NATIONAL REPORT ON SITUATION/STRATEGIES/SUPPORT INSTITUTIONS AND SPECIALISTS/BEST PRACTICES OF THE GENETIC CONSULTANCY/ ONCOGENETICS IN FRANCE

Report created in the framework of the project Promoters of advanced oncogenetics open online training and multimedia raise awareness on multidisciplinary assessment of patients and their families at risk of hereditary or familial cancer, Reference number 2018-1-RO01-KA202-049189, Strategic Partnerships for vocational education and training Erasmus+ programme

1. The current epidemiological situations on cancers, in general, and on hereditary cancers (breast, ovarian, colorectal cancer and other) in France

1.1. Incidence

In 2012, the number of cancers diagnosed in metropolitan France is estimated at 355,354 for the population over 15 years, with respectively 200,350 men and 155,004 women (1). With 56,840 new cases estimated in 2012, prostate cancer remains by far the most common cancer in men, with lung cancer (28,200 cases) and colorectal cancer (23,200 cases). With 48,800 new cases estimated in 2012, breast cancer is the most common cancer in women, with colorectal cancer (18,920 cases) and lung cancer (11,300 cases). The median age at diagnosis of any cancer is estimated at 68 years for men and 67 years for women. For breast cancer in women, the median age at diagnosis was 63 years, while for colorectal cancer it was 71 years in men and 75 years in women. Ovarian cancer is the 7th leading cause of cancer in women, with an incidence of 4,615 cases. He is diagnosed most frequently after 65 years.

The incidence of pediatric cancers (<15 years) was between 1,700 and 2,500 new cases of cancer per year between 2006 and 2010. The main localizations are leukemia (29% of cases), tumors of the central nervous system (24%) and lymphomas (11%) (1).

Between 5 and 10% of breast and ovarian cancers are secondary to hereditary predisposition (HBOC). BRCA1 and BRCA2 are the principal genes involved. 2,500 to 5,000 new HBOC cases are diagnosed each year, with approximately 21,000 cases diagnosed between 2003 and 2014 (2). Other hereditary predisposition syndromes are less frequent. Approximately 5% of colorectal cancer cases are genetically predisposed, representing 2,000

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new cases per year. Other cancers, such as paraganglioma-pheochromocytoma or medullary thyroid carcinoma, are also associated with inherited predisposition

1.2. Prevalence

In 2008, the 5-year partial prevalence of all cancers combined is estimated at 1.1 million people, including 583,580 men and 490,325 women (1). Nearly half of the cases are prostate cancer in men (265,360 cases, or 45%) and breast cancer in women (383,310 or 47%). Colorectal cancer accounts for nearly 10% of all cancers, with 100,240 cases in men and 90,050 cases in women.

The prevalence of individuals with a constitutional mutation in one of the BRCA genes, responsible for hereditary predisposition to breast and / or ovarian cancer (HBOC), is estimated at 2 per 1,000. Lynch syndrome is the most common hereditary predisposition to colorectal cancer, with a prevalence of between 1/800 and 1/1600 for the two main genes, MLH1 and MSH2.

1.3. Risk-Factors

The main modifiable risk factors for cancer include (1):

- The tobacco

In France, the number of cancer deaths attributable to tobacco is about 44,000 per year, or 30% of cancer mortality. It is responsible for 93% of lung cancer deaths and significantly promotes the occurrence of other cancers: oral cavity, pharynx, larynx, pancreas, bladder, kidneys, nasal cavity, sinus, esophagus, stomach, liver, uterine cervix, and to a lesser extent myeloid leukemia, colon, rectum, mucinous ovary and breast cancer. The prevalence of active smoking in France is 31.6% of 15-85 year olds.

- The alcohol:

Alcohol consumption is the second leading cause of preventable cancer mortality in France, with 15,000 deaths in 2009 (9.5% of cancer deaths, 12% in men and 6% in women). Alcohol is convincingly associated with cancer risk for the mouth, pharynx, larynx, esophagus, liver, colon-rectum and breast. France remains among the most alcohol-consuming countries in the world and countries of the European Union (11.8 liters of pure alcohol per inhabitant of at least 15 years).

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- Diet and physical activity:

Dietary or physical activity factors that increase the risk of cancer include alcohol consumption, overweight and obesity (2,300 cancer deaths, 1.6% cancer deaths), consumption of red meat (> 500 g per week) and processed meats, consumption of salt and salted foods, and consumption of food supplements based on beta-carotene. Nutritional factors are responsible for 20 to 27% of cancers in Europe.

Inadequate physical activity is responsible for approximately 2,240 cancer deaths, or 1.6%.

Other cancer risk factors include environmental factors (Radon, ionizing radiation), occupational exposure factors, such as asbestos, and infectious agents such as EBV, HBV, and HCV.

