Efficacy of colonoscopy, colon capsule and fecal immunological test for colorectal cancer screening, in first degree relatives of patients with colorectal neoplasia: a prospective randomized study - FAMCAP Study

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Abstract:

Fecal immunological test (FIT) is the reference screening method in average risk patient. FIT is proposed every 2 years to all asymptomatic subjects with average risk aged from 50 to 74 years in France. Optical colonoscopy (OC) is the gold standard examination for patients at increased risk of colorectal cancer, like those with a first degree relative with colorectal cancer (relative risk between 2 and 4 times that of the general population). Colonoscopy should be performed in this high risk group before 50 years or 5 to 10 years before the earliest case of colorectal cancer. Optical colonoscopy has important limitations: complications (perforation, bleeding), need to use general anesthesia (in France 95% of colonoscopy are performed under general anesthesia), and low acceptability for screening even in high risk persons (40% in the best cases). In this high risk population, there is a potentially important place for alternative methods. FIT could be one of them, with already a significant amount of data suggesting its interest. No data are available in high risk French patients. Colon capsule endoscopy (CC) is a more recent technique with sparse data in this high risk group, and no prospective comparison with optical colonoscopy in this indication. Capsule endoscopy has the advantage of high feasibility, very low risk, probably (but to be demonstrated) increased acceptability, and represents the closest examination as compared to colonoscopy. This justifies a prospective study comparing in a randomized methodology these 3 modalities for the identification of advanced neoplastic lesions of the colon in well characterized group of subjects at high risk of colorectal cancer. We propose a prospective, randomized protocol of non-inferiority in order to compare the two new strategies to the reference strategy for the detection of advanced colorectal neoplasia (colon or rectal cancers, large adenoma > 1 cm or high grade dysplasia ; 1st arm: OC first; 2nd arm: CC first, OC at 3 years for those patients with negative initial CC; 3rd arm: annual FIT for 2 years (t_0, t = 1 year, t = 2 years), colonoscopy at 3 years for those patients with negative FIT during the study). The new strategies will be considered non-inferior to the reference strategy if the study allows to conclude that the absolute reduction of the proportion of detected patients is not greater than 3% in comparison to the reference strategy.

1- Principal project

SUMMARY

Fecal immunological test (FIT) is the reference screening method in average risk patient. FIT is proposed every 2 years to all asymptomatic subjects with average risk aged from 50 to 74 years in France. Optical colonoscopy is the gold standard examination for patients at increased risk of colorectal cancer, such as those with a first degree relative with colorectal cancer (RR 2 to 4). Colonoscopy should be performed in this high risk group before 50 years or 5 to 10 years before the earliest case of colorectal cancer. Optical colonoscopy has important limitations: complications (perforation, bleeding), need to use general anesthesia (in France 95 % of colonoscopy are performed under general anesthesia), and low acceptability for screening even in high risk persons (40% in the best cases). In this high risk population, there is a potentially important place for alternative methods. FIT could be one of them, with already a significant amount of data suggesting its interest. No data are available in high risk French patients. Capsule endoscopy is a more recent technique with sparse data in this high risk group, and no prospective comparison with optical colonoscopy in this indication. Capsule endoscopy has the advantage of high feasibility, very low risk, probably (but to be demonstrated) increased acceptability, and represents the closest examination as compared to colonoscopy. This justifies a prospective study comparing in a randomized methodology these 3 modalities for the identification of advanced neoplastic lesions of the colon in well characterized group of subjects at high risk of colorectal cancer.

RATIONAL

1.1. Stratified risk of colorectal cancer in the general population

In western countries, asymptomatic subjects without any personal or familial medical history present a 4-5% lifetime risk of developing colorectal cancer corresponding to a relatively frequent cancer (80% of the 42 000 new cases each year in France). This situation defines the so called "average risk population". For this average risk population, various screening strategies are implemented in different countries. Fecal occult blood testing using fecal immunological test (FIT) is proposed every 2 years from 50 to 75 years in France.
A second group of subjects corresponds to the "high risk" group for colorectal cancer with a 8 to 20% lifetime risk of developing colorectal cancer. This is a heterogeneous group including subjects with a family history of colorectal cancer or other conditions:

- personal medical history of colorectal cancer and/or adenoma
- colorectal precancerous conditions like chronic inflammation as observed in inflammatory bowel disease
- first degree relatives of patients with a colorectal cancer before 70 years of age
- first degree relatives of patients with a colorectal adenoma before 60 years of age[1]

This definition is evolving with knowledge and obese people have been recently considered as part of this high risk group.[2] People with second degree relatives with colorectal cancer may join this group in the near future.[3] At the present time, colonoscopy is recommended in this population.
Finally, the "very high risk" group corresponds to subjects with genetic predispositions to colorectal cancer like Lynch syndrome or familial adenomatous polyposis. These patients with a 30 to 100% lifetime risk of colorectal cancer are included in specific genetic and surveillance screening programs.

