BRIEF SYNTHESIS OF THE COUNTRY REPORT 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 situation on cancers, in general, and on hereditary cancers (breast, ovarian, colorectal cancer and other) in France

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. . The hereditary predisposition to cancer concerns 5 to 10 % of cancers. Actually, more than 50 syndromes are described. Hereditary Breast and Ovarian Cancer (HBOC) and Lynch syndrome are the most prevalent of them, with respectively 2 cases per 1,000 and 1 case per 800 - 1,600.

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

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

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)

Co-funded by the Erasmus+ Programme of the European Union

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 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.

Other scores can also be used, such as the Manchester score or the BOADICEA score. These scores are the most frequently used in France to determine HBOC risk.

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.

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.

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

Co-funded by the Erasmus+ Programme of the European Union

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.

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.

Polyposis is also part of the genetic syndromes predisposing to colorectal cancer. A genetic test of APC and MUTYH is indicated if one of the following criteria is met :

- 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, as PTEN, STK11, 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:

- presence of two endocrine tumors related to MEN1
- one endocrine tumors and familial history related to NEM1

Co-funded by the Erasmus+ Programme of the European Union

- Atypical primary hyperparathyroidism
- 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.

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

3. 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.

Doctors from main consultations can make advanced consultations in peripheral cities. The main consultations 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

After the consultation, the sample is sent to one of the 25 French accredited laboratories (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 25 laboratories.

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. Their missions are:

- 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
- to provide recourse and expertise for difficult cases.

Co-funded by the Erasmus+ Programme of the European Union

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.

4. The current situation on Research programs on mutation screening and founder mutation for HBOC and CRC.

In 2017, 77 478 patients have benefited from a consultation, with an 8% increase in the number of consultations compared to 2016. The whole territory is covered by the oncogenetic plan. 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). Among these patients, 18 180 probands and 6 653 related have been analysed. The detection rate is 9.5 % 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.

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.

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 2017, the digestive indications represent 17 % of cases (13 374), dominated by Lynch syndrome indication (8 020, increased to 9% in comparison to 2016) and familial adenomatous polyposis (2 311). Among the Lynch syndrome indication, 2 665 were probands and 1 654 were

Co-funded by the Erasmus+ Programme of the European Union

relatives, and an analysis was performed from 2 035 probands and 1 824 relatives. The detection rate was 18.4 % in proband and 43.4 % in relatives. The average time of panel analyses for probands and relatives, and the average time of first consultation in proband are similar to HBOC indication.

Actually, the genes to include in the digestive panel analysis are currently being discussed (guidelines programmed during the first half of 2019).

Co-funded by the Erasmus+ Programme of the European Union