Major non-modifiable risks factors include:

- Age

Age is a risk factor for most cancers. The median age to diagnosis of cancer is 68 years of age in men and 67 years of age in women. The aging of the French population is responsible for 33.7% of the increase in cancer incidence in France (1).

About 80 % of breast cancer is declared after 50 years of age (50 % between 50-69 years and 28 % after 69 years), and only 10 % are declared before 35 years (3). Most ovarian cancer is declared after 65 years (5).

- Personal history of cancer

For all cancer types combined, after a first malignancy, developing a second cancer is associated with a relative risk (RR) of 1.36 (1). This risk varies with the type of first cancer. For example, the RR is 3-4 for a second breast cancer, and is estimated at 8-10 in the case of ductal or lobular carcinoma in situ (3). A personal history of colorectal cancer or advanced adenoma also carries a significant risk of developing a new colorectal cancer (4).

- Hormonal factors

Hormonal factors are involved in occurrence of breast and ovarian cancer. The risk of both cancers is higher in women who have not had a child, who have their first child late, and who have early puberty or late menopause (7). Furthermore, taking oral contraceptives or hormonal treatments for menopause may also increase the risk of breast cancer, which is modulated by the duration of treatment (8).

- Family history of cancer

A familial history of breast cancer in a first degree relative gives an RR of 2 (3). This risk increases with the number of first degree relatives affected and the age of occurrence. A first-

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degree relative with ovarian cancer gives an RR of 3 for developing ovarian cancer in the absence of a predisposing mutation in BRCA1 or BRCA2.

A first degree relative with colorectal cancer exposes to a RR at 2.25. As for breast cancer, this risk increases with number of relatives with colorectal cancer and age of occurrence (6).

- Hereditary cancer predisposition

Hereditary predisposition concerns 5 to 10 % of cancers, with high to very high risk of cancer according to the syndrome. More than 50 syndromes have been described, the most common of which are listed below (9).

Genetic predisposition	Major associated genes
Breast/ovarian syndrome	BRCA1,BRCA2,PALB2,RAD51
Lynch syndrome	MLH1,MSH2,MSH6,PMS2,EPCAM
Familial pituitary adenomas	AIP
Ataxia–telangiectasia	ATM
Hereditary diffuse gastric cancer	CDH1
Hereditary papillary renal cancer	MET,FH
Hyperparathyroidism	CASR,CDC73
Cowden syndrome	PTEN,PICK3CA,AKT1
Fanconi syndrome	FANC
Von Hippel-Lindau disease	VHL
Familial malignant melanoma	CDKN2A,MITF,BAP1,POT1,CDK4
Endocrine neoplasia	MEN1,RET,CDKN1B
Neurofibromatosis	NF1,NF2,LZTR1,SMARCAB1,SPRED1,SMARCE1
Paraganglioma – pheochromocytoma	SDH,TMEM127,MAX,EPAS1
Familial polyposis adenomatous	APC,MUTYH,POLE,POLD1,NTHL1
Retinoblastoma	RB1
Birt hogg-dubé syndrome	FLCN
Bloom syndrome	BLM
Carney syndrome	PRKAR1A,ARMCS
Gorlin syndrome	PTCH1,PTCH2,SUFU
Li-Fraumeni syndrome	TP53
Numegen syndrome	NBN
Peutz Jeghers syndrome	STK11
Juvenile polyposis syndrome	BMPR1A,SMAD4
Werner syndrome	WRN
Xeroderma pigmentosum	XP

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1.4. Mortality

In 2012, cancer mortality was estimated at 148 000 deaths, including 85 000 deaths in men and 63 000 in women (1). Lung cancer was the leading cause of cancer death in men (21,236 deaths), followed by colorectal cancer (9,275 deaths) and prostate cancer (8,876 deaths). Breast cancer was the leading cause of cancer death in women (11,886 deaths), followed by lung cancer (8,623 deaths), colorectal cancer (8,447 deaths) and ovarian cancer (3,140).

2. The current situation on the National Strategies about the models used in genetic risk assessment for hereditary cancers in France

The High Health Authority has published criteria for genetic testing of patients referred to an oncogenetics consultation for suspected HBOC (10):

- Genetic testing recommended due to personal history:

- Breast cancer in a woman less than 31 years old
- Triple negative breast cancer
- Ovarian cancer
- Breast cancer and pancreatic cancer
- Breast cancer in a man
- Breast cancer associated with two other cancers (excluding cancers not associated with deleterious constitutional mutations)

- Genetic testing recommended due to family history.

Evaluation should take into account the localization of the cancers, as well as the age at diagnosis, the degree of relatedness, the branch of affiliation, and the number of affected and healthy relatives. The Eisinger score (Table 1) was developed to simplify this evaluation. Each parental branch is calculated separately, and the higher score is taken into account.

A score greater than or equal to five is a “excellent indication” for an oncogenetic consultation, a score of 3 or 4 is a “possible indication”, and for scores of two or less an oncogenetic consultation is of little medical value.

