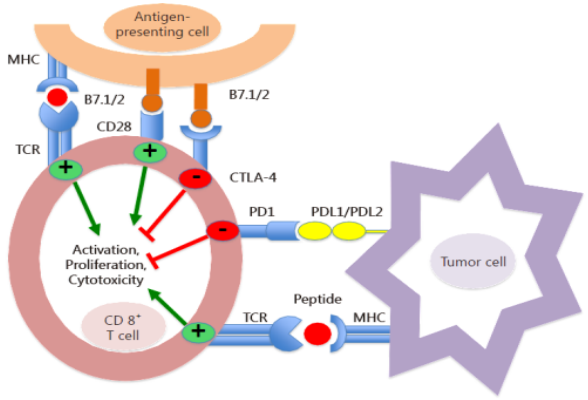


Tumor-infiltrating lymphocytes
(Bethesda Guidelines)

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

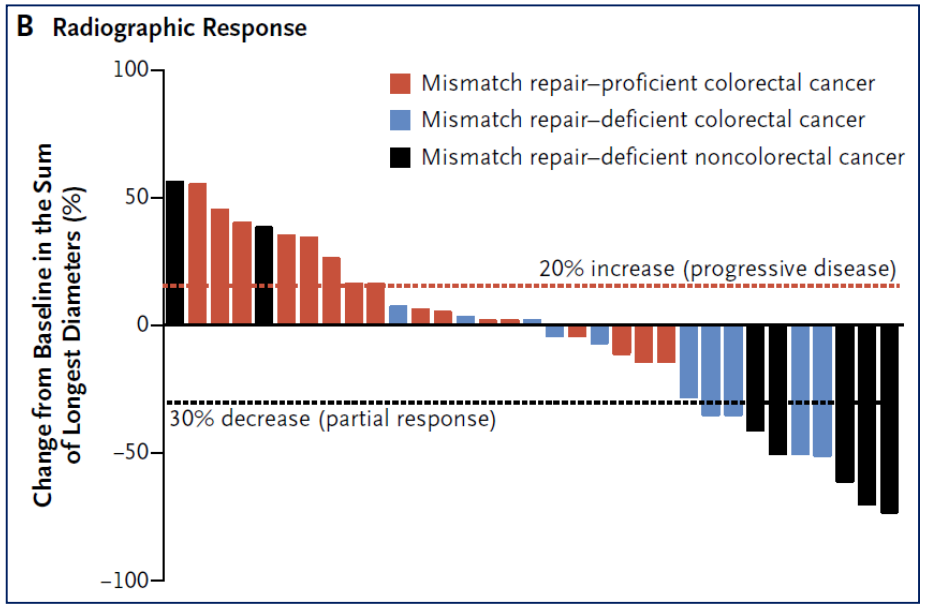
D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, 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.

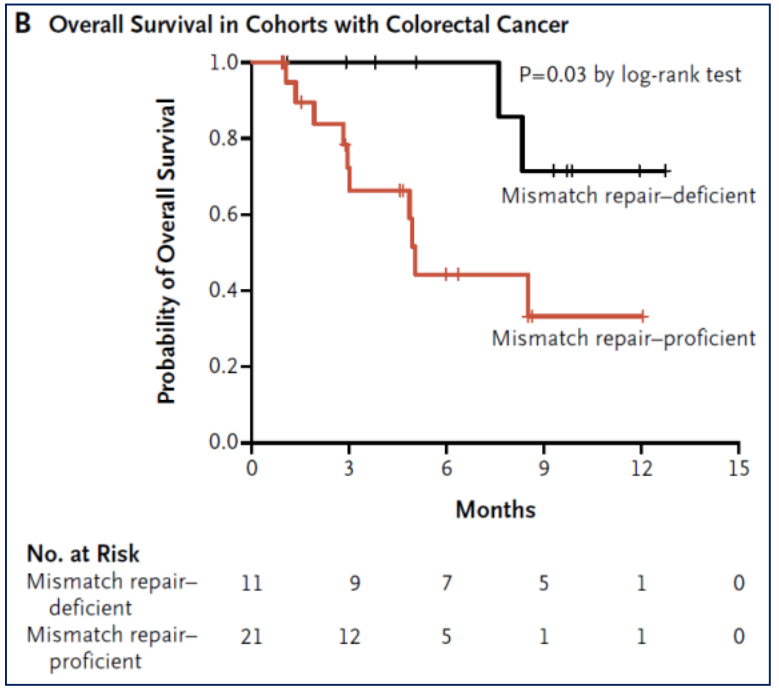
N ENGL J MED 372;26 NEJM.ORG JUNE 25, 2015



[Santarpia et al. Cancer Biol Med 2015]

Phase 2
41 patients with progressive M+ carcinoma dMMR or pMMR
Pembrolizumab (anti-PD1)





Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*

N ENGL J MED 383;23 NEJM.ORG DECEMBER 3, 2020

Phase 3; 307 patients; M+ MSI-H-dMMR CRC; not previously treated;
pembrolizumab vs. chemotherapy (5FU-based ± bevacizumab or caetuximab)

Table 1. Demographic and Patient Characteristics at Baseline.*

Characteristic	Pembrolizumab (N=153)	Chemotherapy† (N=154)
Median age (range) — yr	63.0 (24–93)	62.5 (26–90)
≥65 years of age — no. (%)	73 (48)	71 (46)
Male sex — no. (%)	71 (46)	82 (53)
ECOG performance-status score of 0 — no. (%)‡	75 (49)	84 (55)
MSI-H§ — no. (%)	153 (100)	153 (99)
Region — no. (%)		
Asia	22 (14)	26 (17)
Western Europe or North America	109 (71)	113 (73)
Rest of world	22 (14)	15 (10)
Primary tumor location — no. (%)		
Right side	102 (67)	107 (69)
Left side	46 (30)	42 (27)
Other site or site missing¶	5 (3)	5 (3)
Stage — no. (%)		
Recurrent metachronous‖	80 (52)	74 (48)
Newly diagnosed with metastatic disease	73 (48)	80 (52)
Prior systemic therapy — no. (%)		
Adjuvant	33 (22)	37 (24)
Neoadjuvant with or without adjuvant systemic therapy	5 (3)	8 (5)
None	115 (75)	109 (71)
Mutation status — no. (%)		
BRAF, *KRAS*, *NRAS* all wild type	34 (22)	35 (23)
KRAS or *NRAS* mutant	33 (22)	41 (27)**
$BRAF^{V600E}$ mutant	34 (22)	43 (28)**
Could not be evaluated for *BRAF*, *KRAS*, or *NRAS*††	52 (34)	38 (25)

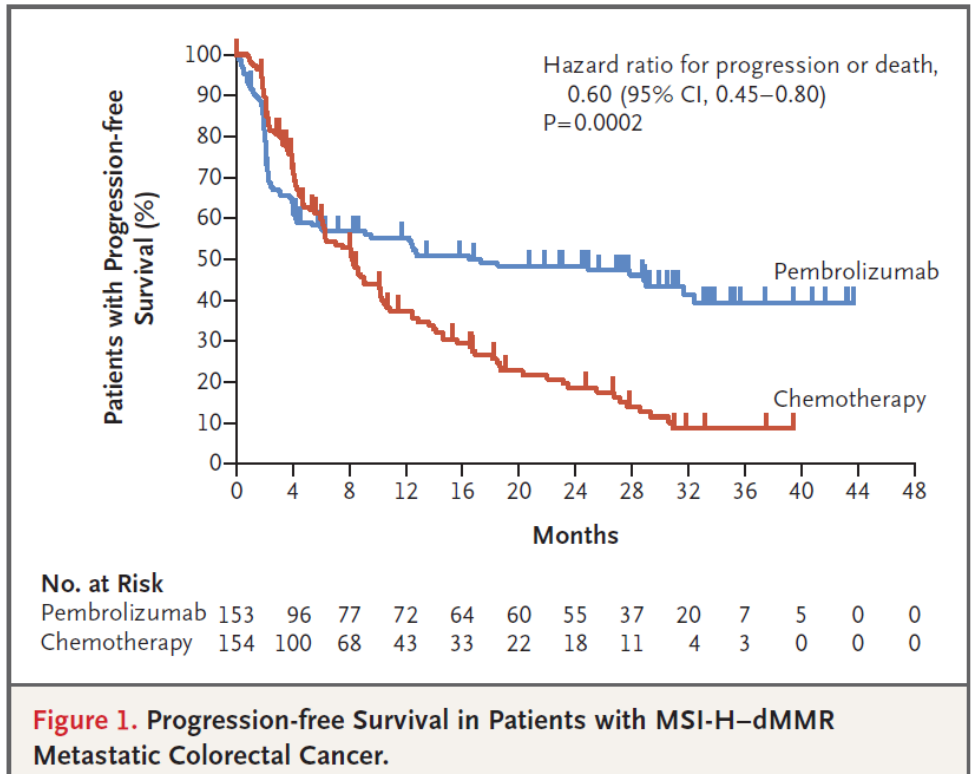


Figure 1. Progression-free Survival in Patients with MSI-H–dMMR Metastatic Colorectal Cancer.

