CANCER GENETIC COUNSELING. PART I - WESTERN EUROPEAN COUNTRIES

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CANCER GENETIC COUNSELING. PART I-WESTERN EUROPEAN COUNTRIES (Abstract): Genetic counseling services represent a relatively new concept aimed to identify patients or relatives with hereditary predisposition for cancer susceptibility and to act accordingly for early diagnosis, cure and prevention. It has become an accepted part of oncology care in many European countries. Unfortunately, despite the same state of knowledge, the patients from different European countries would experience different care. This situation is not in accordance with the European Union directives, which are enacted to implement and protect the idea of free movement of goods, services, people and capital. This study aimed to examining the current practice of genetic counseling for cancer in different European countries, with special accent on familial breast and ovarian cancer management as the most studied and managed hereditary cancer. We also sought to ascertain the needs for the unitary politics in cancer genetics services, to decrease the difference in cancer genetic counseling opportunity and facility. As a first step we compared the national guidelines regarding genetic counseling for familial/hereditary breast and ovarian cancer in some countries from Western Europe. All guidelines recommend embedding genetic testing within a framework of genetic counseling, and all agree to perform genetic testing first in an affected person. However, we found some differences regarding the thresholds, detailed description of selection criteria, the risk calculation methods, the age of diagnosis, the relationship with counselor and physician etc. There are also many open questions that are not covered by the guidelines, for instance: how to deal with phenocopies, unclassified variants, and newly identified breast cancer susceptibility genes or with family that not fitting the criteria, that need to be discussed. New evidence is usually slowly integrated into the guidelines. An exchange process towards the harmonization of the guidelines will ensure high quality health care across Europe. **Keywords:** HEREDITARY BREAST AND OVARIAN CANCER; BRCA, GENETIC COUNSELING.

Cancer genetic counseling represents one of the most innovative new concepts in healthcare. Worldwide, the number of cancer cases is 18.1 million of which 2.1 million new cases of breast cancer, 1.8 million colorectal cancers and 295,414 ovarian cancers. Worldwide, cancer is the second leading cause of death with 9.5 million deaths reported for the year 2018 by *International Agency for Research on Cancer* (IARC). Epidemiological data shows that in Europe, 4.2 million new cases of cancer were reported with 1.9 million new cases in women and 2.3 million new cases in men, according to IARC. Of the total cases recorded in Europe, ovarian cancer encoun-

tered for 67,771 new cases, being responsible for 44,576 deaths. Breast cancer is registered with a total of 522,513 new cases, with a number of 137,707 deaths (1).

Each day, worldwide, millions of people fight a battle against cancer, undergoing devastating therapies that hugely impact on their *Quality of Life*. Over the next two decades, the number of new cases is expected to rise by about 70%. Oncogenetics can contribute to change this future scenario, addressing those people for which prevention is still possible and the disease's onset avoidable. This medical discipline, in progressive expansion, is focused on understanding and monitoring the genetic predispositions of persons at risk, due to mutations or family histories of cancer. The implementation of evidence-based prevention strategies will lead to considerable improvements in clinical decisions and outcomes. In order to move towards this predictive system, it is essential to raise awareness of those vulnerable people and to empower them. On this basis, it will be possible to facilitate an appropriate checking and an early detection of prodromes, as well as the modification of harmful habits and behaviors (2).

The objective of oncogenetics is to understand genetic predisposition to cancers and care for persons at risk. Genetic predispositions are often associated with a family history of cancer. However, cancers are very frequent and family histories exist, so a family history of cancer is not synonymous with a genetic predisposition. The purpose of a genetic consultation is to determine the share of family history and possible predisposition. Genetic tests, stills seldom practiced, sometimes confirm a hereditary origin. If an alteration is identified in a family, it can be sought in its relations. This makes it possible to reassure those having no predisposition and following up those at risk (3).

However, the realization of the full potential of oncogenetic counseling requires close collaboration between diverse kind of specialists and institutions. These include researchers, clinicians, research institutions, healthcare providers, research and technological development funding agencies, public health agencies, policy makers, industry, regulatory authorities, health insurers and, crucially, the citizen. Genetic testing is already finding its way into several specific clinical applications. Breast cancer, for example, is one of disease in which enormous progress has been made in this regard (3, 4).

