

Elaboration of EQID tool for digestive cancer predisposition

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Abstract

Lynch Syndrome is one of the most common diseases that predispose individuals to colorectal cancers. It is caused by mutations in DNA mismatch repair (*MMR*) genes. Genetic counselling is imperative to assist patients and their families in making decisions around surveillance, treatment, and care. Multidisciplinary committees (MDC) are organized by health professionals and specialists to optimize this process. The aim of the study is to examine the evaluation and improvement of quality decision-making for families with a genetic predisposition to colorectal cancer: based on gene test validation as well as proband and family care management. We observed practices among geneticists are diverse and discordant and not always consistent with recommendations made by France's Institute National du Cancer (INCa). We highlight the use of somatic testing via RER and MMR protein immunohistochemistry. We highlight the need of a computerized tool, that was developed and is now widely disseminated to every collaborating partner of our MDC. This tool will enable us to standardize our decision-making and, by comparing decisions through quality criteria, to differentiate and categorize some patients or families groups. As a result, we can achieve a better justification of care management and family prevention.

Introduction

Lynch syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome is a commonly inherited disorder that predisposes patients to colorectal cancers. It is suspected through Amsterdam II criteria [1]. In addition to colorectal cancer, cases of endometrial, small intestine, and urinary tract cancers can also present in these families. Lynch syndrome is defined by mutations in the *MMR* genes. In at-risk patients, a chromo-colonoscopy is recommended, every 2 years, from the age of 20 years. In addition, an annual gynaecologic surveillance is recommended in women beginning at 30 years of age. The second most common syndrome predisposing to CRC is the Familial Adenomatous Polyposis (FAP), which is caused mainly by mutations in *APC* gene. It causes CRC and a high number of polyps [2].

A consultation that includes genetic counselling is mandatory before making a recommendation of genetic testing to an at-risk family. This discussion also should include a surveillance strategy for these patients. Most French genetic centres (76%) organize multidisciplinary committees (MDC) to bring together medical professionals to help optimize decision-making around care management, taking into account advice from relevant experts and specialists [3]. In the Lyon region of France, one MDC is organized every month. Anecdotal evaluations of these MDCs suggested that its management was not standardized. We, therefore, developed a tool to enable us to evaluate and systemize the MDC. The aim the EQID (Assessment and Improvement of Quality Decision-making within digestive cancer MDCs) Study is to evaluate the quality of decision-making for a given family with digestive cancer risk through the MDC in order to improve family management

and optimize the quality of care. In French, the EQID study is known as the EQAD COG Colon (Evaluation et Amélioration de la Qualité de Décision en Comité d'Oncogénétique dédié au Colon) Study.

Patients and methods

EQID is based on an analysis of nearly 200 patient cases which were discussed within the Lyon region's MDC between 2004 to 2012. These cases arose from families who received a genetic consult during that time in one of our clinics. The patients taken into account were those affected by colon cancer with a putative genetic predisposition, according to family history and well-established criteria published among two major consensus conference focusing HNPCC related digestive cancers [4]: Amsterdam criteria and Bethesda guidelines (positive predictive value and sensitivity recognized). Tumour studies, including examination of microsatellite stability through replication error analysis and immunohistochemistry of MMR proteins, were performed and often drove MDC decision-making. DC decision-making.

First, patient cases were reviewed based on Lynch Syndrome criteria to establish the validity of recommending genetic testing

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and a comparison between similar pedigrees was undertaken. Then, surveillance recommendations among cases were compared. As schematically represented in Appendix A (study protocol), a comparative study was proposed with patient cases being placed into 1 of 3 groups according to their somatic test status: RER+/IHC+ (Group 1), RER+/IHC- (Group 2), and RER-/IHC- (Group 3).

Different key points have been targeted and validated by the MDC as decisive indicators for a decision-making: 1) the nature of tumours of a suspected predisposition, 2) the age of diagnosis, 3) the degree of relationship of relatives with the proband, 4) the availability of somatic tests (RER and IHC) and genetic testing, and 5) the care-management recommended for a patient and his or her family. Taking into account these elements, an electronic tool was developed by a clinical informaticist affiliated with the Lyon region's cancer genetic network and was used to gather and analyse the major criteria of a patient's given decision-making process. It is integrated into the electronic medical record system (Easily software).