1.2. Optical colonoscopy as the reference examination in people with a high risk of colorectal cancer

People with a family history of colorectal cancer have at least twice the risk of the general population to develop colorectal cancer.
Colonoscopy is the reference examination for colorectal cancer screening in this population of high risk patients according to national and international guidelines. [4] [5]
Colonoscopy is the best available method to detect and remove colonic polyps and therefore serves as the gold standard. Colonoscopy has a high sensitivity for the detection advanced neoplasia (adenoma > 1 cm or with high grade dysplasia or colorectal cancer any stage). In available prospective studies, advanced neoplasia was detected in 3 to 21% of screened patients.[6] Screening recommendations based on a family history are as follows: (1) patients with a single first-degree relative older than 60 years with CRC should receive CRC screening starting at age 50 years and repeating every 5 years with colonoscopy; (2) patients who have one relative with CRC before 60 years or two first-degree relatives with CRC at any age should be screened every 5 years with colonoscopy, starting at 40 years or at an age 10 years younger than the earliest case in the family; and (3) patients with only second- or third-degree relatives with CRC should receive average-risk CRC screening with colonoscopy or stool-based tests starting at age 50 years and repeating at least every 10 years.

However colonoscopy is not infallible. The pooled miss rate for polyps of any size was up to 22% in 6 studies with a total of 465 patients. Adenoma miss rate by size was, respectively, 2.1% (2/96 adenomas > or =10 mm), 13% (16/124 adenomas 5-10 mm), and 26% (151/587 adenomas 1-5 mm). Colonoscopy also does not detect all cancers. Interval cancers are colorectal cancers diagnosed within a few years after an index colonoscopy. They can arise from missed lesions or from the development of a new tumor. Twelve studies reporting on 7,912 interval CRCs were included in a recent meta-analysis. Pooled prevalence of interval CRCs was 3.7%. These cancers were 2.4 times more likely to arise in the proximal colon (6.5%) as compared with distal colon (2.9%).
Moreover, colonoscopy is poorly accepted in this high-risk population. Meta-analyses of published studies have shown that these high risk patients undergo the required colonoscopy in only 40% of cases.[6]
In this setting, alternative and less invasive methods for screening like fecal immunohistochemical testing for hemoglobin (FIT) or colonic capsule (CC) may represent a satisfying alternative to optical colonoscopy (OC) by improving adhesion to screening and finally the efficacy of screening.

1.3. FIT for colorectal cancer screening

FOBT (fecal occult blood test) is a validated strategy for colon cancer screening. FIT is an immunological test detecting hemoglobin in stools that proved to be more sensitive, more specific, and more cost-effective as compared to fecal test based on guaiac reactivity.[7, 8] This test has been mostly evaluated for colorectal cancer screening in average risk population, specifically in France. In several studies, the sensitivity of FIT for the detection of cancer is about 80-88 % but the number of cancers is always low (2-4 cancers/study). The specificity of FIT testing reaches up to 90 % for the detection of advanced neoplasia.
Recently, attempts have been made to use FOBT in the population at high risk of colorectal cancer because of the limited acceptability of colonoscopy. However, few data regarding diagnostic accuracy of FOBT in familial screening programs are available. In a cohort study of asymptomatic high-risk patients with a personal history of adenomas/CRC or family history of CRC, sensitivity, specificity, positive predictive value and negative predictive value of single FIT sampling were 80%, 89%, 3% and 99.9% for CRC and 28%, 91%, 24% and 92% for advanced adenomas, respectively (Terhaar sive Droste JS et al, BMC Gastroenterol 2012). High accuracy of FIT was confirmed in a multicenter study among FDRs (first degree relatives) of CRC patients, in which AUC was 0.96 (95% CI: 0.95-0.98) for CRC and 0.74 (95% CI: 0.66-0.82) for advanced adenomas.[9]
A randomized study comparing FIT and OC in a Spanish population of patients with colorectal cancer familial history suggested that both strategies had a comparable efficacy as regards the main endpoint, *i.e.* the detection of advanced neoplasia. This study compared a biennial FIT screening strategy (up to 3 years follow-up) with an OC strategy, with all FIT negative patients undergoing OC at the end of the follow-up. In this study, advanced neoplasia were detected in 4.2% (FIT) et 5.6% (OC) of about 800 patients in each arm using a usual cut-off of 50 ng Hb/ml of stools. The resulting sensitivity was of 64% for FIT and 93.6% (43/45) in the OC group as regard the detection of advanced neoplasia. In intention to treat analysis and in a per-protocol analysis, there was no significant difference between FIT strategy and OC strategy at the end of the study in terms of advanced neoplasia detection. In contrast, the FIT strategy detects significantly less non advanced colorectal neoplasia (5.4% vs 19.8%, $p < 0.001$) as compared to OC.[10]
FIT thus represents a relatively sensitive screening method for advanced colorectal neoplasia and cancer in an average or a high risk population. FIT may represent a satisfying alternative to colonoscopy in a high risk population, although more studies (only one available in Spanish population) are needed to confirm this, which justifies the present study.

