Recherche systématique de syndrome de Lynch dans le cancer colorectal: regard critique sur une pratique courante et perspectives d'avenir

Consultations d'Oncogénétique

APHP-Sorbonne Université

GERCOR 20 septembre 2019

Cancer colorectal

- Recherche systématique du syndrome de Lynch
  - «Universal screening»
  - Vs. anciens critères cliniques (Amsterdam, Bethesda)
  - Pour ne rien rater
- Recommandation étendue au cancer de l'endomètre

asco.org/edbook | 2018 ASCO EDUCATIONAL BOOK

Am J Gastroenterol 2015; 110:223–262; doi:10.1038/ajg.2014.435; published online 3 February 2015

Cancer colorectal

- Généralisation des recherches de prédisposition génétique en Oncologie

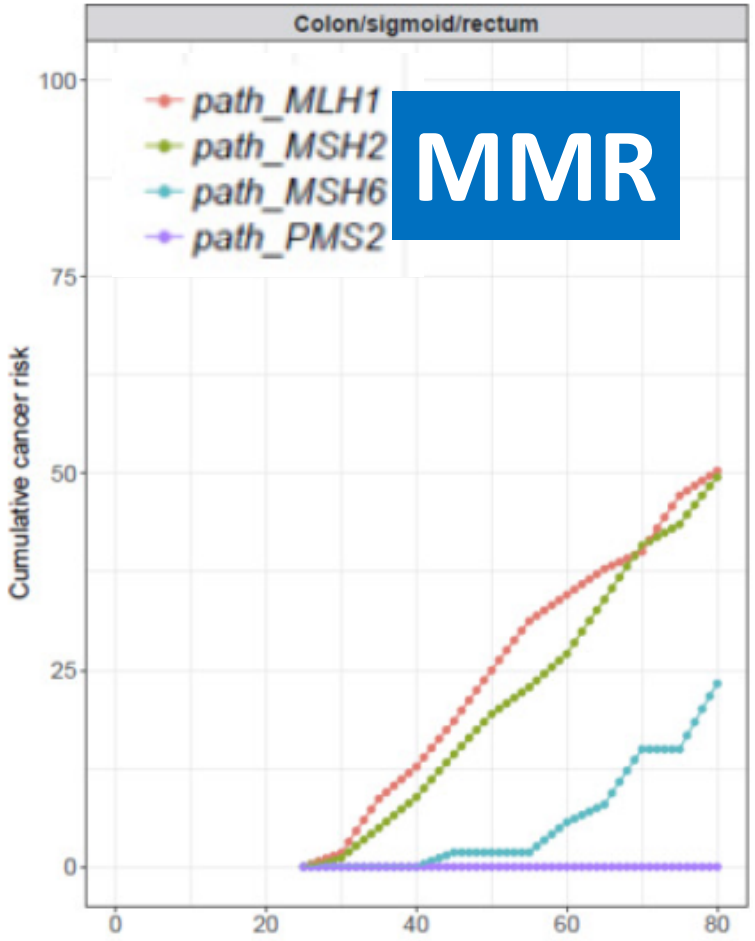
- Difficultés associées
  - Taux de détection très bas
  - Tests non conclusifs → surmédicalisation
  - Ressources à disposition

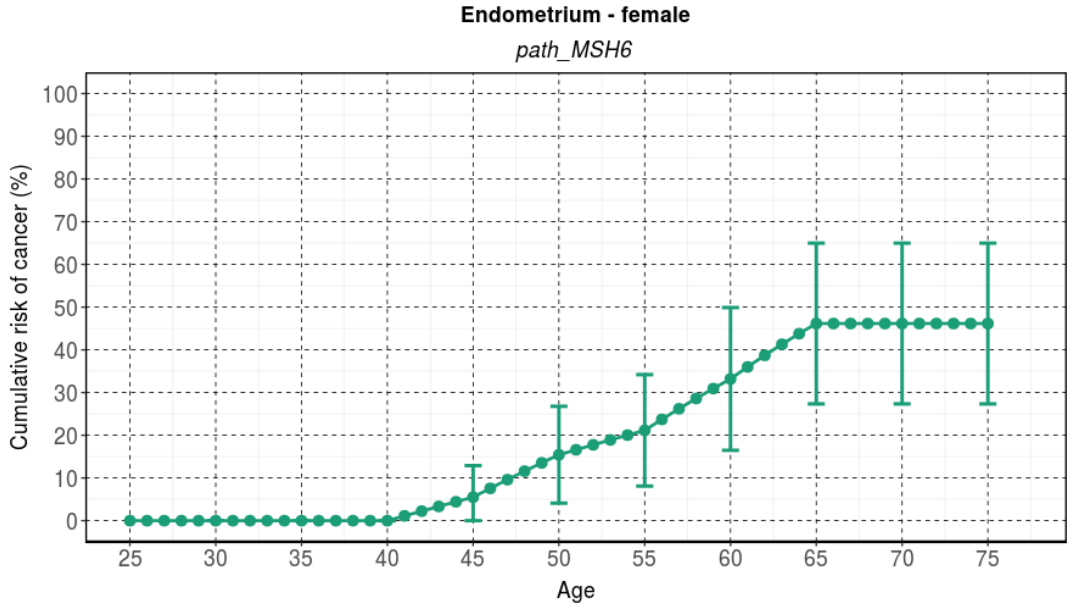
- Développer nouvelles approches
  - Personnalisées
  - Modèles mathématiques
  - Intelligence artificielle
  - Médecine connectée