Results

In our center, a genetic consult starts with drawing a family pedigree, searching Amsterdam criteria, and performing somatic testing on the most appropriate tumour sample. Based on this evaluation, we determine whether or not genetic testing is warranted and propose a plan for care management. (Figure 1: Flow chart figure). The probands' main tumour type for which patients have been referred to our consultation are essentially colorectal cancers (51%), endometrial cancers (10%), polyposis (8%) and gastric cancers (4%). We also find ovarian and cutaneous cancers (less than 2%) (Figure 2).

Somatic tests results

We performed 142 somatic tests in 125 families. Less than half of the tested tumours displayed MSI (microsatellite instability). Less than half of tested tumours showed a loss of one or more MMR proteins in immunohistochemistry. Of note, we found MLH1 protein loss of

expression in 23 cases, of which methylation of *MLH1* gene promotor was studied for only 13 cases (59.09%) (Table 1a).

NB: methylation of a gene promotor correlates with loss of expression of the corresponding protein and can exclude a diagnosis of Lynch syndrome if no familial history.

Genetic tests results

In 59 cases (30.25%) a genetic test was performed prior to the MDC. Among these, 34 (57.63%) were *MMR* gene tests. Thus, within the MDC, in these cases, discussion focused primarily on patient-family care management recommendations. After the MDC, decisions were made regarding additional somatic testing recommendations in relatives prior to rediscussion of the patient case in 24 cases (12.31%). Gene testing was discussed in 74 cases (47%, this number is computed by excluding bias due to retrospective request, where only tested patients where sectioned for our study) (Table 1b).

MMR gene test results and patients/families care management decisions by MDC, based on somatic tests.

We organized gene test and care management decision through 3 groups (Table 2):

Group 1: RER+/IHC+ cases: 48 cases

Genetic analysis indication: Among, RER+/IHC+ cases, there were 15 patients that did not meet Amsterdam or Bethesda criteria, but for whom tumour signature was sufficient to validate the recommendation of genetic testing. These criteria offer a very good positive predictive value since more than 50% (8/15) of tested cases were found to have an *MMR* gene mutation. However, this value underlines that we are not selective enough.

Among the 33 remaining patient cases presented in the MDC, we discussed 25 genetic testing indications and 4 somatic testing indications (of which 3 included discussions of promotor methylation analysis of the *MLH1* gene).

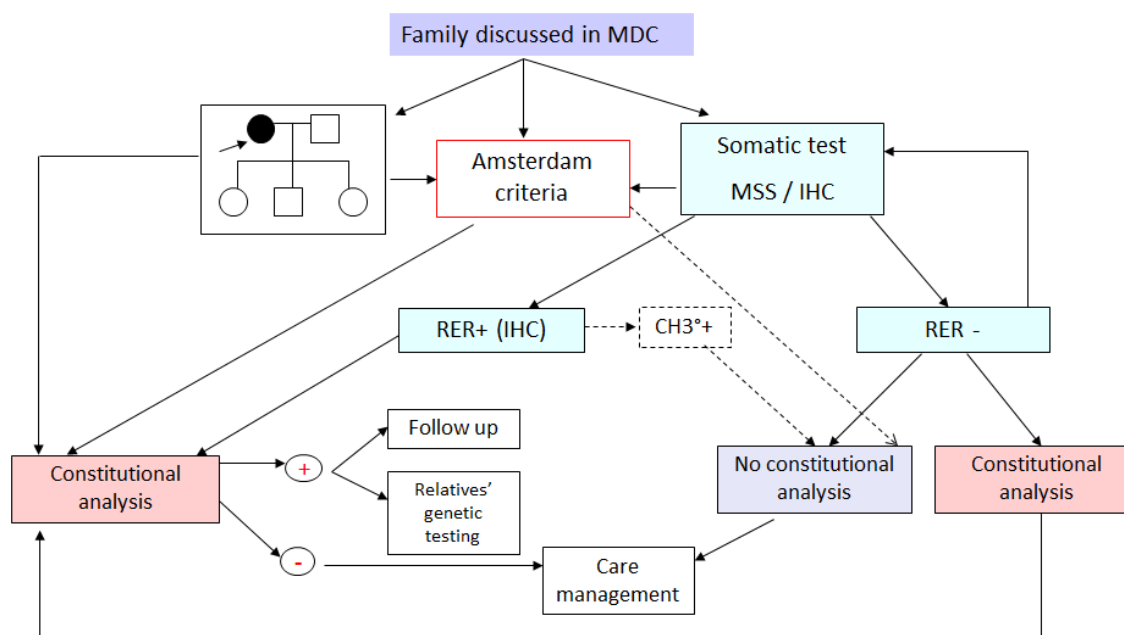


Figure 1. Representation of diagnosis strategy in our Lyon team.