+ fewer ttt-related adverse events (grade ≥3)

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

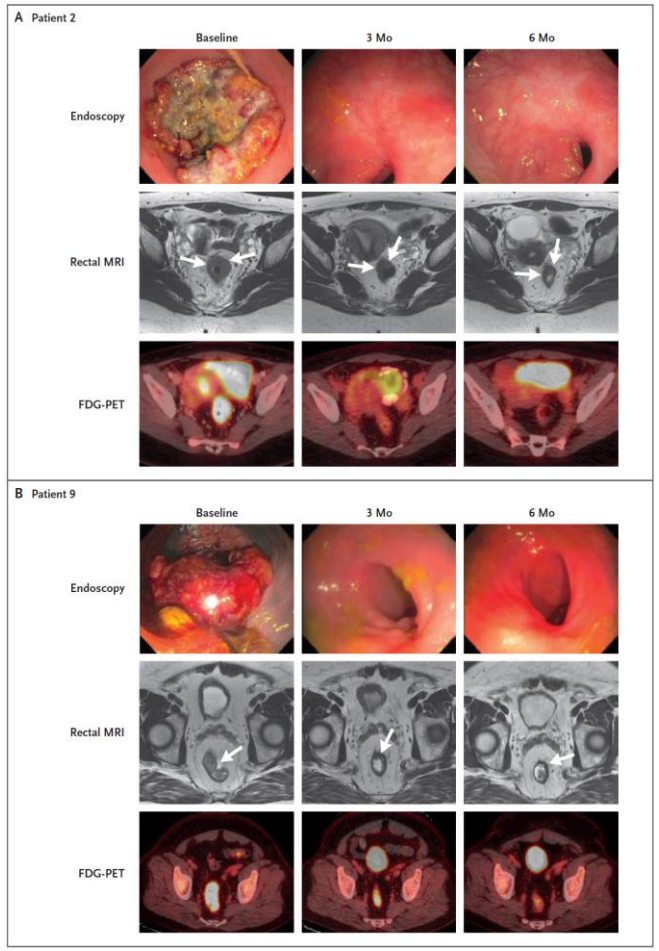
A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty,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

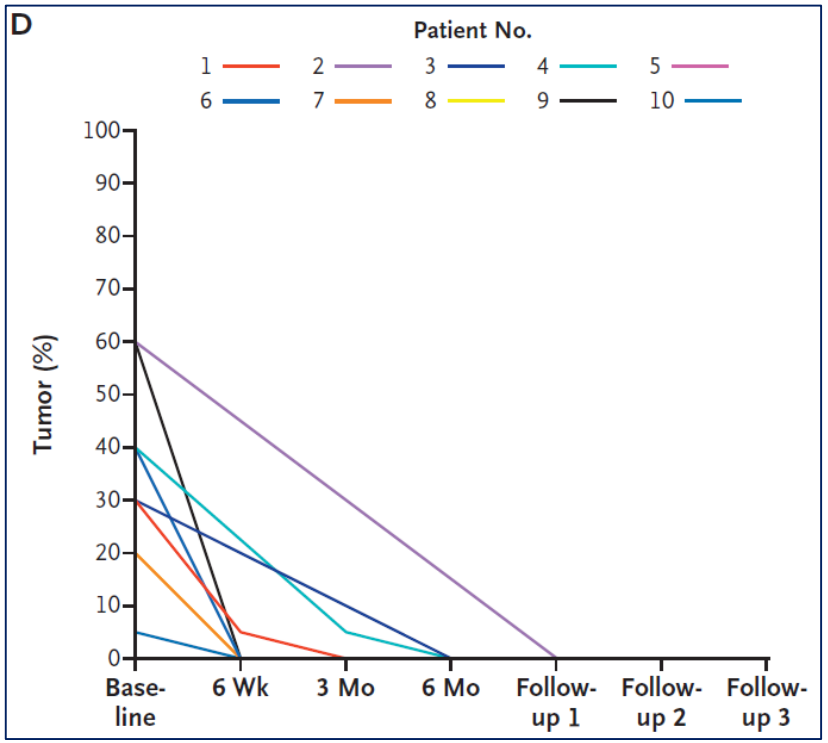
N ENGL J MED 386;25 NEJM.ORG JUNE 23, 2022

Prospective phase 2
Dostarlimab (anti-PD1)
Neoadjuvant ttt (6 months)
dMMR stage II-III rectal adenoCa
12 patients (with 6 m ttt)

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.

Characteristic	Value
Patients enrolled — no. (%)	16 (100)
Female sex — no. (%)	10 (62)
Median age (range) — yr	54 (26–78)
Race — no. (%)*	
White	11 (69)
Asian	3 (19)
Black	2 (12)
Hispanic or Latinx ethnic group — no. (%)*	1 (6)
ECOG performance-status score — no. (%)†	
0	12 (75)
1	4 (25)
Tumor stage — no. (%)	
T1 or T2	4 (25)
T3	9 (56)
T4	3 (19)
Nodal status — no. (%)	
Positive	15 (94)
Negative	1 (6)
Median distance of tumor from anal verge (range) — cm	5 (0.9–8.9)





12/12 clinical complete response
No chemoradiotherapy or surgery
F-up: 6-25 months
No adverse events grade ≥3

CMMRD SYNDROME

Constitutional MMR Deficiency (CMMRD)