1.4. Capsule endoscopy for colorectal cancer screening

Capsule endoscopy is a non-invasive mean of colorectal examination using a wireless camera located in a transparent capsule. Developed initially for small bowel imaging in 2000-2005, this has been adapted to colorectal examination in 2008-2010, including a specific colorectal preparation close to that performed for colonoscopy, a mean of 7 hours examination using the spontaneous/stimulated transit of the capsule into the digestive tract. The last version of colon capsule endoscopy (CCE), Colon Pilcam2°, has been evaluated in 3 main prospective studies against OC.[11-13] The work by Eliakim reported 104 patients (with history of colorectal neoplasia or symptoms, *i.e.* high risk patients) undergoing both colonoscopy and capsule endoscopy, with a sensitivity of CCE of 89% for detecting polyps > 5 mm and of 88 % for detecting adenomas > 9 mm (7/8). One cancer in this series was detected at CCE. The Spada study reported 117 patients in a prospective study showing a 88% sensitivity of CCE for the detection of polyps > 9 mm. Three out of 3 invasive cancers were detected at CE. In the Rex study reporting more than 800 patients at average of high risk for colorectal cancer, the sensitivity of CCE for the detection of advanced adenoma was of 92% and that for the detection of cancer of 100%, in intention to treat.
The potential of CCE for screening for colorectal cancer appears to be high as estimating from these 3 studies. New clinical data are however mandatory to confirm in a large series these results, to clarify the yield of CCE in a homogeneous population of screening, corresponding either to average risk or high risk patients.

Moreover, comparative randomized studies on different screening strategies including CCE have never been performed to the best of our knowledge. Such studies would bring major information regarding efficacy, rate of positive cases, and economic considerations in a specific country like France. This thus highly justifies the present study.

STUDY DESIGN AND JUSTIFICATION

We propose a prospective, randomized protocol of non-inferiority in order to compare the two new strategies to the reference strategy for the detection of advanced neoplasia. (1^{st} arm: OC first; 2^{nd} arm: CC first, OC at 3 years for those patients with negative initial CC; 3^{rd} arm: annual FIT for 2 years (t_0, t = 1 year, t = 2 years), colonoscopy at 3 years for those patients with negative FIT during the study). The strategies will be considered to be equivalent if the 95% confidence interval of the different rate of detected advanced neoplasia won't exceed ±3%.

HYPOTHESIS

We make the hypothesis that the results of the two study groups (colon capsule endoscopy and fecal immunological test) will be non-inferior to the results of the control group (optical colonoscopy).

OBJECTIVE

Main objective

To demonstrate the non-inferiority of CC and FIT to OC in terms of efficacy for the detection of advanced colorectal neoplasia (adenoma > 1 cm or with high grade dysplasia, or colorectal cancer any stage).

Secondary objectives

1. Efficacy of each strategy for the detection of colorectal cancer
2. Safety and complications of each screening strategy
3. Cost-effectiveness analysis of the 3 strategies

METHODOLOGY

Study design

Non inferiority multicenter prospective randomized 3 arm study.

We propose a 3 arms prospective, randomized protocol evaluating the sensitivity of 3 strategies for the diagnosis of colon and rectum cancer and advanced neoplasia:

- 1^{st} arm: OC first
- 2^{nd} arm: CC first, OC at 3 years for those patients with negative initial CC
- 3^{rd} arm: annual FIT for 2 years (t_0, t = 1 year, t = 2 years), colonoscopy at 3 years for those patients with negative FIT during the study.