RER: Replication Error. RER+: microsatellite instability. RER-: stability of microsatellites. CH3⁺: promotor methylation. IHC: immunohistochemistry. MDC: multidisciplinary committee. + : mutation identified. - : no mutation

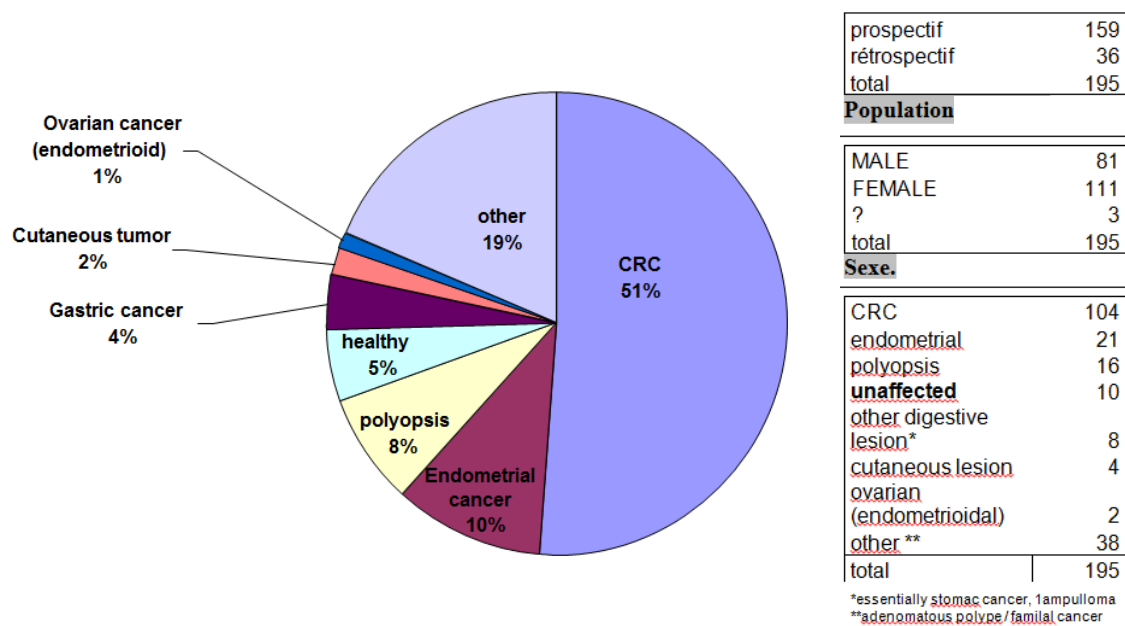


Figure 2. Representation of main tumors of the propositus

Table 1. A) somatic test details. B) Details of somatic/constitutional testings realized before and after MDC

A)	Family's tumours		Tumour 1	Tumour 2
RER status	mss	76	63	9
	msi-l		4	0
	msi	38	6	1
	msi-h		28	3
	failed or impossible	13	9	0
total	4		0	
IHC status	total		114	13
	ihc+	53	48	5
	ihc-	77	68	9
	total		116	14
	MLH1 loss	23	21	1
	MSH2 loss	24	21	3
	MSH6 loss	26	23	3
	PMS2 loss	12	11	1
	total		76	8
	CH3° +	3	3	0
	CH3° -	7	7	0
CH3 failed	3	3	0	
CH3 impossible	0	0	0	
CH3 not done		13	0	

mss : microsatellites stability, msi : microsatellites unstability (msi-high, or msi-low). CH3°: methylation study of *MLH1* gene promotor. CH3°+: methylation, CH3°-: no methylation. IHC: immunohistochemistry. IHC+: loss of the expression of 1 (or more) *MMR* protein in IHC. IHC-: no loss of expression of *MMR* protein.