However, as things presently stand, the full potential of cancer genetic cancelling cannot be realized in all European countries for several reasons. These include fragmentation of European efforts, nationally and regionally restricted activities, and a lack of concerted approaches in the different areas of ontogenetical services. In addition, In Europe, despite efforts in harmonizing standards for genetic testing and further patients care management problems arise mostly due to differences in countries' health care systems and service delivery settings. Therefore, to advance ontogenetical services, it is likely to achieve strategic interaction between key European players. These include decision-makers in diverse scientific disciplines, research policy and funding, patient interest groups, different national healthcare systems, regulatory and governmental bodies and private enterprise. Only then can a well-balanced and successful development of cancer genetic services be achieved (2).

This review aimed to examining the current practice of cancer genetic counseling in different European countries with special accent on familial breast and ovarian cancer management as the most studied

and managed hereditary cancer disease. We also sought to ascertain the needs for the unitary politics in cancer genetics services.

Cancer care and genetic counseling development in Western Europe

Cancer care has always been part of the health care provided within national health systems across the EU, but only in the last 20 to 25 years, more systematic approaches formulating and applying the comprehensive national policies or plans specifically directed at improving the organization of services for people with cancer have been adopted in some countries. The rationale is that outcomes can be greatly improved by more effective clinical organization and better operational delivery of cancer services (3).

The first explicit attempt to prepare a comprehensive national cancer policy was published by the Chief Medical Officers of England and Wales in 1995 (2). The Calman-Hine report, named "Responding to the challenge of cancer in Europe after the Chief Medical Officers involved" was accepted by government as the basis for the future provision of cancer services in the United Kingdom. The first comprehensive national cancer plans followed a few years later in Denmark (National Board of Health, 2000), England (Department of Health, 2000) and France (French National Cancer Institute, 2003). All began around 2000 (3).

The next logical step was to create Cancer Centers because it could offer more expertise to treat different types of cancer at high standards and would provide sustainability to use expensive equipment for treatment and research. In this respect it can be mentioned National Institute for Health and Clinical Excellence (NICE), in UK, French National Cancer Institute (Institute National du Cancer (INCa) in France, German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC include 12 cancer centers in Germany) - there are a few examples of the oldest Cancer Institutions in Western Europe that provide both research and clinical services (3).

Since 2000, in the most of western European countries testing for hereditary cancer susceptibility has become an integral part of medical management. At-risk individuals can be provided with regular surveillance to identify cancer at an early stage. Prophylactic surgery aims to prevent the development of cancer, and moving in the direction of personalized medicine, targeted therapies for affected mutation carriers become available. The essential step towards a rational approach is how to identify individuals who will benefit from testing, without straining the financial budget of the national health system, although recently established techniques like next generation sequencing may significantly reduce the costs (4).

Meanwhile, guidelines have been established on how to identify individuals at risk for familial breast cancer. In UK the National Institute for Health and Clinical Excellence (NICE), develop guidelines for different issues. The NICE clinical guideline (CG) 41 was created in 2004 and focuses on "Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care". In France, access to cancer genetic services and testing is covered by the National Health Care System and since 2003 through the initiative of the Cancer Plan. "The Cancer Plan 2009-2013" has been developed by the French Ministry of Health in coordination with the French National Cancer Institute (Institut National du Cancer (INCa)). It incorporates the knowledge on hereditary predisposition to cancer within the rubric "Oncogénétique"

http://www.e-cancer.fr/soins/prises-en-charge-specifiques/oncogenetique/ (5, 6).

In the Netherlands "Erfelijke Tumoren: Richtlijnen voor Diagnostiek en Preventie" 2010 was published by the Netherlands Foundation for the Detection of Hereditary Tumors (STOET) and the Dutch Society of Clinical Geneticists (VKGN) (2). In Germany, the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) was established in 1996 as a cooperative research project supported by the German Cancer Aid (Deutsche Krebshilfe). Twelve university-based interdisciplinary centers developed a standardized approach for the management of families with hereditary breast and ovarian cancer. This concept, including the genetic counselling, the molecular genetic diagnostics and the clinical surveillance, became part of the regular health care system in 2005 (3, 6).

