JUNE 2011

Summary of report on polyposis associated with *MUTYH* biallelic mutations

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RELATIVES CARRYING A MONOALLELIC MUTATION: RISK OF COLORECTAL CANCER AND RECOMMENDATIONS FOR CARE

INTENDED FOR USE BY HEALTHCARE PROFESSIONALS

INSTITUT NATIONAL DU CANCER
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The Institut National du Cancer (French National Cancer Institute) is a health and science agency dedicated to cancers. Its objective is to promote and coordinate the fight against cancer in France.

This document is published as part of the
COLLECTION
Studies & expertises
published by the Institut National du Cancer

This document is available for download
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THIS DOCUMENT WAS PUBLISHED AS PART OF THE IMPLEMENTATION OF THE 2009-2013 CANCER PLAN.

Measure 23: Develop specific care management for patients with rare forms of cancer or genetic predispositions as well as for children, adolescents and the elderly

Action 23.3: Monitoring people at high genetic risk of cancer

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KEY POINTS

"***MUTYH-associated polyposis***" (**MAP**), related to a **germline mutation of the two alleles of *MUTYH***, was first described in 2002. Its inheritance is autosomal recessive, in contrast to the classic "familial adenomatous polyposis" (FAP), related to an *APC* germline mutation, with autosomal dominant inheritance.

PHENOTYPE OF BIALLELIC MUTYH MUTATIONS CARRIERS

MUTYH-associated polyposis is most often of the "attenuated" type: most patients who are carriers of biallelic *MUTYH* mutations have between 15 and 100 **colorectal polyps**, and an **average age at diagnosis** of **45.**

Patients who are carriers of biallelic *MUTYH* mutations exhibit a **relative risk of colorectal cancer** in the order of **30 to 50** times that of the general population. Colorectal cancer is present at the time of diagnosis of polyposis in approximately 50% of cases. For these cases, the **average age** is **48**.

Extracolorectal manifestations may also be observed. **Duodenal adenomatous polyps** are possible and are associated with a risk of **duodenal adenocarcinoma**. **Dermatological manifestations**, in particular lesions developing on sebaceous glands, have also been reported.

INDICATIONS FOR *MUTYH* ANALYSIS

For **patients with polyposis**, a *MUTYH* mutation study should be conducted if the cumulative number[1] of (histologically confirmed) adenomatous polyps is:

- **Greater than or equal to 15**, regardless of age
- **Between 10 and 14** before the age of 60
- **Between 5 and 9** if somatic analyses do not favour Lynch syndrome[2] and if at least one additional criterion applies (adenomatous polyps appearing before the age of 40, associated colorectal cancer before the age of 60, at least 5 of the polyps are "advanced", associated dermatological manifestations before the age of 50, associated duodenal adenomas)

Analysis of *MUTYH* is indicated for the **siblings** (brothers and sisters) and **children (over 18 years of age)** of biallelic *MUTYH* mutation carriers. The primary objective for testing **parents** is to confirm the biallelic character of the mutations identified in the patient.

[1] The cumulative number of adenomatous polyps is the total number of polyps identified during consecutive colonoscopies.

[2] Absence of microsatellite instability (MSS phenotype) and/or conservation of the expression of MMR proteins in immunohistochemistry

RECOMMENDATIONS FOR CARE BIALLELIC OF PATIENTS WITH MUTYH MUTATIONS

Biallelic *MUTYH* mutation carriers should benefit from specialised care based on:

- **Colorectal surveillance** via colonoscopy with pancolic indigo-carmine chromoendoscopy. This surveillance should begin at the age of 20. If results are normal, the exam should be repeated at the ages of 25 and 30, and at least once every 2 years thereafter.
- Gastric and duodenal surveillance starting from the age of 25. If results are normal, this exam should be repeated at the age of 30, and at least once every 2 years thereafter (at the same time as screening colonoscopies). In the event of a duodenal polyposis, the exam frequency should be adjusted according to the degree of severity.
- **Colorectal surgery** in cases of degenerated polyposis or non-degenerated polyposis if not "controllable" with endoscopy.
- **Dermatological surveillance**, featuring an initial dermatological consultation with the aim of detecting sebaceous tumours requiring special treatment.