B)	Before MDC (performed)		After MDC (to perform)
bio (RER/IHC)	72,82%		12,31%
CH3*	59,09%		/
Gene	30,25%		46,54%**
MMR	57,63%	MMR+	23,73%
		MMR-	33,90%
APC	16,95%	APC+	3,39%
		APC-	13,56%
MYH	22,03%	MYH+	1,69%
		MYH-	20,34%
Other	15,25%		3,76%
MDC discussion	Care management		Analysis validation

*Search for methylation of *MLH1* promotor when there is a loss of expression in immuno - histochemistry. **(74/159): The bias is related to the removed retrospective data (only the tested cases are selected). In some cases, if research of *MMR* gene defects is negative, *APC* gene analysis is proposed by MDC. MDC: multidisciplinary committee. CH3: research of methylation. +: presence of mutation, -: absence of mutation.

Table 2. Group 1, Group 2, Group 3 cases analysis

Group 1: analysis Indication, RER+/IHC+ cases: 48 cases					
met criteria nb of case	Amsterdam II	Bethesda	none	TOTAL RER+/IHC+	
MMR +	2	4	2	8	15
MMR -		6	1	7	
Not tested (To discuss)	1	20	12	33	
To test	1	19	5	25 remaining	
	3	30	15		
Group 1: care management decision					
MMR+ (8/15) 2 women 6 men		No of cases	Rhythm	Age at the beginning	remark
	Colonoscopy	8	/2y.	20	
	Gastroscopy	2	/2y.	/	No gastric cancer in family
	Vaginal echography	6	/1y.	30	
MMR- (7/15) 5 women 2 men		No of cases	Rhythm	Age at the beginning	remark
	Colonoscopy	1	type Lynch		23 y before isolated kc at 43 y
		1	/3 y	*	* Already care-managed, isolated kc 42 y
	gastroscopy	0			
	Vaginal echography	0			1 endometrial cancer!
	nothing	4			2 healthy, 1 study inclusion, 2 isolated cancers
	other	1			Renal echography at 30y. (patient:adenomatous colorectal polyp, mother 2 crc<50y, 1 third degree relative: urothelial cancer ☐tobacco?)
colonoscopy	2	As Lynch		running test	
	4	1 control		running test	
nothing	27			running test	
2 cases of gastric cancers (late, 1 st /2 nd degree relatives) No surveillance recommended for upper gastrointestinal tract			2 bladder cancer (in 1 st degree relative, at 48 y): No surveillance recommended		
Group 2: analysis Indication, RER+/IHC- Cases: 8 family cases					
met criteria nb of case	Amsterdam II	Bethesda	none	TOTAL RER+/IHC-	
MMR +	3	1		4	5
MMR -		1		1	
Not tested (o discuss)		3			
To test		3		remaining 3	
	3	5			
Group 2: care management decision					
MMR+ (4/5) 4 women 0 man		nb of cases	rythm	Age at the beginning	Remark
	Colonoscopy	4	as Lynch	20-25	one 1 st degree relative:crc. and one 2 nd degree relative at 35 y
	gastroscopy	0			
	Vaginal echography	4		30	
MMR- (1/5) 1 woman		nb of cases	rythm	Age at the beginning	Remark
	Colonoscopy	1	as Lynch	20-25	isolated kc at 45 y
	gastroscopy				
	Vaginal echography				
	nothing				
other					
Group 3: analysis Indication, RER-/IHC- cases: 59 family cases					
met criteria nb of case	Amsterdam II	Bethesda	none	TOTAL RER-/IHC-	
MMR +					
MMR -		8	3*	11	
Not tested (to discuss)	6	23	8	37 whose 6 bio	
To test	2	6	3	11	
	8	37	14		