The strategies will be considered to be equivalent if the 95% confidence interval of the difference or the detection of advanced neoplasia won't exceed ±3%.

Evaluation criteria

Evaluation criteria -> Main objective

The primary endpoint is the prevalence of advanced colorectal neoplasia (adenoma > 1 cm, adenoma with high grade dysplasia) or cancer identified by each strategy after 3 years (expected frequency with the reference examination, *i.e.* colonoscopy: 5,6 %).

Evaluation criteria -> Secondary objectives

The secondary endpoints are:

1. Rate of colorectal cancer identified by the 3 different strategies/interval cancers (yearly clinical follow-up and interval colonoscopy), or cancers detected at the end of the 3 years by control colonoscopy in arm 2 and 3
2. Percentage of patient experienced a significant complication from any screening strategy
3. Cumulative costs of each strategy compared to the detection of advanced neoplasia/cost per advanced neoplasia detected and cost/life-years gained
4. Quality assessment of colonoscopy and capsule endoscopy (rate of completion of colonoscopy and capsule endoscopy, caecal intubation rate).

Study population
Patients at high risk of colorectal cancer (first degree relatives of patient with colorectal cancer) will be included prospectively in one of the 3 comparative arms.

Inclusion criteria
- History of colorectal cancers (any age) in first-degree relatives (parents, children, siblings including half-brothers and sisters)
- Age $\geq$ 45 years
- No previous colorectal cancer screening
- Informed patient
- Patient having signed the consent form,
- patient affiliated to a social security system or recipient of such system

Exclusion criteria
- Any previous colorectal cancer screening
- Any known advanced neoplasia or colorectal cancer
- Known genetic predisposition to colorectal cancer (very high risk group)
- Adults protected by law (under guardianship or curatorship)
- Other metastatic cancers
- Life-threatening diseases
- History of blood tests in the stool (hemoccult, fecal immunological test, ...)
- History of colonic capsule screening
- History of colonoscopy

Implemented techniques
Colonoscopy: OC will be performed as usual for each institution, either out-patient or in-patient, with a split preparation, under general anesthesia, without modification of the usual procedure.
Fecal Immunochemical Testing: we will use the OC Sensor test, with a cut-off 10 ·g Hb/gr of stool, without modification of the usual procedure.
Colon capsule endoscopy will be realized by experienced teams with a standardized bowel preparation, usual reading by gastroenterologists, and without modification of the usual procedure.

Number of patients required
The main objective of the study is to compare two alternative methods (CC anf FIT) to optical colonoscopy (OC) in term of non-inferiority for the detection of advanced neoplasia. According to the study by Quintero et al, the expected probability of detection of advanced neoplasia by the OC was fixed at 6%. The sample size was calculated for an expected difference between the alternative methods and the colonoscopy of 0 and a delta of non-inferiority of -3%. The method of the unilateral confidence interval of the difference will be used to test the non-inferiority. For each comparison, the unilateral alpha risk, usually fixed at 5%, will be halved in order to take account of the inflation of the type I error due to the multiple testing. For an unilateral alpha risk of 2.5% for each comparison and a power of 80%, **the needed sample size is of 984 patients in each group (total 2952).** Taking into account 10% lost to follow, the number of patients to be included is 3250 patients in total.

Recruitment
Consecutive first-degree relatives (parents, siblings, or offspring) of patients with non-syndromic CRC referred for screening to the investigator centers will be assessed for enrollment.
Eligible first-degree relatives and index cases will be given a leaflet with detailed information about the study and will be asked to invite any first-degree relatives older than 45 years to participate to the study.
We encouraged them to pass on to their first-degree relatives the leaflet about the study and to stimulate their participation. For this purpose, a contact telephone number will be given to arrange appointments with the study coordinator. We will take advantage of :
- the network of scientific societies to promote the study and inform all members of this protocol, allowing the recruitment of patients through other general/private hospitals into the study
- general practitioner networks of this study to allow a direct recruitment of first degree relatives of colorectal cancer cases
- regional screening structures for breast and colorectal cancer screening to promote the study recruitment by using their registers and contacting patients
- collaboration with private gastroenterology centers who will perform the requested optical colonoscopy for patients included and randomized in the participating centers

Randomization procedure

Central automatized randomization will be used for each screened patient individually, independently of family cluster.