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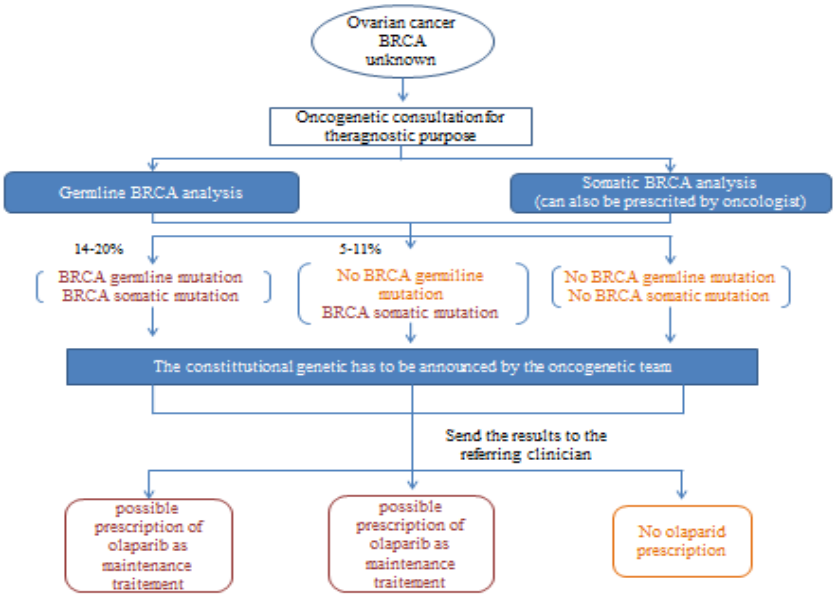
Situation	weight
BRCA ½ mutation in the family	5
Breast cancer in a woman <30	4
Breast cancer in a woman between 30-40	3
Breast cancer in a woman between 40-50	2
Breast cancer in a woman between 50-70	1
Breast cancer in a men	4
Ovarian cancer	3

Table 1: Eisinger score

Other scores can also be used, such as the Manchester score (a score of 16 is equal to a 10% chance of BRCA1 or BRCA2 mutation, a score of 20 is equal to 20% chance of mutation), or the **Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm** (BOADICEA score), to which online access is free. These three scores are the most frequently used in France to determine HBOC risk but many other scores exist.

An analysis of the BRCA1 and BRCA2 genes is indicated in front of any high grade serous ovarian cancer, for predisposition and theranostic purposes. Indeed, the presence of a pathogenic mutation in one of these genes at the constitutional and / or somatic tumor state makes it possible to propose to the patient a PARP inhibitor treatment. Due to the impact of the mutational status on patient management, this analysis is performed according to specific and faster modalities (11).



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Several genetic syndromes predispose to colorectal cancer (CCR). For personal or familial history of Lynch syndrome-related cancers, the Bethesda and Amsterdam criteria are used (12).

A) **BETHESDA** (at least one criterion)

- Colorectal cancer (CCR) < 50 years old
- 2nd CCR (synchronous or metachronous)
- 2nd cancer of any Lynch syndrome-related cancer
- Colorectal tumor tissue with MSI-high histology < 60
- CCR and at least one first-degree relative with any Lynch syndrome-related cancer diagnosed before age 50 years
-CCR and At least two first or second degree relatives with any Lynch syndrome-related cancers regardless of age of cancer diagnosis

Validation of the Bethesda criteria should be accompanied by testing of tumor tissue by molecular biology (microsatellite instability phenotype) and immunohistochemistry (for loss of expression of one or more MMR proteins (MLH1/MSH2/MSH6/PMS2)). Systematic somatic exploration of colorectal cancers before age 60 and of endometrial cancer before age 50 is now recommended (Figures 1 and 2).

B) AMSTERDAM: Each of the following criteria must be fulfilled:

-3 or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis);
-2 or more successive generations affected;
-1 or more relatives diagnosed before the age of 50 years;
-1 should be a first-degree relative of the other two;
- Familial adenomatous polyposis excluded

The validation of Amsterdam II criteria justifies genetic testing without any further requirements.

Bioinformatics algorithm like $PREMM_5$ can also be used to estimates the risk of Lynch's syndrome. The $PREMM_5$ model is a clinical prediction algorithm that estimates the cumulative probability of an individual carrying a germline mutation in the *MLH1, MSH2, MSH6, PMS2,* or *EPCAM* genes.