*1 isolated case at 54y 1 healthy with father TPM since 50y 1 adenomatous colorectal polyp, with one 2nd degree relative with crc					
Group 3: care management decision					
		nb cases	rythm	Age at the beginning	remark
MMR- (11/59) 4 women 7 men	Colonoscopy	2	as Lynch	20	2 Amsterdam (= Sd X)
		4	/3y	20...35	1 indigo (between 5 and 7 years before the youngest cancer)
		2	/3-5y	30...40	15 and 4 years before the youngest cancer
		3	/5y	30...35	1 duodenum (pas de loc duod) 1indigo (family with polyps), between 7 and 9 y before the youngest cancer.
	gastroscopy	0			1 case at 77 y (2 nd degree relative)
	Vaginal echography	2			as Lynch, no uterine cancer!
Not tested: no analysis indication (37/59) 26 women 11 men	Colonoscopy	12	/5 y	20...45	Between 2 and 14 y before the youngest cancer. 2 duodena 1 indigo1Amsterdam)
		11	/3-5y	35...45	Between 7 et 18 y before the youngest cancer. 4 Amsterdam, 6 in the research protocol DOCC
		1	/3y	40	10 y before the youngest cancer.
		3	1 control		2 indigo, 1 duodeno
	gastroscopy	2	1 control		1 cancer at 38 y and, one gastric cancer in 1 st and 2 nd degree relative (>60 y)
	Vaginal echography	1			
	nothing	6			4 study inclusion in the research protocol DOCC
	other				
2 proband: endometrial cancer at 55 and 69 y, 1 1 st degree relative at 48 y: no recommendation					
5 cases: stomach, 1 st degree relative (78 y), 2 nd (38 y), 3 rd (age?): no recommendation					
To test (11/59)	Nothing	8			Running test
	Colonoscopy	1	/5y	30	Running test
		2	1 control		Running test
6 biological tests have to be made					

Care management decision: For all 8 of the 15 cases described above as not meeting criteria but found to carry an MMR gene mutation, surveillance following the Lynch syndrome protocol was recommended for the 1st degree relatives (colonoscopy every 2 years for all beginning at age 20 years old and vaginal echography in women every year beginning as age 30 years old). For 2 carrier cases, a gastric exploration with gastroscopy was recommended every 2 years. No gastric cancer cases were observed in these families.

For the other 7 non carrier cases, Lynch-like surveillance was recommended for 1 case (colon cancer at 43 years old for the index case but no other cancer history reported in the family), beginning at age 20 years old. For 1 case, a colonoscopy every 3 years was recommended. For 1 case, a renal echography at 30 years old was recommended (urothelial cancer observed in a third degree relative). No additional surveillance protocols were recommended in the 4 remaining cases.

For the 33 cases for whom genetic testing was not recommended, Lynch-like surveillance was recommended in 2 cases, 1 exploration by colonoscopy in 4 cases, and no additional surveillance for the remaining cases. Concerning gastric surveillance, there is no clear and written

consensus among professionals. Furthermore, we are also not aware of studies which confirm the benefits of urinary tract surveillance. The decisions regarding these forms of management are best supported by referrals to gastroenterology specialists.

Group 2: RER+/IHC- Cases: 8 family cases

Genetic analysis Indication: For 5 cases, Bethesda criteria were sufficient to recommend testing of the MMR genes. This table corresponds to the case of group 1): Amsterdam and Bethesda seem to confer a good positive predictive value.

It also seems that combining Amsterdam criteria and positive somatic testing (RER+ with IHC+ or IHC-) results in a very good positive predictive value. Nevertheless, a much larger-scale study needs to be carried out, in which a larger sampling of family cases with genetic test results is available to confirm or invalidate this hypothesis.

Care management decision: In 4 of these 5 cases, an MMR mutation was identified. Members of these families were recommended to follow Lynch-like surveillance as previously described. The remaining non-carrier case was also recommended a Lynch-like surveillance protocol

because the RER+ phenotype conferred elevated risk. Concerning gastroscopy, the current professional consensus is undetermined and will probably merit a specific debate.

Group 3: RER-/IHC- cases: 59 family cases

Genetic analysis indication: Only 11 of the 59 cases received genetic testing and no *MMR* mutations were identified in any of these. Among them, 8 met Bethesda criteria. The 3 remaining family cases did not meet either Bethesda or Amsterdam criteria (there were: 1 isolated case at 54 years / 1 healthy case whose father has multiple primitive tumour at age 50 years / and 1 case with adenomatous colorectal polyps and one 2nd degree relative with colorectal cancer).

For 11 cases, we recommended gene test (2 met Amsterdam criteria, 6 met Bethesda criteria, and 3 met no criteria). For the remaining 37 family cases, the recommendation of gene testing was not indicated. Care management was defined. Among these cases, 6 met Amsterdam criteria and 23 met Bethesda criteria. The remaining cases met neither criteria. Further discussion on the 6 cases was held to understand why genetic testing was not proposed and to confirm care management.