EVALUATION OF THE RISK OF COLORECTAL CANCER IN PATIENTS WITH MONOALLELIC *MUTYH* MUTATION AND RECOMMENDATIONS FOR CARE

Monoallelic MUTYH mutations are probably **not associated with a significant increase in the risk of colorectal cancer in the general population** or are associated with a very modest and merely marginal increase in this risk, probably limited to Y165C mutation.

Contrary to that observed in the general population, the existence of a **monoallelic MUTYH** mutation **among first-degree relatives** of patients with MAP may be associated with a moderate **increase in the risk of colorectal cancer**.

The suspected increased risk of colorectal cancer among these relatives justifies the use of **systematic endoscopic surveillance** under the terms established in the first-degree relatives of patients with sporadic colorectal cancers.

SUMMARY OF CURRENT KNOWLEDGE

Recent years have been characterised by an improvement in our knowledge of genetic determinism of adenomatous polyposes and by the description in 2002 of a new entity called "*MUTYH-associated polyposis*" (MAP), related to biallelic mutations of this gene. Its autosomal recessive mode of inheritance contrasts with the autosomal dominant inheritance of the classical "familial adenomatous polyposis" (FAP), associated with an *APC* germline mutation. Although some phenotypic features may be of value to distinguish these two conditions, their clinical “spectra” largely overlap and the differential diagnosis may be difficult.

The purpose of this expertise conducted under the auspices of the French Institut National du Cancer (INCa) was to assess the current state of knowledge on *MUTYH*-associated polyposis and to establish some recommendations in the field of molecular analysis (indications of tests and analysis strategies for affected patients and their relatives) and of clinical management based on available data in the litterature, on the results from the French molecular genetics laboratories performing MUTYH analysis and on the opinions of biologists and clinicians experts (genetic counsellors and gastroenterologists). The risk of colorectal cancer among relatives carrying a monoallelic *MUTYH* mutation was also studied.

FREQUENCY OF DELETERIOUS *MUTYH* MUTATIONS

Y165C (c.494G > A; p.Tyr165Cys) and G382D (c.1145G>A; p.Gly382Asp) are the most common *MUTYH* mutations in Western populations. Their allelic frequency is estimated at 0.2% and 0.6% in the general population, respectively. Other deleterious mutations have been reported. Their frequency has not been properly evaluated and is generally underestimated due to the molecular analysis strategies frequently applied. The global allelic frequency of these other mutations is probably greater than 0.2% and the frequency of deleterious *MUTYH* mutations in the unselected Western population is therefore expected to be higher than 1%. Thus, the frequency of monoallelic *MUTYH* mutation carriers is believed to be at least 2% in the general population and between 1 and 2 persons out of 10,000 are supposed to have biallelic mutations.

In Western countries, the frequency of biallelic *MUTYH* mutations is estimated at 14% among patients with colorectal adenomatous polyposis not associated with *APC* germline mutation. This frequency depends on the colonic phenotype. In fact, it is estimated to be twice higher (approximately 20%) in patients with a number of polyps comprised between 15 and 99 as in patients with a number of polyps less than 15 or greater than 100.

The allelic frequency of deleterious *MUTYH* mutations in patients with colorectal cancers (without polyposis) is similar to the estimated frequency in the general population. This observation suggests that these mutations play no or only limited role in "sporadic" colorectal carcinogenesis. Likewise, no difference was found for the frequency of *MUTYH* mutations between patients suffering from different types of cancers and the general population.