Contexte non métastatique

  - Sélectionner patients en amont
  - Guider les investigations et la prise en charge à chaque étape de la démarche

Lynch rappel





Ovaire non séreux, estomac, grêle, tumeurs urothéliales, voies bilaires, pancréas, tumeurs cutanées sébacées

Lynch : u

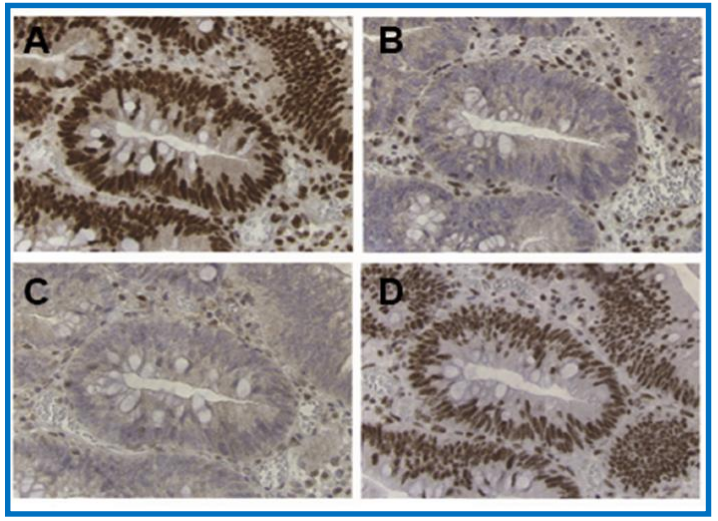
Phénotype dMMR

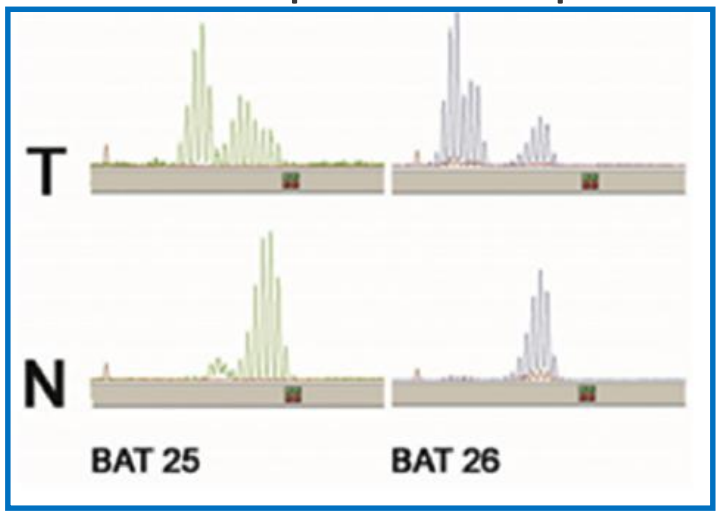
Recherche ~~MLH1-hyper~~

- IHC des p
  codées par les gènes
- BioMol: Instabilité microsatellite

Analyse constitutionnelle (germline) des gènes MMR

aires sur ces
ves





Phénotype dMMR

- Peut survenir hors-Lynch
- P.ex inactivation purement tumorale des gènes MMR
  - Hyperméthylation promoteur MLH1
  - Deux évènements somatiques