Care management decision: For the 11 non-carrier family cases, familial surveillance recommended was colonoscopy every 2 years beginning at age 20 years (N=2); every 3 years from age 20-30 years old (N=4); every 3-5 years from 30-40 years old (N=2); and every 5y beginning at age 30 years old (N=3). In these cases, surveillance for 1st degree relatives do not depend on the age of the youngest cancer in the family. We also observed 2 cases in which a recommendation of vaginal echography was made despite not seeing a history of uterine cancer in the family.

For the 37 cases not receiving genetic testing, surveillance recommended to relatives was variable: colonoscopy every 5 years from 20-45y (N=13); every 3-5 years from 35-45 years old (N=11); and every year from 40 years old (N=1); single baseline colonoscopy (N=3). No additional surveillance was recommended for the remaining cases. In general, the surveillance was recommended to begin starting between 2 and 18y before the youngest colorectal cancer case in the family.

Uterine echography recommendations were similarly variable. The procedure was recommended in 1 case in which the family did not show endometrial cancer, however it was not recommended in 2 cases in which the proband presented with endometrial cancer (at 55 and 69 years old, respectively) and in an additional case where a 1st degree relative was observed to have endometrial cancer at 48 years of age. In 2 cases, control by gastroscopy was proposed.

Decision-making by the MDCs were therefore observably heterogeneous and patient care management was inconsistent. A global overview of criteria that allows for decision-making regarding whether or not to recommend *MMR* gene analysis is shown on table 3. This has not currently been implemented as a national strategy.

EQID tool creation and validation

Overall, we observed heterogeneity of the recommendations made by the MDC in Groups 2 and 3. As for the Group 1, (RER+/IHC+), when families with positive somatic tests are considered to be "at (high) risk", the recommendation to implement a Lynch-type surveillance plan should be considered whatever the familial context.

Through this study, we observed a heightened awareness of our work during the MDC. In particular, we noted the difficulties that are encountered and the discrepancies that occur in our decision-making process. The work provided by the members of the MDC is not trivial. Cases are dealt with on an individual basis and at varying dates. Therefore, it is not unusual, given the absence of a standardization of the process, that differences will exist in the patient care recommendations that are made.

Therefore, we propose an easy-to-use database that can be diffused regionally or even more globally. This database consists of four chapters (proband information, family history, genetic status, and surveillance recommendation) using drop-down menus to simplify the synthesis of data needed for decision-making. For each drop-down menu, a list of response choices is provided. These responses are those generally found in MDC conclusions based on our cohort. A free-text field is also available for cases where the answer could be different or needs to be clarified (Figure 3).

It is not easy to standardize every decision-making (due to time, upsurge of new technologies), and the final goal is to improve patients and families follow-up, for an optimal quality of care management.

Conclusion

Colorectal cancer is a public health issue. Because it can be inherited, a diagnosis may have implications for both the patient and his or her relatives. To facilitate patient care management, French hospitals utilize multidisciplinary committees in certain cases. MDCs enable professionals and experts to optimize decision-making, taking into account relevant expert advice. In response to the observation of discordance of decisions made within MDCs, we developed a computerized system to aid in standardization of the decision-making

Table 3. Overview of criteria which allow to validate or not a genetic analysis. MMR: Mismatch Repair genes

Nb of cases	met criteria			
	Amsterdam II	Bethesda	none	
RER+/IHC+	2	4	2	tested MMR +
		6	1	tested MMR -
	1	20	12	Not tested (to discuss)
	1	19	5	To test
RER+/IHC-	3	1		tested MMR +
		1		tested MMR -
				Not tested
		3		To test
RER-/IHC-				tested MMR +
		8	3	tested MMR -
	6	23	8	Not tested (no indication)
	2	6	3	To test

MMR+: mutation in MMR gene. MMR-: no mutation in MMR gene. RER+: instability of microsatellites. RER-: stability of microsatellites. IHC +: loss of MMR proteins expression. IHC-: no loss of MMR protein expression.