- 1ère description en 1999 (Ricciardone et al. Cancer Res 1999 ; Wang et al. Cancer Res 1999)
- Porteurs de mutations bi-alléliques sont **viables** (dévt normal)
- Dans l'enfance :
  - gliomes et PNET
  - leucémies/lymphomes
  - polypose gastro-intestinale avec cancers gastro-intestinaux précoces
  - phénotype NF1 (taches café au lait,…)
- Consanguinité fréquente
- Perte d'expression dans le tissu N; phénotype « ultramutator »
- **60% des cas : *PMS2***

[Felton *et al*., Clin Genet 2007; Wimmer *et al*., Hum Genet 2008; Aronson et al. J Med Genet 2022; C4CMMRD Consortium]

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Survival Benefit for Individuals With Constitutional Mismatch Repair Deficiency Undergoing Surveillance

J Clin Oncol 39:2779-2790. © 2021

Table 2 Surveillance protocols for patients with CMMRD

Cancer site	Screening	US Task Force (Durno *et al*[18])	C4CMMRD (Vasen *et al*[2])	AACR (Tabori *et al*[17])
All tumours	Education	Educate on signs/symptoms associated with CMMRD-associated malignancies		
	Clinical examination		Every 6 months from birth	Every 6 months from diagnosis
	WBMRI			Annually from age 6
Brain tumours	Brain MRI	Every 6 months from age 2 (optional: U/S at birth)	Every 6–12 months from age 2	Every 6 months from diagnosis
Digestive tumours	Ileocolonoscopy	Annually from age 6	Annually from age 8	Annually from age 6
	OGD, videocapsule	Annually from age 8	Annually from age 10	Annually from age 8
Leukaemias	Blood count	Every 6 months from age 1	Every 6 months from age 1	Every 6 months (optional) from birth
Lymphomas	Abdominal ultrasound		Every 6 months (optional) from age 1	Every 6 months (optional) from age 1
Gynaecological	Gynaecological examination, transvaginal U/S, pipelle curettage	Annually from age 20	Annually from age 20	Annually from age 20
Urological	Urine cytology, dipstick	Annually from age 10	Annually from age 20	Annually from age 20

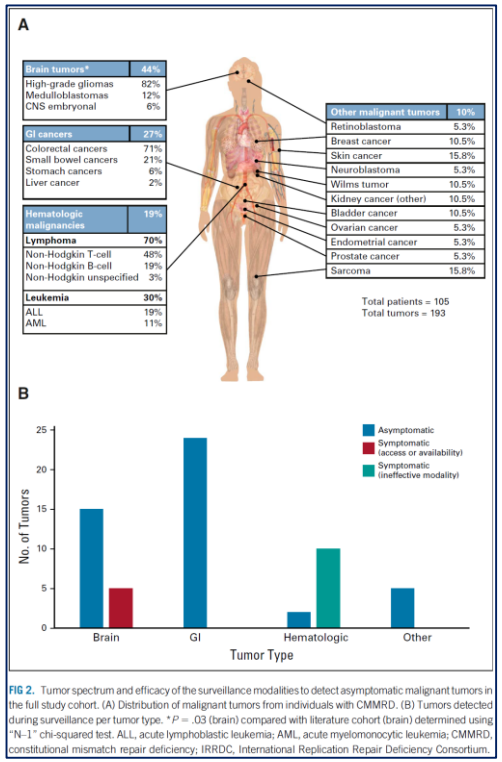
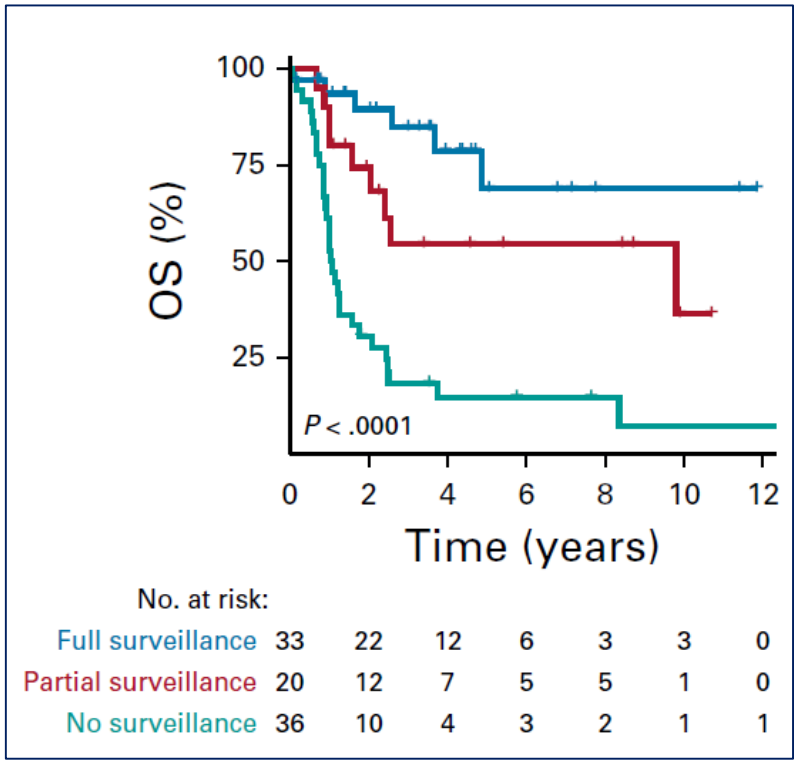