Available data on the frequency of *MUTYH* mutations in Eastern populations are scarce. However, it appears that this frequency is much lower than in Western populations, especially in patients with adenomatous polyposis in whom biallelic mutations are found in less than 1% of cases). In addition,

the mutational spectrum is notably different (rarity of Y165C and G382D mutations, identification of mutations not reported in Western populations).

PHENOTYPE OF PATIENTS WITH BIALLELIC *MUTYH* MUTATIONS

The data concerning the phenotype associated with biallelic *MUTYH* mutations must be interpreted with caution because of the poor quality of the currently available studies: numerous missing data, no standardised endoscopic exploration, selection bias for polyposis in retrospective series often published by laboratories, selection bias for cancer and inaccuracies in case-control studies, limited number of patients for the reported cases and series. This argues in favour of conducting descriptive prospective studies with optimal and standardised endoscopic examination procedures in unselected individuals.

1. Colorectal phenotype

1.1. Colorectal polyposis

- *MUTYH*-associated polyposis is most often of "attenuated" type: the total count of colorectal polyps being usually comprised between 15 and 100 in patients with biallelic *MUTYH* mutations.
- The diagnosis of colorectal polyposis occurs in adulthood with an average age at diagnosis of 45 years.
- It does not appear to be any preferential location of the polyps in the colon (proximal *versus* distal) or in the rectum.
- The association of adenomatous polyps with serrated lesions (hyperplastic polyps and serrated adenomas), even in large numbers, is possible and should not rule out the diagnosis of *MUTYH*-associated polyposis.

1.2. Colorectal cancers

- Colorectal cancer is present at the time of diagnosis of polyposis in approximately 50% of cases. This high frequency is probably explained by the absence of significant family history due to the autosomal recessive mode of inheritance of the disorder in many patient. In this situation, patients do not benefit from systematic colorectal examination and the diagnosis is established when symptoms appear which may correspond to malignant transformation.
- The relative risk of colorectal cancer with respect to the general population is estimated between 30 and 50. The absolute risk has not been properly evaluated but is obviously high in the absence of adequate care.
- The average age at the time of colorectal cancer diagnosis is estimated at 48 years. Several cases of colon cancers diagnosed between the age of 20 and 30 years have been reported, but they are in the minority.
- Several cases of multifocal onsets (multiple synchronous cancers) have been reported.

- The time of progression from adenoma to adenocarcinoma in the specific context of *MUTYH*-associated polyposis is not known.
- Colorectal cancers arising in the context of *MUTYH*-associated polyposis do not exhibit specific pathological characteristics compared with sporadic cases.
- Microsatellite instability (MSI or Deficient MMR phenotype) and/or traditionally associated histological features (e.g mucinous type and dense lymphocytic infiltration of tumour stroma or "Crohn-like" reaction) are possible and should not rule out the diagnosis of *MUTYH*-associated polyposis.

1.3. Phenotype-genotype correlations

Clinical and biological data argue in favour of a worse pathogenicity and an earlier penetrance of Y165C mutation compared with G382D mutation. In fact, the age at diagnosis for colorectal polyposis and more specifically for colorectal cancers is younger in Y165C homozygous patients ([Y165C + Y165C]) than in patients with another genotype (such as [Y165C + G382D] and [G382D + G382D]).

The phenotype-genotype correlation for other mutations is much more difficult to assess because their allelic frequencies are far lower.

2. Upper digestive tract onset

Duodenal adenomatous polyps or polyposis are possible in patients with biallelic *MUTYH* mutations and are associated with an increased risk of duodenal adenocarcinoma. The available data do not allow to estimate the prevalence of these lesions to quantify the risk of duodenal cancer.

Gastric polyps, glandulocystic fundic polyposis and gastric cancers have also been described in this context.

3. Extradigestive manifestations and other tumoral risks

3.1. Cutaneous manifestations

Lesions deriving from sebaceous glands have been reported in patients with biallelic *MUTYH* mutations: sebaceous adenomas and sebaceous carcinomas, as well as sebaceous hyperplasia lesions; typically in large numbers and/or sizes. The available data do not allow to evaluate their prevalence.