Different chapters :

En-tête administratif

N° Famille N° Extérieur

Proposant

Indemne RER ⓘ IHC ⓘ Méthylation promoteur ⓘ
 CCR1 (âge ans)

Polypose oui diffuse oui atténuée Type majoritaire âge de début ans
Polypes Adénomateux (tub. vill) Nombre Dysplasie maximum Taille max
 Chronicité âge de début ans
 RER ⓘ IHC ⓘ Méthylation promoteur ⓘ

Hyperplasique Nombre âge de début ans
 Autre type Nombre âge de début ans

Localisation duodénale oui non non précisé

RER ⓘ IHC ⓘ Méthylation promoteur ⓘ

Tumeur cancéreuse autre
 (âge ans)

Lésions non cancéreuses ?
 (âge ans)

Famille

RER ⓘ IHC ⓘ Méthylation promoteur ⓘ

Parenté ⓘ âge de début ans

Type de tumeur

Polypes âge de début ans

Dysplasie max si adénome Nombre total

Génétique

Cas index Gène

Surveillance

Qui ? Type de surveillance Examen Rythme

âge de début ans

Chirurgie ? Référentiel ?

Proban:

Polyposis :

Choose yes/no
 - yes diffuse
 - yes attenuated
 - yes ?
 - no

Majority type
 - adenomatous
 - hyperplastic
 - juvenile
 - scalloped
 - hamartomatous
 - other

polyps :

max dysplasia
 - High
 - Low
 - Unspecified

Chronicity
 - synchronous
 - metachronous
 - not defined

Duodenal localization

choose
 yes
 no
 unspecified

other cancerous tumor
 - digestive
 - endometrium
 - desmoid
 - cutaneous
 - cerebral
 - endometrioid ovary
 - other

Non-cancerous lesions?
 - Benign skin lesion
 - other
 - no
 - not specified

Family:

relationship*
 - 1(father)
 - 1(mother)
 - 1(children)
 - 1(siblings)
 - 2(paternal uncles/aunts)
 - 2(maternal uncles/aunts)
 - 3(paternal grand-parents/1st cousins)
 - 3(maternal grand-parents/1st cousins)
 - 4 and more (maternal grand-parents' hand)
 - 4 and more (paternal grand-parents' hand)

type of tumor
 - colorectal cancer
 - endometrium cancer
 - stomach cancer
 - ovarian cancer
 - skin cancer
 - desmoid tumor
 - brain tumor
 - benign cutaneous lesion
 - other

polyps
 - adenomatous
 - hyperplastic
 - juvenile
 - scalloped
 - hamartomatous
 - other

Dysplasia if adenomatous
 - High
 - Low
 - Unspecified

*information « i »: 1, 2, 3, 4 correspond to degree of relationship between patient and proban.

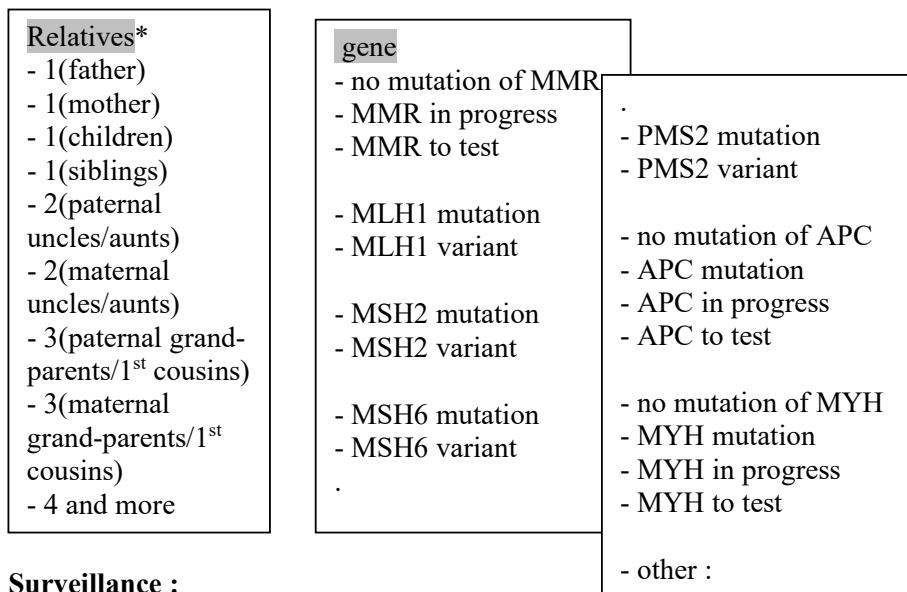
RER Statut
 - MSS (microsatellite stability)
 - MSI (microsatellite instability)
 - MSI-high
 - MSI-low
 - failure
 - impossible
 - in progress
 - to do

Expression of proteins in IHC
 - persistence
 - loss (specify)
 - heterogeneous (specify)
 - failure
 - impossible
 - in progress
 - to do

date of test
 ../../..