FIG 2. Tumor spectrum and efficacy of the surveillance modalities to detect asymptomatic malignant tumors in the full study cohort. (A) Distribution of malignant tumors from individuals with CMMRD. (B) Tumors detected during surveillance per tumor type. *$P = .03$ (brain) compared with literature cohort (brain) determined using "N−1" chi-squared test. ALL, acute lymphoblastic leukemia; AML, acute myelomonocytic leukemia; CMMRD, constitutional mismatch repair deficiency; IRRDC, International Replication Repair Deficiency Consortium.



PERSPECTIVES & CONCLUSION

BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-019-0462-y
nature medicine

Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer

Jakob Nikolas Kather[1,2,3,4,5*], Alexander T. Pearson[4], Niels Halama[2,5,6], Dirk Jäger[2,3,5], Jeremias Krause[1], Sven H. Loosen[1], Alexander Marx[7], Peter Boor[8], Frank Tacke[9], Ulf Peter Neumann[10], Heike I. Grabsch[11,12], Takaki Yoshikawa[13,14], Hermann Brenner[2,15,16], Jenny Chang-Claude[17,18], Michael Hoffmeister[15], Christian Trautwein[1] and Tom Luedde[1*]

NATURE MEDICINE | VOL 25 | JULY 2019 | 1054–1056 |

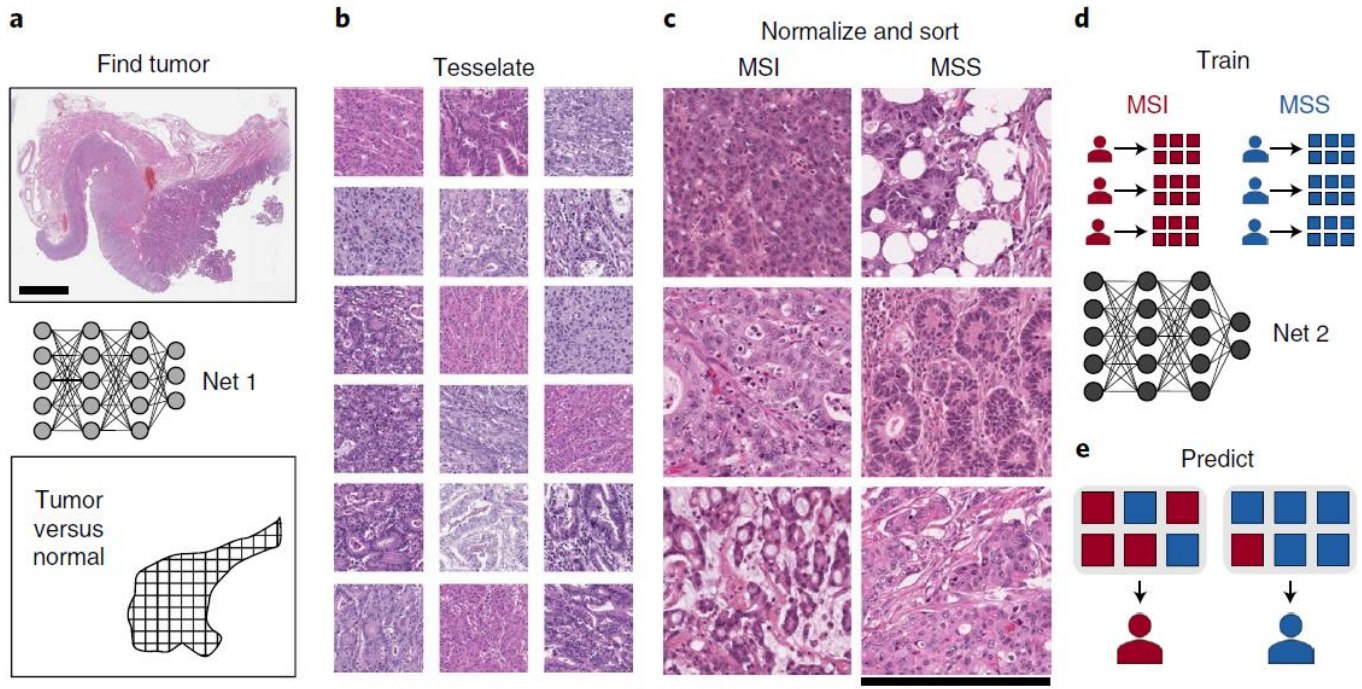


Fig. 1 | Tumor detection and MSI prediction in H&E histology. a, A convolutional neural network was trained as a tumor detector for STAD and CRC. Scale bar, 4 mm. **b**,**c**, Tumor regions were cut into square tiles (**b**), which were color-normalized and sorted into MSI and MSS (**c**). Scale bar, 256 µm. **d**, Another network was trained to classify MSI versus MSS. **e**, This automatic pipeline was applied to held-out patient sets.