Lynch : prise en charge

- Surveillance
- Chirurgie de réduction de risque
- Tests au sein de la famille

Universal screening

1) Taux de détection très bas

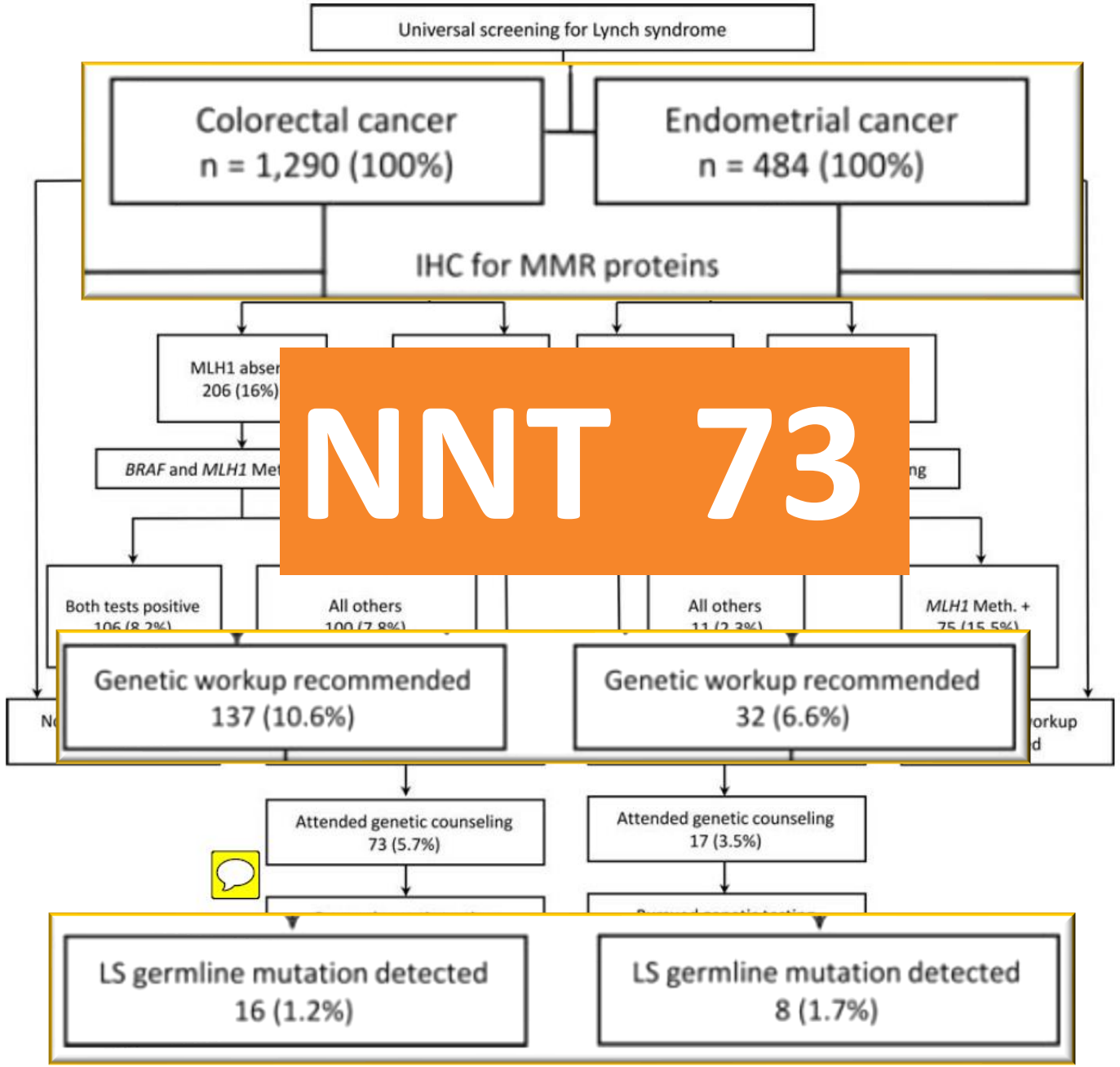
Original Article

Universal Screening of Both Endometrial and Colon Cancers Increases the Detection of Lynch Syndrome

Tomer Adar, MD [1]; Linda H. Rodgers, MGC, LCGC[2]; Kristen M. Shannon, MS, LCGC[2]; Makoto Yoshida, MD[1]; Tianle Ma, MD[1]; Anthony Mattia, MD[3,4]; Gregory Y. Lauwers, MD[3]; Anthony J. Iafrate, MD-PhD[3]; M
Esther Oliva, MD[3]; and Daniel C. Chung, MD[1,2]

Cancer August 1, 2018

BACKGROUND: Lynch syndrome (LS) is the most common hereditary cause of colorectal cancer (CRC) and endometrial cancer (EC). Screening of all CRCs for LS is currently recommended, but screening of ECs is inconsistent. The objective of this study was to determine the added value of screening both CRC and EC tumors in the same population. **METHODS:** A prospective, immunohistochemistry (IHC)-based screening program for all patients with newly diagnosed CRCs and ECs was initiated in 2011 and 2013, respectively, at 2 centers (primary and tertiary). Genetic testing was recommended for those who had tumors with absent mutS homolog 2 (MSH2),


Universal screening for Lynch syndrome
Colorectal cancer
n = 1,290 (100%)
Endometrial cancer
n = 484 (100%)
IHC for MMR proteins
MLH1 abser
206 (16%)
BRAF and MLH1 Met
ng
NNT 73
Both tests positive
All others
All others
MLH1 Meth. +
Genetic workup recommended
137 (10.6%)
Genetic workup recommended
32 (6.6%)
Attended genetic counseling
73 (5.7%)
Attended genetic counseling
17 (3.5%)
LS germline mutation detected
16 (1.2%)
LS germline mutation detected
8 (1.7%)

Et les autres?