In all these countries *genetic diagnostics* is available to search for mutations in the breast cancer genes *BRCA1* and *BRCA2* (3, 4, 5). Although a similar frequency of mutation is assumed each country has established its own genetic testing including criteria. The individual guidelines and recommendations are roughly similar for most selection criteria. All guidelines recommend embedding genetic testing within a framework of genetic counseling, and all agree to perform genetic testing first in an affected person. The access to genetic counseling differs within the countries. While in the UK and the Netherlands for referral from primary care, a general practitioner or secondary care, a specialist is required, in France and Germany referral is usual, but not obligatory. An individual also has direct access to genetic counselling. In this case, difficulties can arise for reimbursement (3).

According to French guidelines, in order to increase the percentage of detected *BRCA1/2* mutation carriers, the including criteria for genetic counselling have been extended and include isolated ovarian cancers diagnosed before the age of 70 and even at an older age (7, 8).

Regarding the approach towards genetic testing, it is recommended first to test the index patient. After a mutation is identified in index patient in all Western European countries, a predictive testing can be offered to healthy relatives from the beginning of a young adult age. The health insurance covers all genetic counseling and testing costs while the threshold for testing a family is quite different between the countries (6, 7).

Risk prediction models are known and used in each country; however, the purpose or reason for their use differs. For example, Tyrer-Cuzick or BOADICEA can be used as prediction tool in UK (9) but should not totally replace careful manual assessment of family trees by a genetic specialist. The Manchester scoring system was developed in 2003 and updated in 2009 to facilitate a simpler and more accurate selection of families for *BRCA1/2* testing (10). Although it is known that all available risk calculation models show considerable weaknesses (11, 12), Cyrillic 2.1 is a helpful tool and allows uniform decision-making across Germany. Thresholds of a risk of heterozygosity of ≥20% or a residual lifetime risk for breast cancer of ≥30% qualify a woman for management in the high-risk group (3).

Recommendations for the clinical management have also been developed. Intensified surveillance strategies including MRI screening and prophylactic surgical options are offered for people who caring a mutation in all western European countries.

There are some specific accents in different county guidelines. In the current French guidelines, the prenatal or preim-

plantation diagnostics could be allowed for people with cancer syndromes after a favorable assessment by a specific advisory board. The request for opinions of French cancer geneticists and prenatal center professionals can differ according to the type of hereditary cancer involved (2, 4).

Furthermore, the Dutch guidelines for clinical geneticists take into consideration the occurrence of phenocopies among breast tumors and deal with unclassified variants (UV) as genetic test results. It is suggested to perform segregation analysis within the family to clarify the effect of the UV (13).

In the German Act on Genetic Diagnostics (14) informed consent is defined as the main purpose of the law, which regulates the conditions for genetic analysis and utilization of genetic data to avoid disadvantages and discrimination. The right "not-to-know" is deeply anchored in the law and has the same value as the right "to-know". Before a genetic test can be initiated, the test person must be informed about the prospects and limitations of the test at-issue as well as about the consequences of the possible results and must agree to the test in written form. In the case of predictive genetic testing, pre- and post-test genetic counseling is mandatory, and refusal must be documented (3, 15).

CONCLUSIONS

Despite a real progress on genetic testing a further data management at the European level, there was a lack of consensus about the best way to carry out genetic counselling, which meant that there were many different approaches to this subject. Counseling has been an area that has had a widespread investigation, leading to each country coming up with its own legislations, guidelines and definitions. Due to this, at a European level, the EuroGenTest (www.eurogentest.org) was established to "*harmonize genetic testing across Europe.*" This was a tool developed to aid professionals of genetic counseling and allowing the creation of a network that would help in the sharing of experiences and information between health professionals also aids patients to understand their rights and to guide them through genetic testing and genetic counseling. A reasonable approach to harmonize the thresholds for inclusion criteria and other guidelines details would be beneficial. It could be a compromise between the strict family history-orientated NICE guidelines from the UK and the less constrained French criteria. The Dutch and German guidelines already represent something in between, so it could be a good start for guidelines harmonization. Only the Dutch guidelines take into consideration the phenomenon of phenocopies, and triple-negative tumors within *BRCA1*-associated breast cancer. There are still a lot of open questions as families with male relative or the situation that no index patient is available for testing that are not covered in any guidelines. A simple scoring method to classify the family, like the Manchester scoring system, seems to be a reasonable and an easy to use tool and suitable to assert throughout different European countries. Guidelines must be orientated on different levels and disciplines, and the access for every player involved should be thereby facilitated. General practitioners, clinical specialists, geneticists and researchers need different information and different support for decisions. An open communication process including all these topics seems most promising to react adequately to the current level of knowledge and to improve the quality of genetic counselling and testing for familial/ hereditary breast and ovarian cancer across Europe.