Patient follow-up

- 1st arm: OC first, then annual follow-up for 3 years by phone call.
- 2nd arm: CC first, yearly follow-up for 3 years by phone call, OC at 3 years for those patients with negative initial CC.
- 3rd arm: annual FIT yearly for 2 years (t_0, t = 1 year, t = 2 years) and yearly follow-up for 3 years by phone call, OC at 3 years for those patients with negative FIT during the study.
- Pathological examination of detected and resected colorectal neoplasia will follow the usual conditions of pathological examination. There will be no centralized pathological analysis.

Measured parameters

The following data will be recorded: number and age of the index case(s) with colorectal cancer; number, size and dysplasia of neoplastic colorectal lesions; toxic habits (tobacco, alcohol); BMI; type of familial link (parent, offspring and siblings) with the index case; pathological characteristics of neoplastic lesions. Quality assessment of colonoscopy and capsule endoscopy (caecal intubation rate; capsule completion rate with rectal visualization and capsule excretion).

Blinding

Pathological analysis of colorectal lesions will be performed blindly.

Supply of medical devices

The colon capsules needed for the study will be graciously provided by MEDTRONIC, which will deliver them directly to the reference centers upon demand.
The FIT kits needed for the study will be graciously provided by MAST DIAGNOSTIC, which will dispatch them to the reference centers upon demand.
FIT analysis will be carried out by the Laboratory of Functional Coprology (Pitié-Salpêtrière Hospital) on a measuring device and with reagents both graciously provided by MAST DIAGNOSTIC.

STATISTICAL ANALYSIS

1. Descriptive analysis

The quantitative characteristics of the patients will be described in each group by the mean and the standard deviation, or by the quartiles and the minimum and maximum values according to the shape of the distribution. The qualitative characteristics of the patients will be described in each group by the absolute and relative frequency. The comparisons between the 3 groups will be carried out using an analysis of variance or the Kruskal Wallis test for the quantitative characteristics, and using the chi-2 test of homogeneity or the Fisher exact test for the qualitative characteristics.

2. Non-inferiority analysis

The main analysis will be carried out in per protocol analysis. In this analysis, only the patients having received the assigned strategy will be considered. All patients with a major deviation to the protocol will be excluded. In the FIT group, the patients complying with at least one of the three screening rounds will be considered for per protocol analysis.
An analysis in intention to treat will also be conducted. In this analysis the patients will be analysed according to their randomisation group, irrespective of whether they will have received or not, the assigned strategy.
The proportion of patients detected with advanced neoplasia by the received strategy at the end of the three years of follow-up will be estimated in each group with its 95% confidence interval.
For each new strategy group (FIT or CCE), the difference of proportion between the group with new strategy and the reference group will be estimated with its 95% bilateral confidence interval. The method of the unilateral confidence interval of the difference will be used for non-inferiority testing. For each comparison, the unilateral alpha risk usually fixed at 5% for one comparison, will be halved and fixed at 2.5% in order to take into account that two comparisons will be carried out. The non-inferiority of the new strategy will be retained if the inferior bound of the confidence interval of the difference is superior to -3%.

3. Analysis for secondary objectives

The efficacy of each strategy for the detection of advanced neoplasia will be estimated on the patients who will have actually received the strategy, whatever their initial randomization group. It will be estimated by the proportion of detected patients at 3 years. They will be estimated with a 95% confidence interval and compared using a chi-2 test or a Fisher exact test.
The observed complications will be described in each group. The proportion of complications will be compared

between the three groups using a chi-2 test or a Fisher exact test.
A bilateral P-value ≤ 0.05 will be considered for statistical significance.
The methodology of the cost-effectiveness analysis is described in a specific paragraph.

STUDY DURATION / CALENDAR

This work needs a 7 years working period including:

- 6 months for study preparation
- 3 years of inclusion
- 3 years of follow-up for all patients before colonoscopy/end of study
- 6 months for data management and analysis, and publication

FEASIBILITY OF THE STUDY

Capacity of patients' inclusion

According to the design and usual recruitment of the numerous participating centers, the feasibility of the study is excellent.
Indeed, we need to include 3250 patients from 19 already ready to participate expert centers. This represents 55 patients/center/year during 3 years or 4 to 5 patients/center/month. This is a relatively frequent situation *i.e.* colorectal cancer screening of high risk patients with family history of advanced neoplasia. Centers participating will be high volume endoscopy centers performing more than 1000 screening colonoscopies a year, from which at least 20% represent patients corresponding to the inclusion criteria. Population of candidate for the study: for the 19 centers, at least 160 index cases/center/year with colorectal cancer thus 3250 index, *i.e.* a mean of at least 6500 possible relatives to be recruited each year, or 19 500 in 3 years.