Phénotype dMMR sans mutation germline

Universal screening

2) Résultats non-conclusifs

pas de mutation germline → Lynch-like

Lynch-like

- Suspicion de Lynch non avérée
  - Suivi … Lynch-like
  - Idem pour apparentés au 1er degré

GASTROENTEROLOGY 2013;144:926–932

Risk of Cancer in Cases of Suspected Lynch Syndrome Without Germline Mutation

MARÍA RODRÍGUEZ–SOLER,[1,2] LUCÍA PÉREZ–CARBONELL,[2] CARLA GUARINOS,[2] PEDRO ZAPATER,[3]

Table 4. Differences in the Prospective Appearance of New Cases of Cancer Between Families With LLS and Families With LS/Sporadic CRC During Follow-up

	LS (n = 41)	*P* value[a]	LLS (n = 89)	*P* value[b]	Sporadic CRC (n = 403)
CRC (%)	3 (7.3)	.16	2 (2.2)	.2	3 (0.7)
Non-CRC LSRC (%)	4 (9.8)	.05	2 (2.2)	.02	1 (0.2)
Total cancers (%)	7 (17.1)	.01	4 (4.5)	.01	4 (0.9)

[a]Comparing the percentage in the LS and LLS groups.
[b]Comparing the percentage in the LLS and sporadic CRC groups.

Universal screening

Différence plus flagrante

Lynch-like

- Suspicion de Lynch non avérée
  - Suivi … Lynch-like
  - Idem pour apparentés au 1er degré
- Anxiété
- Surmédicalisation?
  - Complications, coûts, surdiagnostics..

Phénotype dMMR

- Peut survenir hors-Lynch
- P.ex. inactivation purement tumorale des gènes MMR
  - Hyperméthylation promoteur MLH1
  - **Deux évènements somatiques**

Séquençage des gènes dans la tumeur

Lynch-like: complément d'investigations

- Séquençage des gènes dans la tumeur
  - Récupérer matériel de qualité
  - Circuits en place
  - Infrastructure et personnels nécessaires
  - Coûts associés

BRIEF REPORTS

Somatic Mutations in *MLH1* and *MSH2* Are a Frequent Cause of Mismatch-Repair Deficiency in Lynch Syndrome-Like Tumors

Arjen R. Mensenkamp,[1,*] Ingrid P. Vogelaar,[1,*] Wendy A. G. van Zelst–Stams,[1] Monique Goossens,[2] Hicham Ouchene,[1] Sandra J. B. Hendriks–Cornelissen,[2] Michael P. Kwint,[2] Nicoline Hoogerbrugge,[1] Iris D. Nagtegaal,[2] and Marjolijn J. L. Ligtenberg[1,2]

[1]*Department of Human Genetics,* [2]*Department of Pathology, Radboud university medical center, Nijmegen, The Netherlands*

genes. We conclude that 2 acquired events explain the MMR-deficiency in more than 50% of the MMR-deficient tumors without causal germline mutations or promoter methylation.

Universal screening

3) Ressources à disposition

-phénotype dMMR → consultation d'oncogénétique

-encombrement

-surcharge de travail pour les laboratoires sous-financés

Alternatives

- Modèle mathématique performant
- Et facile d’utilisation
  - **PREMM5**
    - régression logistique

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PREMM5 MODEL | LYNCH SYNDROME

Lynch syndrome prediction model

MLH1, MSH2, MSH6, PMS2, and *EPCAM* gene mutations

The $PREMM_5$ model is a clinical prediction algorithm that estimates the cumulative probability of an individual carrying a germline mutation in the *MLH1, MSH2, MSH6, PMS2,* or *EPCAM* genes. Mutations in these genes cause Lynch syndrome, an inherited cancer predisposition syndrome.

In addition to information about the individual being evaluated, the model requires:

- A personal or family history of colorectal cancer, endometrial (uterine) cancer, or other Lynch syndrome-associated cancers
- Types of cancer and ages at diagnosis of first-degree relatives from the affected side of the family (parents, siblings, children)
- Types of cancer and ages at diagnosis of second-degree relatives from the affected side of the family (grandparents, grandchildren, aunts, uncles, nieces, nephews)

1 Patient information

Sex

- Male
- Female

Current age (years)