Melanomas, squamous cell carcinomas, basal cell carcinomas and benign lesions (such as lipomas and pilomatricomas) have also been reported, but it is not possible to determine their prevalence and even to establish a clear link with this genotype.

3.2. Other phenotypic manifestations

Miscellaneous manifestations (retinal pigment epithelial hypertrophy, dental abnormalities, osteomas, etc.) and different types of cancers have been reported. However, it is doubtful that these manifestations can be attributed to biallelic *MUTYH* mutations.

TESTING INDICATIONS

1. Indications of *MUTYH* analysis in patients with colorectal adenomatous polyposis/multiple adenomatous polyps (probands)

Based on available literature and on the French molecular genetics laboratories data, the indications for *MUTYH* analysis have been retained in probands with one of the following conditions:

- Cumulative number[3] of (histologically confirmed) adenomatous polyps ≥ 15, regardless of age.
- Cumulative number of (histologically confirmed) adenomatous polyps between 10 and 14 before the age of 60.
- Cumulative number of (histologically confirmed) adenomatous polyps between 5 and 9, if at least one of the following additional criteria is met and if the somatic analyses do not argue for a Lynch syndrome[4]:
  - ✓ These adenomatous polyps are diagnosed before the age of 40.
  - ✓ These adenomatous polyps are associated with a colorectal cancer diagnosed before the age of 60.
  - ✓ At least 5 of these adenomatous polyps are of "advanced" type (≥ 10 mm in diametre and/or with tubulovillous or pure villous architecture and/or architecture associated with high-grade dysplasia lesions).
  - ✓ These adenomatous polyps are associated with one or more sebaceous adenomas or carcinomas or multiple and/or large sebaceous hyperplasia lesions before the age of 50.
  - ✓ These adenomatous polyps are associated with duodenal adenomas.

These indications correspond to a likelihood of identifying biallelic *MUTYH* mutations of more than 10%.

MUTYH analysis is not indicated in the following situations:

- Cumulative number of adenomatous polyps < 5, regardless of their histological and macroscopic characteristics or the age at diagnosis
- Isolated colorectal cancers, regardless of age at diagnosis
- Other types of cancer, in particular gastric, endometrial and breast cancers
- Hamartomatous and serrated polyposis

Molecular characterisation of polyps and colorectal cancers (frequency and profile of transversions, in particular in *APC* and *KRAS* genes, may be promising identifying patients candidate for *MUTYH*

[3] The total number is the total number of adenomatous polyps identified during consecutive surveillance exams and therefore accumulated over time.

[4] Absence of microsatellite instability and/or conservation of the expression of MMR proteins evaluated by immunohistochemistry

germline analysis. This remains to be validated, and cannot currently be taken into account to define the indications of *MUTYH* analysis.

Because of the complexity of this type of prescription and of the possible alternative diagnoses (Lynch syndrome and *APC*-associated familial adenomatous polyposis), it is recommended that any *MUTYH* testing prescription is made within a specific consultation of genetic counselling. Moreover, all relevant information (colonoscopy and pathological reports) should be transmitted to the laboratory.

2. Indications for testing relatives of patients with biallelic *MUTYH* mutations.

The indications of *MUTYH* testing are limited to individuals in whom the result has a direct impact on medical care.

Therefore, these indications concern the first-degree relatives of probands with biallelic *MUTYH* mutations and, in particular:

- Their siblings (who have a 25% chance of being carriers of both of the proband's deleterious mutations)
- Their children who could be carriers of biallelic *MUTYH* mutations; one inherited from the "proband" parent and the other one from the other parent whose genotype is unknown[5].

It is also recommended to test the parents of the proband. The primary aim of this approach is to demonstrate that the two mutations identified are truly biallelic.