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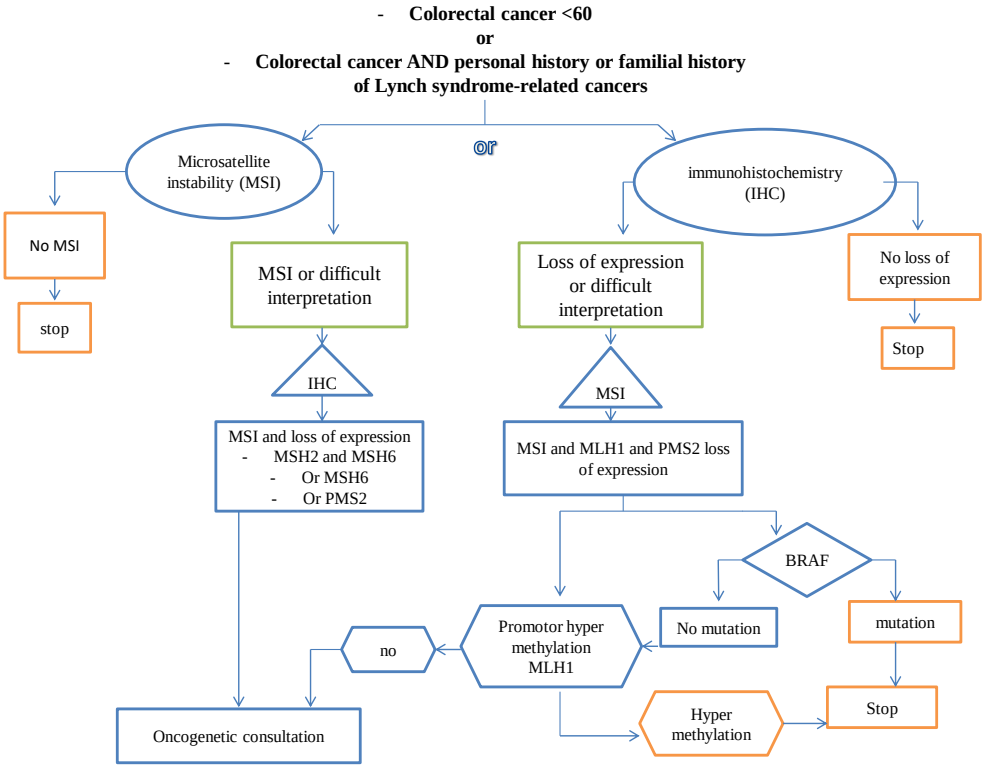

Figure 1

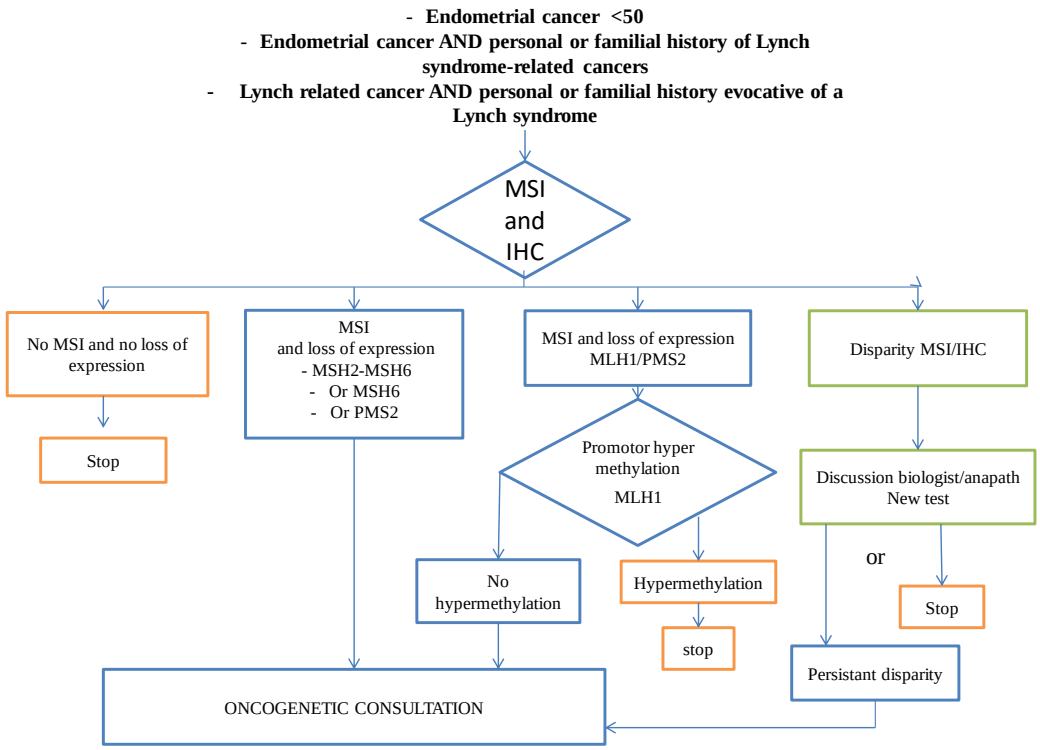

Figure 2

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Polyposis is also part of the genetic syndromes predisposing to colorectal cancer. Two main genes are involved: APC and MUTYH. A genetic test is indicated if one of the following criteria is met (13):

- At least 15 adenomatous polyps regardless of age
- Between 10 and 14 adenomatous polyps before 60 years
- Between 5 and 9 and a secondary criterion (an adenomatous polyp before the age of 40, a colorectal cancer before 60 , at least 5 polyps with have high grade dysplasia, duodenal polyps, dermatologic signs before 50)

Other genes are known to predispose to colorectal cancer, including syndromic forms (PTEN, STK11) and non-syndromic forms (POLE, POLD1). The recommendations of analysis are specific to each form.