Constitutional *MLH1* Methylation Is a Major Contributor to Mismatch Repair–Deficient, *MLH1*-Methylated Colorectal Cancer in Patients Aged 55 Years and Younger

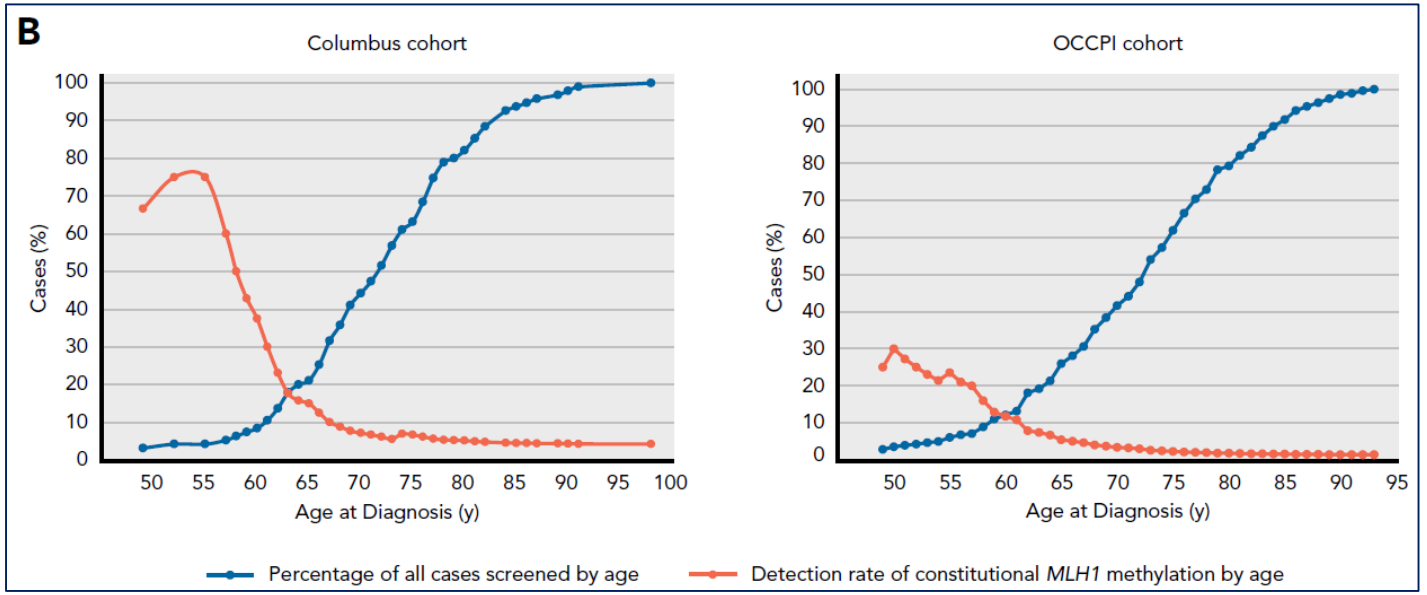
Megan P. Hitchins, PhD[1,2]; Estela Dámaso, PhD[2,3]; Rocio Alvarez, MS[1]; Lisa Zhou, MS[1]; Yajing Hu, PhD[2]; Marcio A. Diniz, PhD[4]; Marta Pineda, PhD[3,5]; Gabriel Capella, MD, PhD[3,5]; Rachel Pearlman, MS, CGC[6,7]; and Heather Hampel, MS, CGC[6,7,8]

J Natl Compr Canc Netw 2023;21(7):743–752.e11

- Retrospective population-based study; CRC with MMRd, *MLH1* methylated tumors
- Pyrosequencing and RT methylation-specific PCR; confirmation by bisulfite sequencing
- Constitutional *MLH1* methylation: 4/95 (4%) in Columbus cases and in 4/281 in OCCPI cases, 3 with low-level mosaic methylation

Table 1. Demographic and Clinicopathologic Features of CRC Cases With Constitutional *MLH1* Methylation Identified as Likely Cause for Their MMRd, *MLH1*-Methylated Tumor