On the other hand, there is no indication to perform a test in:

- the non-first-degree relatives of patients with biallelic *MUTYH* mutations;
- On first-degree relatives of patients with colorectal polyposis in whom the genetic analysis only identified a single deleterious mutation isolated or associated with a variant of unknown significance, or two variants of unknown significance

These recommendations are based on experts' opinions and are subject to future revisions. They are only applicable in the absence of inbreeding.

In any case, genetic testing should be prescribed in relatives within a specific consultation of genetic counselling[6], and there is no benefit in performing the test before the age of 18. Finally, the identification of an adenomatous polyposis or of multiple adenomatous colorectal polyps in a putative monoallelic *MUTYH* mutation carrier must lead to perform an exhaustive molecular analysis of *MUTYH*, or consider another type of genetic alteration.

ANALYSIS STRATEGIES

[5] Performing a molecular analysis in the other parent is another valuable approach as it is possible to rule out biallelic *MUTYH* mutations in the couple's children if no mutation is identified in this parent (except in cases of false paternity).

[6] Decree No. 2008-321 of 4th April 2008: "For asymptomatic individuals with a family history, a genetic trait test can only be prescribed with the framework of a personal medical consultation. This consultation must be conducted by a physician working in a multidisciplinary team featuring both clinical and genetics experts". This consultation must be conducted by a physician working in a multidisciplinary team featuring both clinical and genetics experts".

1. Types and distribution of *MUTYH* variants

At least 164 different variants of *MUTYH* have been reported in the literature, 30% of which being almost certainly deleterious.

The 10 French molecular genetics laboratories conducting *MUTYH* analyses identified, after exclusion of non-causal variants, 73 different variants, 45.2% of which corresponding to deleterious mutations (other variants are of unknown significance).

96.1% of all identified deleterious mutations are located in exons 7, 9, 10, 12, 13 and 14.

On the other hand, the 7 most frequently identified deleterious mutations, which are located in exons 7, 10, 12, 13, 14 and 15, represent 91.2% of all deleterious mutations:

- c.494A>G; p.Tyr165Cys (also referred to as Y165C)
- c.891+3A>C; p.Gly250TrpfsX7
- c.1105del; p.Ala371ProfsX23
- c.1145G>A ; p.Gly382Asp (also referred to as G382D)
- c.1185_1186dup; p.Glu396GlyfsX43
- c.1395_1397del; p.Glu466del
- c.1435G>T; p.Val479Phe

No *MUTYH* rearrangements have been identified so far. Nevertheless, because of the limited number of patients tested for *MUTYH* rearrangements and of the lack of sensibility of applied techniques, no meaningful conclusions can be drawn to date

2. Molecular analysis strategy for probands

The methods used for the genetic diagnosis of *MUTYH*-associated polyposis in probands must have the objective to identify the two responsible deleterious mutations.

There are therefore two possible strategies for the molecular analysis, depending of the laboratory organisation:

- Either an exhaustive analysis of the *MUTYH* gene (analysis of exons 1 to 16)
- Or a "cascading" or "sequential" analysis, which stops as soon as two deleterious mutations have been detected. This strategy involves first testing for some specific mutations (for instance, the 7 most frequent deleterious mutations) or exons (such as exons 7, 9, 10, 12, 13, 14) and then proceeding with the analysis for persons in whom 2 deleterious mutations were not detected at the end of the first analysis phase (only 1 deleterious mutation identified, isolated or associated with a variant of unknown significance; 1 or 2 variant(s) of unknown significance).