The national recommendations for neuroendocrine tumors include:

A) Genetic testing for multiple endocrine neoplasia type 1 (MEN1) is recommended for (14):

- presence of two endocrine tumors related to MEN1
- one endocrine tumors and familial history related to NEM1
- Primary hyperparathyroidism with strict criteria: before 50 years, calcemia below 3.3 mM without hypocalciuria
- macroadenema before 30 years or corticotrope/somatotroph microadenoma in childhood
- more than one endocrine tumors of the gastro-entero-pancreatic (GEP) tract or one before 50 years
- Zollinger-Ellison syndrome

B) Genetic testing for multiple endocrine neoplasia type 2 (MEN2) is recommended for any case of medullary thyroid carcinoma (15).

C) Genetic testing for paraganglioma – pheochromocytoma syndrome is recommended for any case of paraganglioma and / or pheochromocytoma (16).

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3. The current practical situation on Genetic Testing Availability for HBOC and CCR in France

The diagnosis of an inherited predisposition to cancer is based on the national oncogenetic plan, which is organized around 148 consultations in 104 cities, and 25 laboratories (17).

In 2017, 77 478 patients have benefited from a consultation, with an 8% increase in the number of consultations compared to 2016. The average number of consultations for 100 000 inhabitants is 105. The whole territory is covered by the oncogenetic plan. About 50 % of consultations have been performed by 15 centres. The first consultations for probands, the results rendering consultations and related consultations represent respectively 39 %, 46% and 15% of cases. The average time of consultation is 12 weeks for probands and 6 weeks for the related. About 29 500 probands have benefited from genetic analysis. Among the probands, 92 % have been analysed using panel sequencing.

In HBOC indication, 54 936 patients have benefited of an oncogenetic consultation (21 498 probands and 7 624 related, 75 consultations per 100 000), increased about 6% in comparison to 2016. Among these patients, 18 180 probands and 6 653 related have been analysed. The detection rate is 9.5 % (7.1% to 21%) in probands and 42.4 % in relatives. The average time of panel analyses is 22 weeks for probands. The oriented analysis of a familial mutation in relatives requires an average of 3 months.

The French expert groupe “Genetic et Cancer” determined the genes to include in a panel analysis for HBOC indication: BRCA1, BRCA2, PALB2, RAD51C, RAD51D, CDH1, TP53, PTEN, MLH1, MSH2, MSH6, PMS2, and EPCAM. CHEK2, ATM, BARD1, BRIP1, NBN, RAD51B, and STK11 are not routinely analysed actually in HBOC indications (18).

In addition to the hereditary predisposition to cancer, the genetic analysis of a patient with ovarian carcinoma also has a theranostic interest with the onset of PARP inhibitor therapy. Having an impact on the patient's therapeutic management, the analysis integrates an accelerated care path. In 2017, 3724 patients have benefited of this approach, with an average time to consultation of 12 days and an average time of 48 days for BRCA1 and BRCA2 analysis.

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Actually, a national guideline recommends a time limit of 7 weeks from the histological diagnostic to the result rending. The classical course includes a constitutional and somatic tumor analysis in parallel.

In the presence of a mutation in the constitutional state, the result is rendered by the geneticist. A somatic tumoral mutation can be rendered by the geneticist or the oncologist.
An identical approach is under discussion in the context of breast cancer, in anticipation of the obtaining of a national authorization of PARP inhibitor in this indication.

In 2017, the digestive indications represent 17 % of cases (13 374), dominated by Lynch syndrome indication (8 020, 11 consultations per 100 000, increased to 9% in comparison to 2016) and familial adenomatous polyposis (2 311) (17). Among the Lynch syndrome indication, 2 665 were probands and 1 654 were relatives, and an analysis was performed from 2 035 probands and 1 824 relatives. The detection rate was 18.4 % (7.7 to 45.5%) in proband and 43.4 % in relatives. The average time of panel analyses is 22 weeks for probands. The oriented analysis of a familial mutation in relatives requires an average of 3 months. The average time of first consultation in proband is estimated to 12 weeks.

In 2017, 18 420 micro-instability analysis (MIA) were performed, most often associated with immuno-histochemical analysis. The MIA identified 1 733 tumors with MMR deficiency. However, only 620 patients have been oriented to an oncologic consultation in this context.