Overall predicted probability of *MLH1, MSH2, MSH6, PMS2,* or *EPCAM* mutation

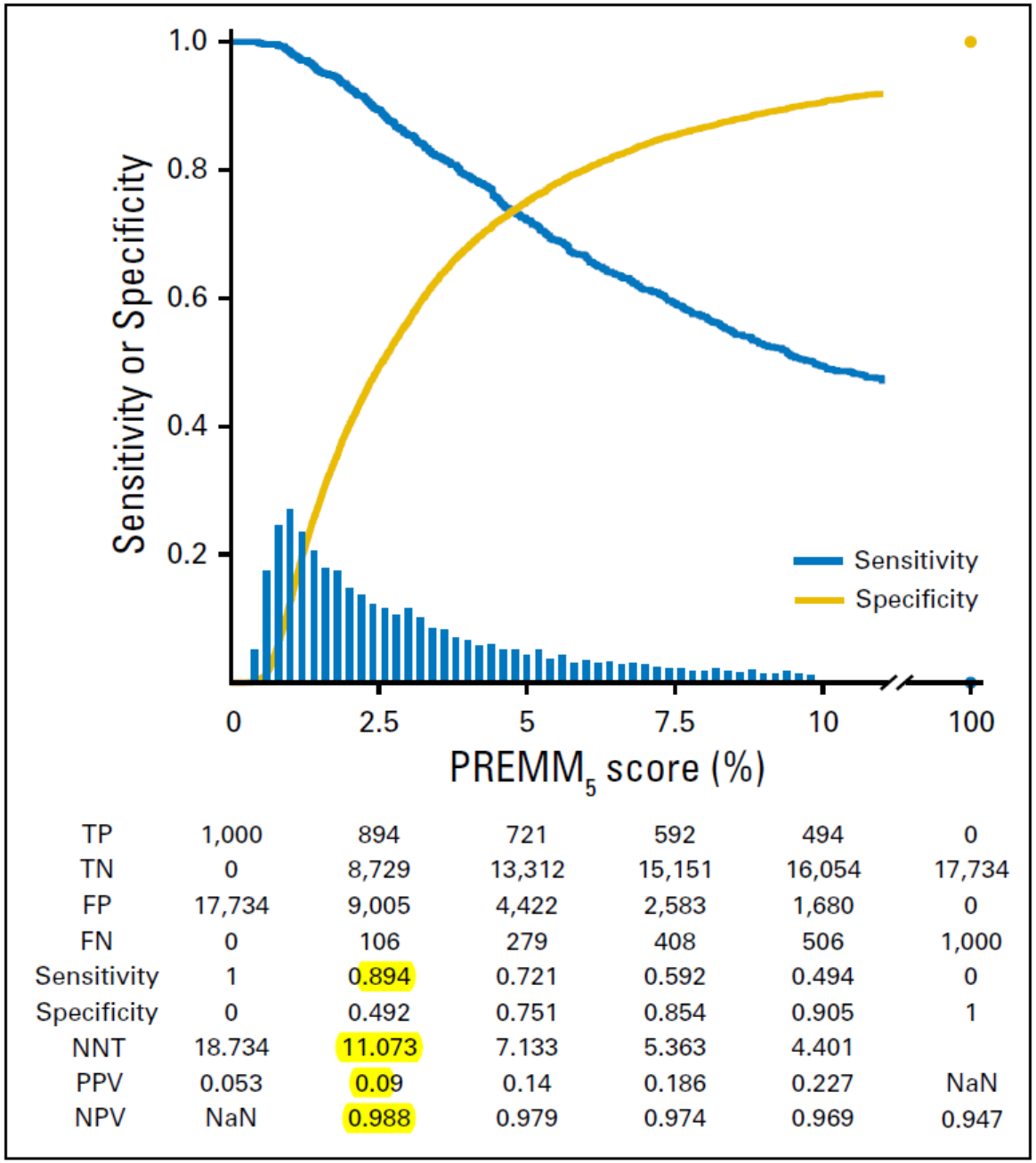
2.1%

Has the patient had any other Lynch syndrome-associated cancer?

Other Lynch syndrome-associated cancers include ovary, stomach, small intestine, urinary tract/bladder/kidney, bile ducts, brain, pancreas, and sebaceous gland skin tumors.

- No
- Yes

2 Relatives: First-degree



TP	1,000	894	721	592	494	0
TN	0	8,729	13,312	15,151	16,054	17,734
FP	17,734	9,005	4,422	2,583	1,680	0
FN	0	106	279	408	506	1,000
Sensitivity	1	0.894	0.721	0.592	0.494	0
Specificity	0	0.492	0.751	0.854	0.905	1
NNT	18.734	11.073	7.133	5.363	4.401	
PPV	0.053	0.09	0.14	0.186	0.227	NaN
NPV	NaN	0.988	0.979	0.974	0.969	0.947

VOLUME 35 · NUMBER 19 · JULY 1, 2017
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Development and Validation of the $PREMM_5$ Model for Comprehensive Risk Assessment of Lynch Syndrome

Fay Kastrinos, Hajime Uno, Chinedu Ukaegbu, Carmelita Alvero, Ashley McFarland, Matthew B. Yurgelun, Matthew H. Kulke, Deborah Schrag, Jeffrey A. Meyerhardt, Charles S. Fuchs, Robert J. Mayer, Kimmie Ng, Ewout W. Steyerberg, and Sapna Syngal

Original Article

Universal Screening of Both Endometrial and Colon Cancers Increases the Detection of Lynch Syndrome