Network

This work will be held with the help of the French society of gastroenterology (SNFGE, 2000 members) and the French Society of Endoscopy (SFED, 1300 members). This network, highly used for research promotion, will allow a quick recruitment of patients with also the help of the private gastroenterologists affiliated to one of the 19 reference centers listed above. The network of scientific societies will be used to promote the study and inform all members of this protocol, allowing the recruitment of patients through other general/private hospitals into the study.
We will take advantage of collaboration with i) general practitioner networks of this study to allow a direct recruitment of first degree relatives of colorectal cancer cases; 2) regional screening structures for breast and colorectal cancer screening to promote the study recruitment by using their registers and contacting patients; 3) collaboration with private gastroenterology centers which will perform the requested optical colonoscopy for patients included and randomized in the participating centers.

SPECIFIC ROLE OF EACH PARTICIPATING TEAM

Coordination of the study will be under the responsibility of a research assistant.
The study scientific committee will include: JC Saurin, R Benamouzig, AM Schott, S Touzet, and the research assistant (coordinator).
An independent scientific committee will be constituted of gastroenterologists, methodologists and statisticians.
Biostatistical analysis will be performed by an independent team (M Rabilloud).
Recruitment and patient's follow-up will be performed by each of the 19 independent gastroenterology team, helped in each site by a local part-time research assistant.

STUDY COORDINATION

The study will be coordinated by the clinical research unit of Hospital Edouard Herriot in Lyon.
A research assistant located in Lyon will be responsible for the national coordination. He will work in collaboration with the DRCD (Direction de la Recherche Clinique of Hospices Civils de Lyon) and be in charge of financial aspects in collaboration with a senior administrative manager.

EXPECTED CLINICAL VALUE OF THE PROJECT

This study aims to validate with a high methodological requirement two strategies of colorectal cancer screening compared to the reference examination in the population of patients at high risk of colorectal cancer. Both strategies have never, or in only one Spanish study (for the FIT strategy) been evaluated in this population of patients. Colon capsule itself is a very new approach in colorectal cancer screening developed in the last years in

this indication, and the present study will for the first time evaluate its efficacy for the detection of advanced neoplasia. There is no recommendation of any alternative to colonoscopy in patients at high risk of colorectal cancer worldwide and this study has the potential to modify this paradigm and open a window toward improving highly an important but difficult cancer screening with at present low acceptability. Such a study can be considered as an important advance in screening strategies for colorectal cancer in developed countries.
The efficacy of the two alternative strategies (colon capsule and FIT) for colon cancer and advanced adenoma detection has been mainly evaluated in average risk patient populations, which represents the main target for improving colorectal cancer detection. For this reason, data on the efficacy of colon capsule for the detection of cancer and advanced adenomas are lacking as these lesions are infrequent in average risk patients. Thus, this series, with an expected much higher frequency of advanced lesions will add major data on the feasibility of capsule endoscopy in colorectal cancer screening. On the other hand, the FIT strategy in high risk patients has been poorly studied and the efficacy of this method in this specific population is uncertain. This represents the second major knowledge improvement of the present study, and the value of the result will be high as a control group with colonoscopy will be used, and as a systematic control of missed lesions will be performed with optical colonoscopy.
If this study proves the non-inferiority of these 2 strategies as compared to optical colonoscopy, a major improvement of colorectal cancer screening can be expected in this population. Indeed, the main limitation of colorectal cancer screening in first degree relatives of patients with colorectal neoplasia is the acceptability rate of colonoscopy with a figure of about 40 % in published population-based studies. This limitation is responsible for colorectal cancer deaths. Alternative screening methods like FIT and colon capsule are expected to improve dramatically the acceptability of screening in this particular population, and this has to be proven by a second study.
Moreover, this high-risk group for colorectal cancer is a model for the general population and improving screening in the general population (acceptability rate is about 30% as a mean in France with Hemoccult° testing) is an even greater objective to reduce colorectal cancer death in developed countries. Data on the efficacy of alternative methods like the 2 methods proposed in this study will be a first step before a possible "multi option" screening strategy in order to improve, in the future, colorectal screening in the average risk/general population.

ETHICS AND REGULATORY PROCESS

Risk-Benefit for patients

The risk for patients is to miss any cancer at initial examination other than colonoscopy. However i) even colonoscopy is not a perfect diagnostic mean, as 10% of patients develop interval cancers during the follow-up after usual colonoscopy; ii) no cancer has been missed in comparative studies published, including that of Quintero in 2014; iii) the lesions that are expected to be missed, *i.e.* 30-40% of advanced lesions, or 2-3% of patients, represent (> 1 cm adenoma, high grade dysplasia) benign lesions that will be detected in all patients at last colonoscopy examination (performed for all patients with negative FIT or negative capsule at 3 years). In this setting, there is no important risk of cancer miss by the study.