Actually, the genes to include in the digestive panel analysis are currently being discussed (guidelines programmed during the first half of 2019). The panel analysis should include: APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, POLE, and POLD1. Other genes involved in hereditary digestive cancers predisposition could be proposed according to the clinical presentation

4. Research Programs on mutation screening and founder mutation detection for HBOC and CCR in France

A variety of research programs focused on the exploration of hereditary predisposition to breast and / or ovarian cancer and colorectal cancer are currently supported by the National Cancer Institute. The diversity of pathogenic variants observed in French HBOC and CCR families has shown that targeting founder mutations is not appropriate for this population.

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Five programs concern HBOC (19):

TUMOSPEC

This national program aims to determine the tumor spectrum and the penetrance of genes that are known or suspected to be involved in hereditary predisposition to breast and ovarian cancer. A panel of 24 genes is analyzed, and potentially pathogenic variants are followed by segregation analysis in appropriate families.

COVAR

This program aims to resolve the classification of variants of unknown significance in the BRCA1, BRCA2 and PALB2 genes as either pathogenic or neutral for cancer risk. The program is a segregation study proposed to family members of probands discovered to carry variants in these genes.

GEMO:

This program aims to identify modifier genes in carriers of pathogenic variants in the BRCA1 or BRCA2 genes which could explain inter- and intra-familial variability in the occurrence of breast and / or ovarian cancer.

SIGNAL:

This study aims to identify genetic determinants of resistance / sensitivity and / or toxicity to adjuvant therapy and genetic determinants predisposing to breast cancer:

- determinants of resistance or sensitivity after adjuvant therapy including Herceptin®
- determinants of cardiac toxicity after adjuvant therapy including Herceptin®
- genetic determinants predisposing to different types of breast cancer: HER2 +, triple negative, RH +
- genetic determinants predisposing to breast cancer

SAO3:

This study aims to assess the incidence of constitutional mutations in breast cancer predisposition genes (BRCA1, BRCA2, PTEN and PALB2) in patients with triple-negative breast cancer.

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Three programs concern predisposition to CCR (19):

DOCC:

The objective of this study is to compare the frequency of genetic variations and to evaluate the association of these variations with the occurrence of colorectal cancer in patients with increased risk of colorectal cancer.

GENCOLON:

The objective of this study is to determine whether gene mutations found more often in people with colorectal cancer than in healthy individuals could be associated with the development of colorectal cancer.

MYH:

This is a study to evaluate the risk of colorectal polyposis in patients with mono-allelic mutation of the MUTYH gene.

5. List of Institutions, cancer centres that provide genetic testing and counselling services in France

The diagnosis of an inherited predisposition to cancer is based on the national oncogenetic plan, which is organized around 148 consultations in 104 cities, and 25 laboratories (17).

In 2017, 77 478 patients have benefited from a consultation, with an 8% increase in the number of consultations compared to 2016. Doctors from main consultations can make advanced consultations in peripheral cities (Figure 1). The main consultations (85) are from Cancer Center and Public Hospital. The National Cancer Institute (INCA) on his web site have a link to the coordinates of each oncogenetics center and theirs doctors

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Figure 3

After the consultation, the sample is sent to one of the 26 French accredited laboratories (Figure 2, 38 606 analysis in 2016). If each laboratory has its own specialty, all are able to test HBOC and/or CCR. All genetic predispositions currently known to cancers can be tested within these 26 laboratories.