Tomer Adar, MD[1]; Linda H. Rodgers, MGC, LCGC[2]; Kristen M. Shannon, MS, LCGC[2]; Makoto Yoshida, MD[1]; Tianle Ma, MD[1]; Anthony Mattia, MD[3,4]; Gregory Y. Lauwers, MD[3]; Anthony J. Iafrate, MD-PhD[3]; Nicole M. Hartford[3]; Esther Oliva, MD[3]; and Daniel C. Chung, MD[1,2]

TABLE 3. Patients With Colorectal Cancer Who Were Diagnosed With Lynch Syndrome

Patient No.	Age, y	Sex	Tumor Location	Absent Protein in IHC	Germline Mutation	A-II	Bethesda	Model, % PREMM$_{1,2,6}$	Model, % PREMM$_5$
1	53	Woman	Transverse colon	MLH1, PMS2	*MLH1*, c.588del4	Positive	Positive	88.8	>50.0
2	53	Man	Splenic flexure	MSH6	*MSH6*, c.3939_3957dup19	Negative	Negative	6.3	5.4
3	85	Woman	Sigmoid colon	PMS2	*PMS2*, c.1021delA	Negative	Negative	1.7	1.1
4[a]	55	Man	Rectosigmoid	MSH2, MSH6	*MSH2*, c.388_389delCA	Positive	Positive	85.8	>50.0
5	53	Woman	Hepatic flexure	MLH1, PMS2	*MLH*c, c.790 + 1G>A	Positive	Positive	7.8	7.3
6[b]	49	Man	Right transverse colon	PMS2	*PMS2*, c.137G>T	Negative	Positive	16.4	4.8
7[b]	68	Man	Cecum	PMS2, MSH6	*PMS2*, c.137G>T[c]	Negative	Negative	3.0	2.1
8	54	Woman	Cecum	MSH6	*MSH6*, c.10C>T	Negative	Positive	22.7	16.7
9	48	Woman	Rectum	MLH1, PMS2	*MLH1*, c.207 + 1G>A	Positive	Positive	9.3	3.5
10	59	Man	Rectum	MSH2	*MSH2*, c.942 + 3A>T	Positive	Positive	30.6	23.4
11	77	Man	Ascending colon	PMS2	*PMS2*, 1407ins46[d]	Negative	Negative	2.1	1.5
12	43	Woman	Proximal transverse	MLH1, PMS2	*MLH1*, c.676C>T	Positive	Positive	50.1	9.4
13[a]	63	Man	Proximal right colon	MLH1, PMS2	*MLH1*, del exons 1-6	Positive	Positive	96.6	>50.0
14[a]	42	Man	Cecum	MLH1, PMS2	Germline *MLH1* promoter meth.	Negative	Positive	10.2	8.5
15	33	Woman	Ascending colon	MSH2, MSH6	*MSH2*, c.2633_2634delAG	Positive	Positive	42.9	46.5
16	46	Man	Rectum	MSH6	*MSH6*, c.3202C>T	Negative	Positive	13.1	11.6

PMS2 doit-il vraiment être considéré comme un gène du Lynch

ARTICLE | Genetics inMedicine

Open

Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database

A full list of authors and affiliations appears at the end of the paper.

brain, and particularly prostate. Pathogenic *MSH6* variants caused a sex-limited trait with high endometrial cancer risk but only modestly increased colorectal cancer risk in both genders. We did not demonstrate a significantly increased cancer risk in carriers of pathogenic *PMS2* variants. Ten-year crude survival was over 80% following colon, endometrial, or ovarian cancer.

Conclusion: Management guidelines for Lynch syndrome may require revision in light of these different gene and gender-specific

Innover/personnaliser

Modèle mathématique

Estimer la probabilité de Lynch

IHC / test MSI?

Suivi Lynch-like

Analyse germline?

A toutes les étapes du diagnostic

Intelligence artificielle

Ming *et al. Breast Cancer Research* (2019) 21:75
https://doi.org/10.1186/s13058-019-1158-4

Breast Cancer Research

RESEARCH ARTICLE Open Access

Machine learning techniques for personalized breast cancer risk prediction: comparison with the BCRAT and BOADICEA models

Chang Ming[1*], Valeria Viassolo[2], Nicole Probst-Hensch[3], Pierre O. Chappuis[2,4], Ivo D. Dinov[5,6,7,8] and Maria C. Katapodi[1,8]