3. Molecular analysis strategy for relatives

For first-degree relatives of probands with biallelic deleterious *MUTYH* mutations, the following analysis strategies are recommended for molecular analysis:

- **Parents**: targeted analysis for the two mutations identified in the proband, provided that polyposis/multiple polyps are not detected during the screening colonoscopy for a person over 60 years of age[7].
- **Siblings (brothers and sisters)**: targeted analysis for the two mutations identified in the proband, provided that polyposis/multiple polyps are not detected during the screening colonoscopy in individuals diagnosed with only one of the mutations identified in the proband.
- **Children (of legal age)**: depending on the laboratory organisation
  - ✓ Either an exhaustive analysis of *MUTYH* gene
  - ✓ or screening for the two mutations identified in the proband along with a further analysis to identify any mutations inherited from the other parent with a sensitivity higher than 90% (analysis of at least exons 7, 9, 10, 12, 13, 14, enabling the identification of 93.9% of variants, deleterious mutations and variants of unknown significance).

    If the second strategy is selected, complementary analyses must take into account the geographic origin of tested individuals (for example, analysis of exon 3 is mandatory in patients of Pakistani descent).

The identification of an adenomatous polyposis or of multiple adenomatous polyps at screening colonoscopy in any relative in which only one *MUTYH* mutation has been identified must lead to perform an exhaustive *MUTYH* analysis in order to identify a second mutation, or even to consider another type of genetic alteration.

These recommendations are based on experts' opinions and are subject to future revisions. They are only applicable in the absence of inbreeding.

RECOMMENDATIONS FOR CARE OF PATIENTS WITH BIALLELIC *MUTYH* MUTATIONS

Care for patients with biallelic *MUTYH* mutations is dominated by colorectal surveillance. It should also include gastric and duodenal surveillance and at least one initial dermatological evaluation. At the current state of our knowledge, there are no other phenotypic manifestations or other at-risk tumoral locations justifying systematic analysis and surveillance.

The recommendations below were established based on available published data and result from a consensus among the experts.

1. Care for colorectal polyposis

1.1. Colorectal surveillance

- Colorectal surveillance is based on colonoscopy with pancolic indigo-carmine chromoendoscopy. The objective, when deemed reasonable, is to proceed to polypectomy for all identified polyps.

[7] The normality of colonoscopies after 60 years of age allows us to reasonably exclude *MUTYH* biallelic mutations. In the rare cases in which one parent is less than 60 years of age, the same analysis strategy recommended for the children can be used.

- The first colonoscopy must be performed at the age of 20 years. In the absence of colorectal polyps, the colonoscopy should be repeated at the ages of 25 and of 30 years, and at least once every 2 years thereafter.
- There is no alternative to "optical" colonoscopy for colorectal surveillance. In particular, surveillance with virtual colonoscopy, CT scan with water enema water enema or colonic video capsule, is not recommended.

1.2. Colorectal surgery: indications and modalities

1.2.1. Polyposis associated with colorectal cancer

- Carcinologic total colectomy with ileorectal anastomosis is the recommended surgical procedure in cases of colonic polyposis complicated with colon cancer when the rectum is not or only moderately involved and when its preservation is considered acceptable.
- Carcinologic coloproctectomy with ileoanal anastomosis is recommended in cases of colorectal polyposis complicated with rectal cancer (when the preservation of the sphincter is possible) or with colon cancer and significant or severe polyposis of the rectum incompatible with its preservation.

1.2.2. Polyposis or multiple polyps without obvious malignant transformation

- Total colectomy with ileorectal anastomosis or coloproctectomy with ileoanal anastomosis are also recommended in the absence of colorectal cancer when colorectal polyposis is not amenable to endoscopic complete “clearing”. In these situations, the choice between the two surgical procedures is based on the meticulous evaluation of the rectum involvement and of its severity.
- There is no indication for a "true prophylactic" colectomy, in patients without or with a limited number of colorectal polyps amenable to endosopic polypectomies.

In any case, the indications and the modalities of colorectal surgery in the context of *MUTYH*-associated polyposis must be discussed and established by a multidisciplinary team involving surgeons, gastroenterologists and oncogeneticists.