General Process

The trial will be carried out in compliance with the protocol, the principles laid down in the declaration of Helsinki, version as of October 1996, in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP).
Institutional Review board (IRB)/Independent Ethics Committee (IEC): The trial protocol, protocol amendments, informed consent forms, and other relevant documents, *e.g.* advertisements, if applicable, will be approved by an IRB/IEC.
The protocol was examined by the Ethics Committee (CPP Sud-Est III, Groupement Hospitalier Est, Bâtiment Pinel, 59 Boulevard Pinel, 69500 BRON), which authorized the realization of the research on October 18th 2016.
The processing of study data will be done according to the law (2004-806 of August 09th 2004), by respecting the authority directives (CNIL).
Patient information and informed consent: The informed consent form used in this trial must be prospectively approved by both the Sponsor and IRB/IEC, and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.
The investigator will obtain a written informed consent from each subject before any trial-specific activity is performed (*i.e.* at the inclusion visit). The informed consent form will be signed in duplicates by the investigator and the subject, and each signature must be dated by each signatory. An original of each subject signed consent form and any additional subject information form will be retained by the investigator as part of the study records, while the other signed consent form and any additional subject information form will be given to each subject or subject's legally accepted representative.

Safety evaluation
The investigator will evaluate each adverse event in terms of its severity.
The expected adverse events for this study are: complication of the capsule, complication of colonoscopy, colorectal cancer, other cancer, cardiovascular disease, death.
Each adverse event observed will be documented individually on the adverse events collection forms in the observation booklet. The Declaration of Serious Adverse Events will be carried out via the usual reporting circuit provided for by the law.

CONCLUSION

Main impact of the study
This study aims to validate with a high methodological requirement two strategies of colorectal cancer screening compared to the reference examination in the population of patients at high risk of colorectal cancer. Both strategies have never, or in only one Spanish study (FIT) been evaluated in this population of patients. Colon capsule itself is a very new approach in colorectal cancer screening developed in the last years in this indication, and the present study will for the first time evaluate its efficacy for the detection of advanced neoplasia. Our study will allow to:

- Precise the efficacy of fecal immunological testing and colon capsule endoscopy for the detection of advanced neoplasia and cancer in the French population at high risk of colorectal cancer,
- Evaluate the safety of theses alternative strategies,
- Evaluate the cost-effectiveness of theses alternative strategies compared to optical colonoscopy.

Finally, the present study has the potential to modify the paradigm of only optical colonoscopy in patients at high risk of colorectal cancer, and of improving this unsatisfying screening by offering a "multimodal approach" to this population.

Remaining questions regarding the development of alternative methods to optical colonoscopy in a population presenting a high risk of colorectal cancer
Screening for colorectal cancer in a specific population requires two major knowledges: the first one is the efficacy (sensitivity, specificity) of the different screening methods. This is the aim of the present study. The second one is the acceptability of the different screening methods in the population. After this study will demonstrate the efficacy of alternative screening methods (FIT, colon capsule endoscopy), additional prospective studies will be required to respond to this acceptability question before implementing these alternatives into clinical practice.

2- Ancillary study

MEDICO-ECONOMIC EVALUATION

The optimal test to use for CRC screening is still under debate. Medico-economic analyses can contribute to this health public issue but data are still scarce in France. Using a Markov model, two studies investigated the efficience of the guaiac faecal occult blood test (G-FOBT) and faetal immunochemical tests (FIT).
Lejeune et al. (2014) compared a biennial guaiac faecal occult blood test (G-FOBT) and three faetal immunochemical tests (FIT) at different cut-off levels for positivity and stool-sample collection.[8] All strategies presented a discounted incremental cost-effectiveness ratio under 3500 € per life-year gained in comparison with the G-FOBT strategy. Authors concluded that the one-stool sample FIT test could be of real interest from a cost-effectiveness point of view.
Sobhani et al. (2011) estimated the incremental cost-effectiveness ratio of biennial screening using FIT test compared to screening using G-FOBT test at 8 821 € per quality adjusted life years gained. According to the authors, FIT test should be considered as an interesting alternative to the guaiac test for use in a primary screening program for CRC.[14]
These studies highlights the interest of FIT test but none of them take into account endoscopic screening. A cost effectiveness of CRC screening in France was carried out recently (Hassan et al. 2011) to compare screening strategies using colonoscopy, flexible sigmoidoscopy, second-generation colon capsule endoscopy (CCE), FIT and G-FOBT.[15] This work was based on the creation and validation of a model to simulate the progression from no lesions to death related to CRC, through all the polypoid phases. According to this study, FIT repeated every year is the most cost-effective strategy. If results provided interesting information on the efficiency of colorectal cancer screening in France, authors highlighted, in discussion, limits of their results mainly due to the lack of clinical studies data, particularly patient compliance to tests. In this study, they assumed an equal adherence to colonoscopy and non-invasive screening options. They concluded that more comparative studies