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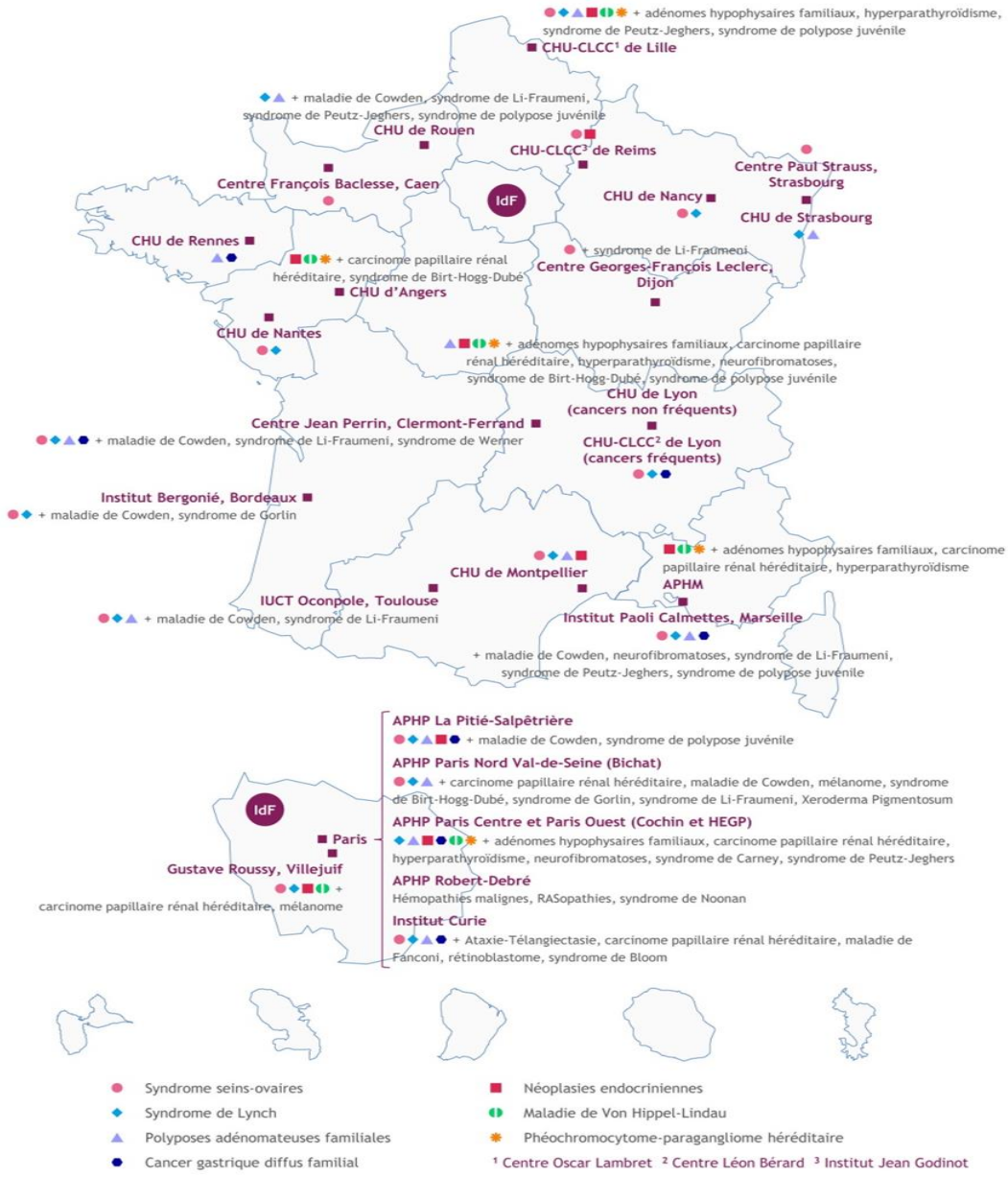

Figure 4

Patients with a mutation predisposing to cancer or patients considered at very high risk of cancer without identified mutation benefit from a personalized follow-up, based on screening and prevention measures, coordinated by 17 regional or interregional programs (Figure 3). Their missions are (20):

- to set up an individualized follow-up of people predisposed hereditarily to cancer;
- to coordinate this monitoring at the regional or even inter-regional level;
- to ensure access to multidisciplinary skills

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- to provide recourse and expertise for difficult cases.

These networks are organized across the territories, covering the set of syndromes of hereditary predisposition to cancer. For example, PREDIR network is oriented to renal cancer predisposition, while TENGEN network is oriented to neuroendocrine tumors indication.