Identifier	Sex	Race	Cancer History	Age at Diagnosis	FH	MLH1 IHC	MSI-H	*BRAF* V600E	Constitutional *MLH1* Methylation Levels: Pyrosequencing, qMSP (PMR), Clonal bis-seq
Columbus-area HNPCC study cohort									
Columbus-1	M	Black	Ascending colon	34 y	Neg	Absent	Pos	N/T	3.6%, 1.5%, low-level mosaicism (~1% alleles methylated)
Columbus-2	F	White	Splenic flexure	38 y	Neg	Absent	Pos	WT	27.4%, 13.8%, mosaic (~9% alleles methylated)
Columbus-6	M	White	Cecum, synchronous	52 y	Neg	Absent	Pos	N/T	47.6%, 42.9%, hemiallelic (~50% alleles methylated)
Columbus-65	M	White	Ascending colon	74 y	Pos	Absent	Pos	N/T	3.2%, 1.2%, monoallelic and mosaic (methylation on ~11% of "A" alleles at heterozygous c.-93G>A SNP)
OCCPI study cohort									
OCCPI-1	M	White	CRC unspecified	20 y	Neg	Absent	Pos	WT	4.2%, 1.6%, monoallelic and mosaic (methylation on ~20% "G" alleles at heterozygous c.-93G>A SNP)
OCCPI-2	F	White	Ascending colon	34 y	Neg	Absent	Pos	WT	45.6%, 39.5%, hemiallelic (~50% alleles methylated)
OCCPI-10	F	Black	Cecum	50 y	Neg	Absent	Pos	N/T	47.6%, 35.6%, hemiallelic (~50% alleles methylated)
OCCPI-15	M	White	Transverse colon	55 y	Neg	Absent	Pos	WT	50.4%, 50.4%, hemiallelic (~50% alleles methylated)



Vaccines for immunoprevention of DNA mismatch repair deficient cancers

Alejandro Hernandez-Sanchez ,[1] Mark Grossman,[2] Kevin Yeung,[2]
Shizuko S Sei,[3] Steven Lipkin,[2] Matthias Kloor[4]

J Immunother Cancer 2022;**10**:e004416

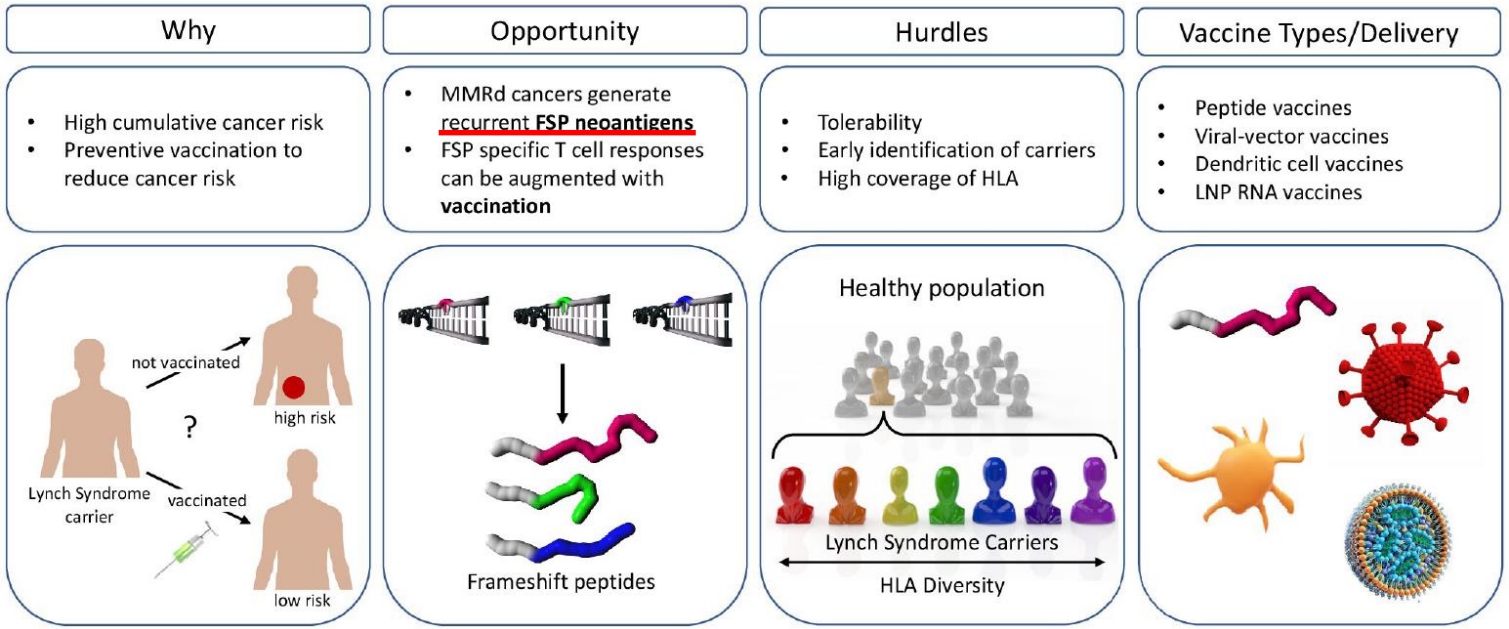
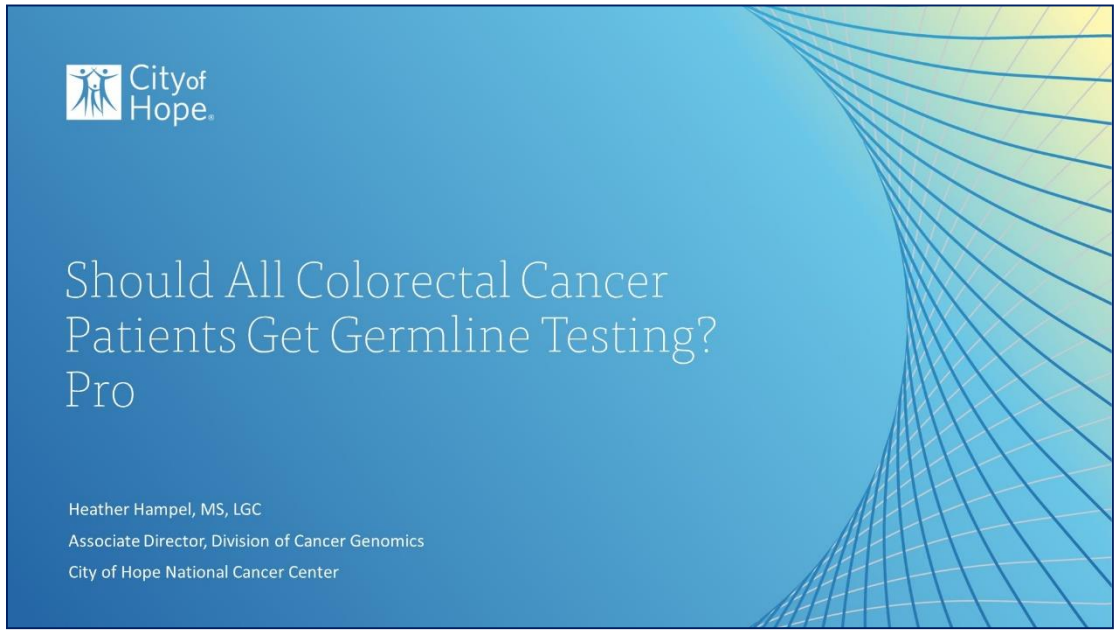