between FIT and endoscopy programs are needed.

Objective of the health economic evaluation

Thus, in parallel to the FAMCAP clinical trial, we propose to perform a medico-economic evaluation, based on the simulation model created by Hassan al. (2011), to compare three strategies for screening of CRC:

- OC first,
- CC first, OC at 3 years for those patients with negative initial CC
- Annual FIT for 2 years, colonoscopy at 3 years for those patients with negative FIT during the study

To do this, we will adapt the model according to these three strategies and update parameters using:

- Data from FAMCAP study, especially patient compliance to tests,
- Data from literature,
- And if necessary, expert opinions.

Economic evaluation design

The design retained for the economic study is a cost-effectiveness analysis, which provides information on the additional cost per additional effectiveness. Incremental cost-effectiveness ratio will be calculated based on the incremental cost and the incremental effectiveness of each compared couple of strategies.

Viewpoint for analysis and time horizon

The analysis will be conducted from the viewpoint of the French Public Health Insurance on a lifetime horizon.

Cost

We will take into account only hospital costs because CRC patient are essentially cared at a hospital.
Hospital costs include mainly screening, surveillance procedures and CRC treatment costs.
Consumed resources will be identified according to Hassan et al. study (2011), French guidelines and colorectal cancer experts.
Hospital stays will be valued by the current tariff of the corresponding hospital stay related group (GHS).
For external acts, we will use the current tariffs of the Common Classification of Medical Acts (CCAM) and those of the general classification system for the professional activities (NGAP) for consultations.

Measure of effectiveness and ICER

The clinical effectiveness will be measured in terms of life-years gained so that the incremental cost-effectiveness ratio (ICER) will be expressed as the additional cost by life-years gained of a specific strategy (A) in comparison with the next least efficient strategy (B) :

$$ICER = \frac{\text{Cost of strategy A} - \text{Cost of strategy B}}{\text{Effectiveness of strategy A} - \text{Effectiveness of strategy B}}$$

Robustness of the economic analysis results

To investigate the robustness of the results of the cost-effectiveness analysis, a sensitivity analysis will be carried out by changing some parameters of the study to measure the impact of the variation of these parameters on the final result. The sensitivity analysis will include parameters related to cost data as well as parameters related to effectiveness data.
A Tornado diagram will be used to visualize the influence of variables based on the results of the uncertainties on the values used.

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APPENDIX 2: *Skills and expertises*

➢ *Coordinator(s)*

Major scientific publications in indexed journals and peer-reviewed with international committees or any other significant publications during the past five years (titles and references)
1. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Pennazio M, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, Rondonotti E, Adler SN, Albert J, Baltes P, Barbaro F, Cellier C, Charton JP, Delvaux M, Despott EJ, Domagk D, Klein A, McAlindon M, Rosa B, Rowse G, Sanders DS, Saurin JC, Sidhu R, Dumonceau JM, Hassan C, Gralnek IM. Endoscopy. 2015 Apr;47(4):352-76.
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➢ *Methodologist*

Major scientific publications in indexed journals and peer-reviewed with international committees or any other significant publications during the past five years (titles and references)
1. Bolze PA, Attia J, Massardier J, Seckl MJ, Massuger L, van Trommel N, Niemann I, Hajri T, Schott AM, Golfier F; EOTTD group. Formalised consensus of the European Organisation for Treatment of Trophoblastic Diseases on management of gestational trophoblastic diseases. Eur J Cancer. 2015 Sep;51(13):1725-31.
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Associated teams :

➢ *Team 2 : Hôpital Avicenne Paris*

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➢ *Team 3 : Colmar*

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➢ *Team 4 : Rennes*

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➢ *Team 7 : Nice*

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➢ *Team 9 : Rouen*

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➢ *Team 10 : Cochin*

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