Médecine connectée

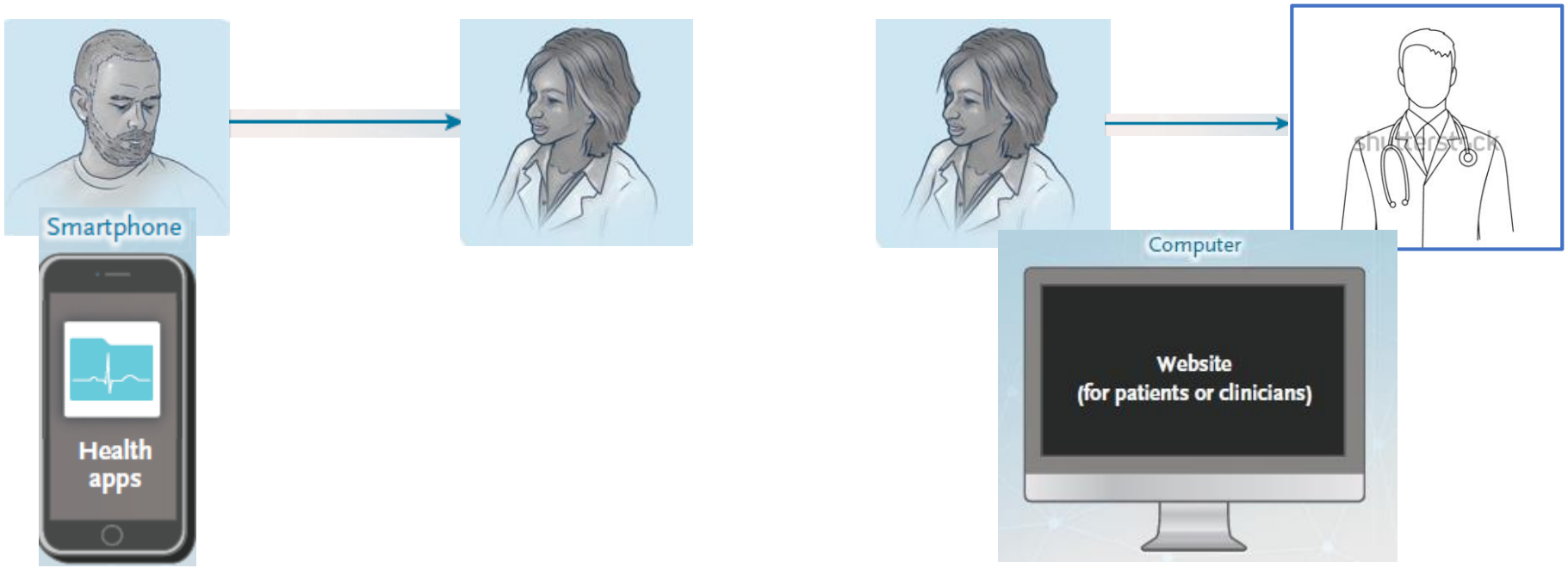
The NEW ENGLAND JOURNAL of MEDICINE

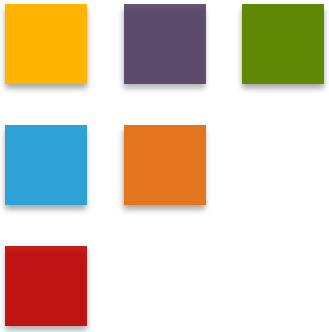
REVIEW ARTICLE

FRONTIERS IN MEDICINE

Mobile Devices and Health

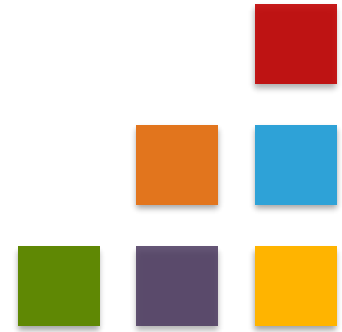
Ida Sim, M.D., Ph.D.





Merci pour votre attention

PBenusiglio



Backup

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Gastroenterology 2018;155:1410–1415

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Routine Molecular Analysis for Lynch Syndrome Among Adenomas or Colorectal Cancer Within a National Screening Program *Fecal immunochemical testing*

Anne Goverde,[1,2] Anja Wagner,[2] Marco J. Bruno,[1] Robert M. W. Hofstra,[2] Michael Doukas,[3] Marcel M. van der Weiden,[3] Hendrikus J. Dubbink,[3] Winand N. M. Dinjens,[3] and Manon C. W. Spaander[1]

Table 2. Results of Molecular Diagnostics

	n	Age, y (IQR)	Male gender, n (%)	MMR deficiency	MHL1 promoter methylation	Germline MMR mutation
Patients included for IHC	456	67 (63–71)	296 (65)	8	5	0
Colorectal cancer	56	69 (63–72)	36 (64)	7	5	0
Advanced adenoma	370	66 (62–71)	237 (64)			
Villous component	186	65 (61–69)	124 (67)	1	0	0
High-grade dysplasia	42	67 (63–74)	30 (73)	0	0	0
4–10 nonadvanced adenomas	30	67 (63–74)	23 (77)	0	0	0

CME

ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes

Sapna Syngal, MD, MPH, FACG[1,2,3], Randall E. Brand, MD, FACG[4], James M. Church, MD, FACG[5,6,7], Francis M. Giardiello, MD[8], Heather L. Hampel, MS, CGC[9] and Randall W. Burt, MD, FACG[10]

Am J Gastroenterol 2015; 110:223–262; doi:10.1038/ajg.2014.435; published online 3 February 2015

Lynch syndrome (LS)

All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency.