Methylation of promoter
 - yes
 - no
 - failure
 - impossible
 - In progress
 - to do

Genetic :



Surveillance :

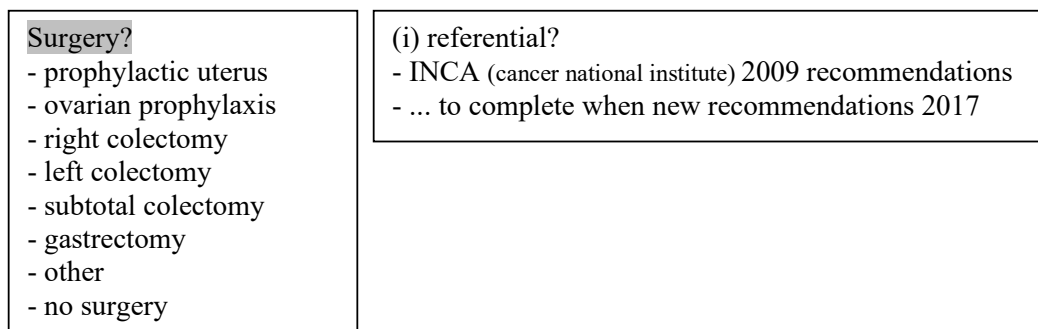
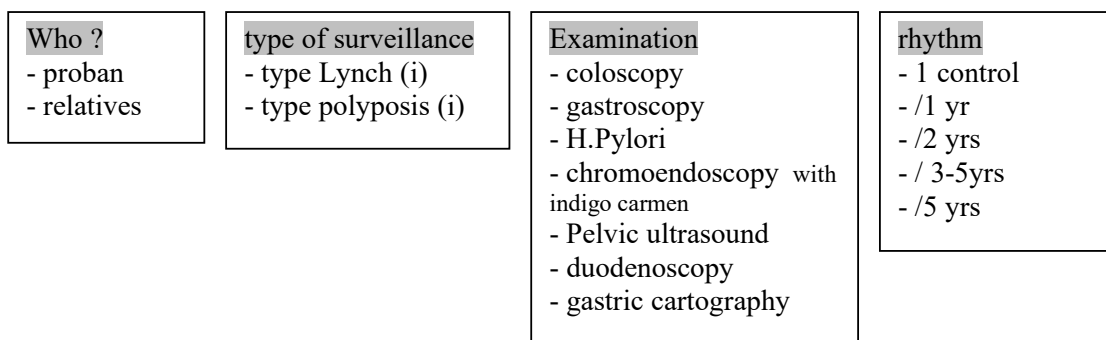


Figure 3. bdd: EQID database

process. and diffused it to every collaborating partner of our MDC. By comparing how decisions were made among different groups of patient families, we were able to differentiate and categorize surveillance protocol recommendations. It appears indeed paramount to establish homogenous groups of patients/families through pedigrees in order to judiciously manage and follow-up with care. As a result, we targeted a better rationalization of care management and family prevention. Further studies are necessary to evaluate the quality control of our work by testing the software against fictive pedigrees, discussing them within MDCs, and comparing decisions with those previously given.

The EDIQ system is thus essential and will allow for the formalization and standardization of our MDC's decision-making process in patient cases. Based on our initial observations, it will be important to perform further studies at a national level to evaluate and improve the quality and consistency of decision-making processes in other MDCs as well.

This should also help us to improve the quality of genetic counselling provided to patients and their families. Somatic testing (RER/IHC) remains an important step prior to the decision by the MDC to recommend genetic testing for colorectal cancer related genes.

We need to prescribe somatic testing more often, even if there is not a familial context of predisposition. In France, these analyses are under-used (less than 30% of testing is made for newly diagnosed colorectal cancer, because of old tumour, no availability of medical professional, or maybe ignorance). These tests are not more expensive than a genetic test and this approach could, therefore, avoid genetic testing if the tumour phenotype is not in favour of hereditary predisposition.

We also studied PREMM1.2.6, a software that provides mutation risk calculation for Lynch syndrome. A threshold of 5% validates *MMR* gene test indication. We highly recommend it [5].

Acknowledgment

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