2. Gastric and duodenal surveillance

- Gastric and duodenal surveillance is based on œsogastroduodenal fibroscopy with duodenal chromoscopy and on duodenoscopy, at least if the papilla cannot be viewed with a forward-viewing fiberscope.
- This first examination is recommended at the age of 25 years. If normal, it should be repeated at the age of 30 years and at least once every 2 years thereafter (at the same time as screening colonoscopies).
- In patients with duodenal polyps/polyposis, the periodicity of surveillance depends on the severity of duodenal involvment evaluated acording to the modified Spigelman's score.

- There is no alternative to "optical" endoscopy for surveillance of the upper digestive tract in these patients.

3. Dermatological surveillance

At least one initial dermatological evaluation is recommended.

The objectives of this consultation are to detect sebaceous lesions requiring specific treatment, to inform patients of the risk of developing these kinds of lesions and other potentially severe cutaneous manifestations (melanoma, carcinoma) and to raise awareness and to "educate" the patients to improve their identification.

EVALUATION OF THE RISK OF COLORECTAL CANCER IN PATIENTS WITH MONOALLELIC *MUTYH* MUTATION AND RECOMMENDATIONS FOR CARE

1. Risk of colorectal cancer associated with monoallelic *MUTYH* mutations

1.1. General population

Monoallelic *MUTYH* mutations are probably not associated with a significant increase in the risk of colorectal cancer in the general population, or are associated with a very modest and merely marginal increase in this risk, probably limited to Y165C mutation.

1.2. First-degree relatives of patients with MUTYH-associated polyposis

Several observations of "pseudo-dominant" inheritance (due to a history of adenomatous polyps or colorectal cancer in parents or children of patients with MUTYH associated polyposis) reported in the literature and the results of the only available study specifically addressing the question in parents of patients with *MUTYH*-associated polyposis indicate that monoallelic *MUTYH* mutations in these individuals may be associated with a moderate increase in the risk of colorectal cancer. There is some degree of uncertainty on the "magnitude" of this risk.

The discrepancy between the absence of an increased risk conferred by monoallelic *MUTYH* mutations in the general population and the possible increase in this risk among first-degree relatives of patients with *MUTYH*-associated polyposis could be explained by associated susceptibility genetic factors for colorectal polyps/cancers.

2. Recommendations for care for first-degree relatives of patients with *MUTYH*-associated polyposis carrying one of the two mutations identified in the proband

The suspected increased risk of colorectal cancer among these relatives justifies the performance of systematic endoscopic screening under the terms established in the first-degree relatives of patients with sporadic colorectal cancers.

- The colonoscopies must be performed once every 5 years starting at the age of 45 years. In case of identification of at least one "advanced" adenomatous polyp (≥ 10 mm in diameter and/or tubulovillous and pure villous architecture and/or high-grade dysplasia lesions) or of multiple adenomatous polyps (≥ 3) at one control, the following colonoscopy should be performed at 3-year intervals.

- There is no reason to recommend systematic chromoendoscopy with indigo-carmine and the available data do not favour endoscopic screening at younger ages.
- Virtual colonoscopy has no place in the "1st line" exploration of the colon and should be reserved for those rare situations in which video colonoscopy is contraindicated or not feasible.
- The Hémoccult® faecal occult blood test, which is the recommended test for colorectal cancer screening in the French general population, is not indicated in this situation.

- There is no indication for systematic endoscopic surveillance of the upper digestive tract in these individuals.
- There is currently no rationale for modulating these recommendations according to the nature of the mutation identified.
- There is no indication for systematic colonoscopic screening in monoallelic *MUTYH* mutation carriers, who are relatives of the 2nd-degree or higher of a patient with *MUTYH*-associated polyposis.

These recommendations were established based on literature data and represent a consensus among the experts.

They should be subject to future revision following advances in our knowledge of the risk of colorectal cancer in these persons.