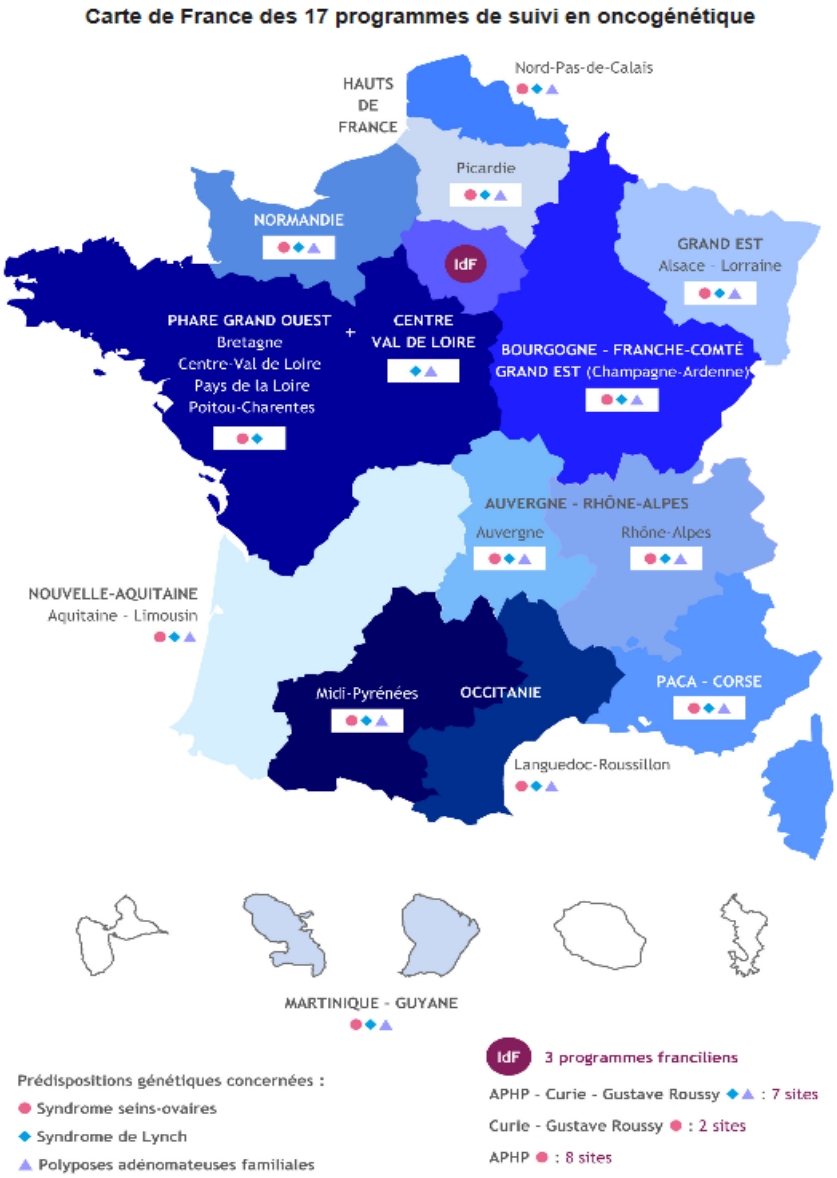

Figure 5

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6. The situation of Education Programs regarding Oncogenetics in France

6.1 – Oncogenetics Training Programs for Health Care Professionals and Medical Specialists

These programs include university diploma courses and continuing education programs. They are intended for all health professionals, and particularly for doctors treating cancer patients, in order to provide appropriate care. These programs include:

- Inter-University Diploma "Oncogénétique" proposed by Paris-Descartes University, in collaboration with other Parisian schools of medicine. This training includes the general principles of oncogenetics, the molecular mechanisms involved, clinical diagnostic and testing criteria, and the management of patients. The course content is updated annually (21).
- The national genetics conference ("Assises de Génétique"), held every two years in France, presents new discoveries and progress in medical genetics and medical practices. Oncogenetics is well represented at these conferences (22).
- Oncogenetics teaching is carried out during the training of interns of medical genetics, during their four years of study as part of the specialized medical genetics degree.
- Two very high output sequencing pilot platforms have been created in France. These platforms propose to perform whole-exome-sequencing and whole-genome sequencing analyzes in a diagnostic and theranostic setting in oncology. In order to train non-geneticist prescribers in this type of analysis, a short 30-minute training is proposed, dealing with the general principles of hereditary predisposition to cancer, as well as the ethical and regulatory aspects to be respected within the framework of an analysis of the genetic characteristics of an individual. Continuing professional development, lasting 7 hours, will complete this training.

Medical genetics is taught in 2nd and 3rd years of medical studies in all schools of Medicine in France. The program is based on the French College of Medical Genetics, and includes training in clinical genetics, oncogenetics, chromosomal and molecular genetics. The teaching of oncogenetics continues through the 6th year of medical studies, in order to prepare for the national classification examination in 6th year, giving access to the status of medical resident. The teaching program is integrated into the national college of medical oncology, and concerns the identification of the main syndromes of hereditary predisposition to cancer by organ, the genes involved in these predispositions, as well as the management of HBOC and Lynch syndrome patients. University education in oncogenetics is also offered to

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paramedical disciplines, thus integrating during the studies of midwives, nurses and pharmacy.

6.2– Health Education Programs for patients and their families at risk for hereditary cancer

Associations of patients and their families with hereditary predisposition to cancer have been formed. Most hereditary predispositions to cancer are attached to an association, which are frequently sponsored by medical specialists and provide information on the progress of oncogenetic consulation, the modes of transmission and the management recommended for patients. HBOC families may join for example the associations BRCAFRANCE (23) or GENETICANCER (24). HNPCC-Lynch association (25) and Familial Adenomatous Polyposis association (26), among others, are open to those with predisposition to digestive cancers.

Information booklets are also available in oncogenetic consultations in France.

6.4 - Health Education Programs for the General Public

The French National Institute of Cancer presents open access educational programs for the general public, mainly concerning HBOC and Lynch syndrome.

ORPHANET (26) is an international information portal dedicated to rare diseases, created in France in 1996. This portal includes open access information documents intended for the general public, including diseases predisposing to cancer.

The website “Oncogenetique”, anticipated in 2019, presents information about hereditary predisposition to cancer for the general public.

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7. The identification of practical needs (infrastructure, human and financial resources) in order to establish and to develop an Oncogenetic Network

The development of an Oncogenetic Network between the differents HOPE partners requires human, material and financial needs.

Indeed, the access to very high-throughput sequencing, the increase in the number of indications in oncogenetic, and this for diagnostic or therapeutic purposes, requires additional human resources, which can be based on the creation of a position of doctor geneticist in 0.3 full time.

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