Table 1 Summary of clinical and preclinical studies assessing the prevention of Lynch syndrome

Phase	Study type	Agent	Disease	Delivery platform	Animal model	Clinical trial no	Clinical trial title	Status	Publication
I and II	Immuno-prevention	FSPs: 209 Neoantigens	Lynch Syndrome	Adenovirus and Modified vaccinia Ankara virus	n/a	NCT05078866	Cancer Preventive Vaccine Nous-209 for Lynch Syndrome Patients	Not yet recruiting	n/a
I and II	Immuno-prevention	FSPs: CASP-5 and TGFBR2; TAA: CEA	Lynch Syndrome	Dendritic Cell	n/a	NCT01885702	Dendritic Cell Vaccination in Patients with Lynch Syndrome or Colorectal Cancer With MSI	Active, not recruiting	[121]
I and II	Immuno-prevention	FSPs: AIM2, HT001 and TAF1B	Lynch Syndrome	Peptide vaccination	n/a	NCT01461148	Vaccination Against MSI Colorectal Cancer	Completed	[115]
Preclinical	Immuno-prevention	Cancer neoantigens	Melanoma, Lymphoma, other	RNA	dogs	n/a	Vaccination Against Canine Cancer	Recruiting	[114]
Preclinical	Immuno-prevention and chemoprevention	Aspirin, Naproxen; FSPs: Nacad, Xirp1, Maz, Senp6	Lynch Syndrome	Peptide vaccination	Lynch syndrome mouse model	n/a	Recurrent Frameshift Neoantigen Vaccine Elicits Protective Immunity with Reduced Tumor Burden and Improved Overall Survival in a Lynch Syndrome Mouse Model	Completed	[120]
Preclinical	Immuno-prevention	FSPs: Senp6	Lynch Syndrome	Dendritic Cell	tumor transplantation mouse model	n/a	On the development of a neoantigen vaccine for the prevention of Lynch Syndrome	Completed	[130]

Dépistage constitutionnel universel ??



[ASCO GI 2023]

Formes héréditaires mendéléiennes

Gènes modificateurs

Prédispositions multigéniques (polygenic risk scores)
[Thomas et al., Am J Hum Genet 2020; Jia et al., JNCI Cancer Spectrum 2020]

Influence de l'environnement, microbiote, …

Epigénétique, …