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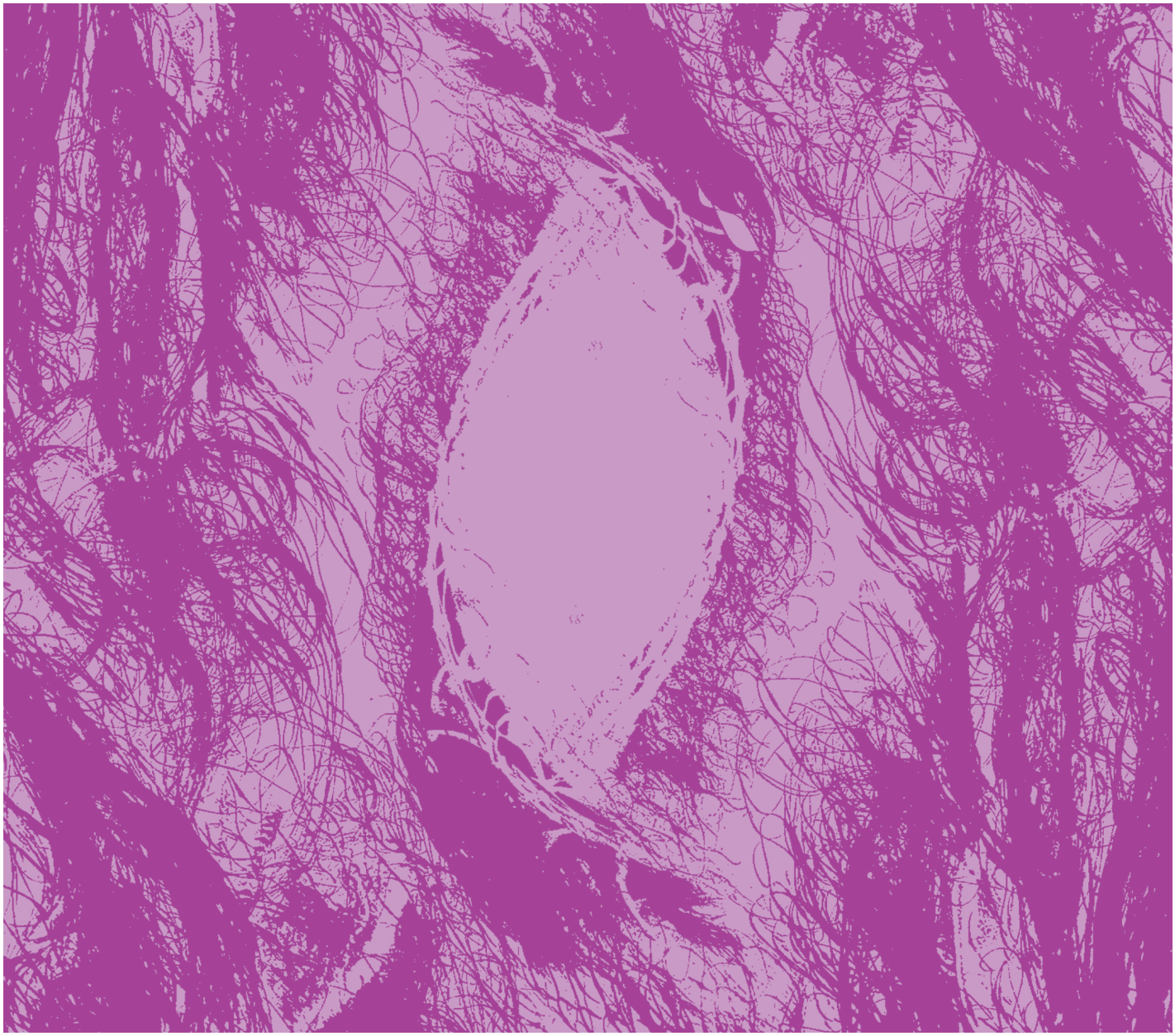

Edited by the Institut National du Cancer
Design/production: Institut National du Cancer

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