REFERENCES

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. *Global Cancer Observatory: Cancer Today*. Lyon, France: International Agency for Research on Cancer. 2018. Available from: https://gco.iarc.fr/today. Accessed 08.08.2018.
2. Coleman MP, Alexe DM, Albreht T, McKee M (editors). *Responding to the challenge of cancer in Europe*. Institute of Public Health of the Republic of Slovenia: Ljubljana, 2008.
3. Gadzicki D, Evans DG, Harris H, *et al*. Genetic testing for familial/hereditary breast cancer-comparison of guidelines and recommendations from the UK, France, the Netherlands and Germany. *J Community Genet* 2011; 2(2): 53-69.
4. ***Expert Advisory Group on Cancer. A policy framework for commissioning cancer services - the Calman - Hine Report. *A Report by the Expert Advisory Group on Cancer to the Chief Medical Officers of England and Wales*. London, UK: Department of Health; 1995.
5. Andrieu N, *et al*. Synthèse du rapport sur l'estimation des besoins de la population pour les 10 années à venir en termes d'accès aux consultations et aux tests d'oncogénétique l'Institut National du Cancer *Études & expertises* 2009. Available at www.e-cancer.fr. Accessed 06.08.2018.
   ***NICE (National Institute for Clinical Excellence). NICE guideline CG041: familial breast cancer. *The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care*. National Institute for Clinical Excellence, London, 2006. Available at http://www.nice.org.uk. Accessed 06.08.2018.
6. Schmutzler R, Schlegelberger B, Meindl A, Gerber W, Kiechle M. Counselling, genetic testing and prevention in women with hereditary breast-and ovarian cancer. Interdisciplinary recommendations of the consortium "hereditary breast and ovarian cancer" of the German Cancer AiD. *Zentralbl Gynäkol* 2003; 125: 494-506.
7. Bonaïti-Pellié C, *et al*. Cancer genetics: estimation of the needs of the population in France for the next 10 years. *Bull Cancer* 2009; 96: 875-900.
8. Antoniou AC, *et al*. Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. *Med Genet* 2008; 45: 425-431.
9. Evans DG, *et al*. Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for BRCA1 and BRCA2 testing. *J Med Genet* 2009; 46: 811-817.
10. Antoniou AC, Easton DF. Risk prediction models for familial breast cancer. *Future Oncol* 2006; 2: 257-274.
11. Amir E, Freedman OC, Seruga B, Evans DG Assessing women at high risk of breast cancer: a review of risk assessment models. *J Natl Cancer Inst* 2010; 102: 680-691.
12. Smith A, Moran A, Boyd MC, Bulman M, Shenton A, Smith L, Iddenden I, Woodward E, Lalloo F, Rahman N, Maher ER, Evans DGR. The trouble with phenocopies: are those testing negative for a family BRCA1/2 mutation really at population risk? *J Med Genet* 2007; 44: 10-15.
13. Julian-Reynier C, Chabal F, Frebourg T, Lemery D, Noguès C, Puech F, Stoppa-Lyonnet D. Professionals assess the acceptability of preimplantation genetic diagnosis and prenatal diagnosis for managing inherited predisposition to cancer. *J Clin Oncol* 2009; 27: 4475-4480.
14. ***Gendiagnostikgesetz. German act on genetic diagnostics, 2009. Available at http://www.gesetze-im-internet.de/bundesrecht/gendg/gesamt.pdf.
15. Kreienberg R, *et al*. *Interdisziplinare S3-leitlinie fur die diagnostik, Therapie und Nachsorge des Mammakarzinoms*. Germering: W. Zuckschwerdt Verlag, 2008.