Recent Advances in Lynch Syndrome: Diagnosis, Treatment, and Cancer Prevention

Matthew B. Yurgelun, MD, and Heather Hampel, MS, LGC

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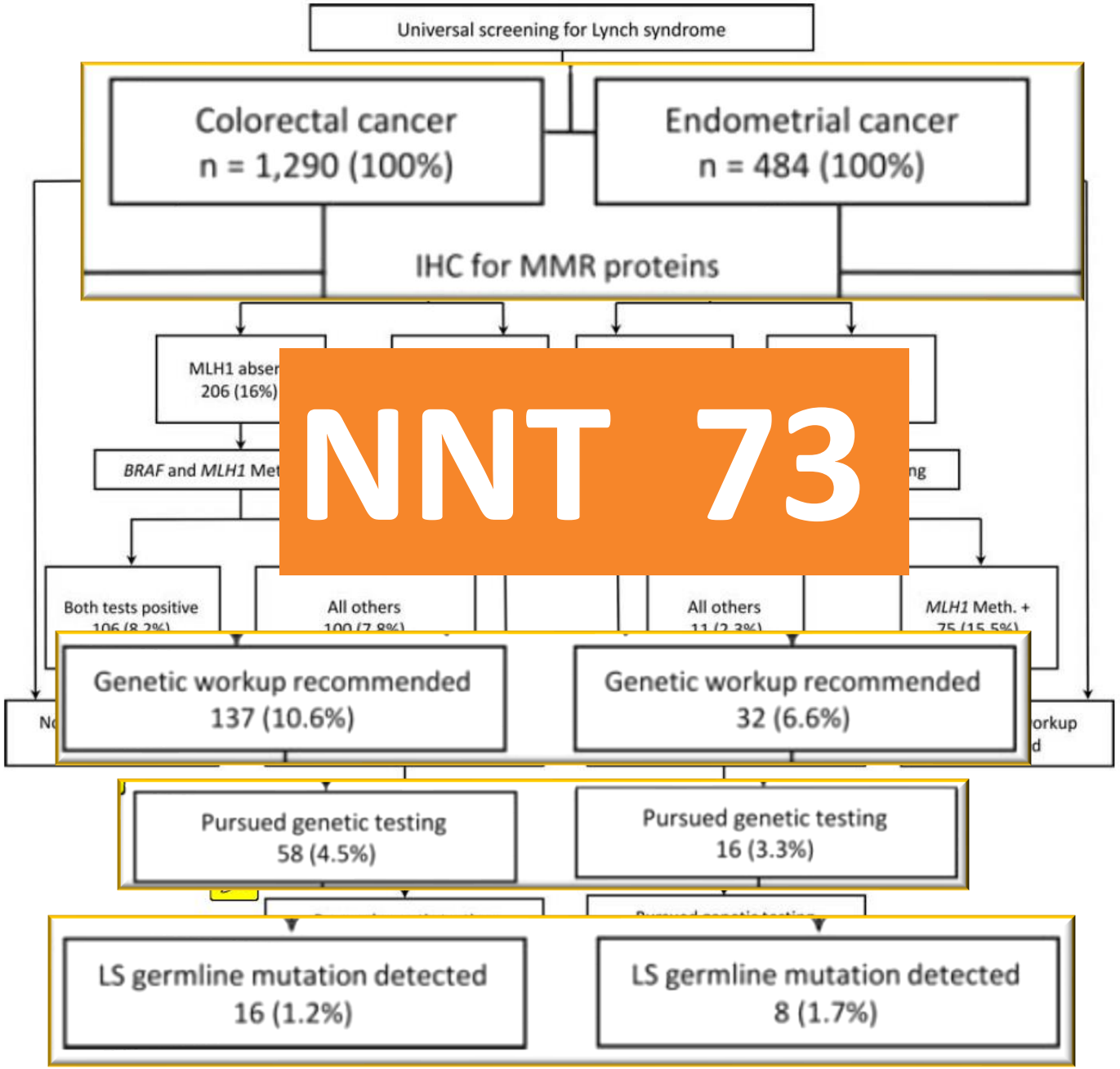
Regardless of the test used, the underlying principle of universal tumor screening for Lynch syndrome is the same: (1) screen all patients with newly diagnosed colorectal and endometrial cancer for Lynch syndrome with one of these tumor tests; (2) follow up with *MLH1* methylation analysis (with or without *BRAF* V600E mutation analysis in colorec-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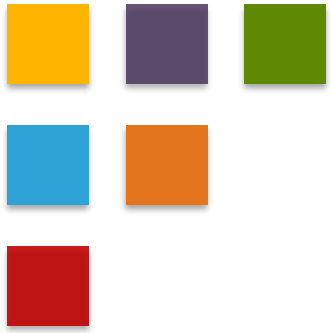
NNT 73



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