HOW ONCOGENETICS PREDICTS & EDUCATES

CHART ON ONCOGENETICS STANDARDS AND PROCEDURES FOR MEDICAL INSTITUTIONS

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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
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INTRODUCTION

Cancers are diseases with multifactorial etiology but, in some situations, they can be considered genetic diseases induced by the accumulation of alterations in the genome of cells. Most often, family aggregations of a cancer occur due to the presence of the same exogenous risk factors as lifestyle. However, under certain conditions, an inherited risk may be suspected on the basis of clinical or epidemiological criteria. In these people, the risk of cancer (sometimes even more aggressive) is increased, compared to the general population.

The identification of genetic mutations allows the quantification of the risk of cancer as well as the application of prophylaxis measures aimed at reducing the incidence and implicitly of cancer mortality. These measures are an integral part of personalized medicine.

The purpose of this guide is to familiarize physicians and health decision makers with clinical and epidemiological criteria that raise the suspicion of the presence of a genetic syndrome at risk for the development of hereditary cancer, as well as the consequences of their identification.

WHAT IS ONCOGENETICS?

Oncogenetics is defined as the medical and diagnostic monitoring of patients and their families, who have an inherited monogenic risk (or caused by a mutant gene of high penetration) or familial cancer / tumors.

This new medical activity of oncogenetics developed in the early 1990s, with the discovery of major cancer predisposing

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genes (such as BRCA1 and BRCA2 for breast cancer, or MMR genes involved in colon cancer).

The effectiveness of oncogenetics has been demonstrated in the Western world for many years, in terms of cancer incidence and prognosis, especially in patients with breast, ovarian or colon cancer. It allows the stratification of cancer risk, offers the possibility of genetic testing and customized risk reduction solutions.

In terms of prevention, oncogenetics has become in recent years, in countries where it is practiced, a major economic solution for health systems. Although patients addressing these forms of the disease do not represent major categories in the proportion of cancers, at the level of these patient groups ***oncogenetics can save lives.***

In fact, the main objective of Oncogenetics is the early detection of people with hereditary predisposition to cancer and thus the reduction of suffering or mortality in these people, and molecular testing is addressed to both cancer patients and their family members.

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RISK FACTORS AND GENETIC SYNDROMS

Cancers are not absolutely hereditary diseases and inheriting a predisposition does not mean the obligatory development of a cancer. There are several examples of genetic mutations that induce a familial predisposition to neoplasms such as retinoblastoma, colon and rectal cancer, breast, ovarian, renal cancer, etc.

A number of genetic mutations are needed to induce cancer. In general, we can classify malignant neoplasms as sporadic or as a result of a genetic predisposition. Therefore, some individuals inherit a genetic predisposition and will develop tumors later in life if additional mutations such as point mutations, deletions, chromosomal abnormalities or alterations in gene expression (epigenetic phenomena) occur.

Of all the risk factors for cancer, the hereditary predisposition is the only one that reaches the threshold of predictive value, which justifies a specific medical monitoring.

A relevant example would be the difference between oncogenetic hereditary risk *versus* lifestyle.

The nutritional risk of ovarian cancer is from 1/100 to 1/75 which means an increase of 1.3 times.

The hereditary risk of ovarian cancer is from 1/100 to 1/2 representing an increase of 50 times.

The hereditary risk of breast cancer may determine that 90% of women with this predisposition will develop the disease.

One can conclude that the hereditary factor defines an dextremely important risk

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MAIN HERITAGE PREDISPOSITION SYNDROMES THAT ARE MONITORED

HEREDITARY BREAST AND OVARIAN CANCER - HBOC

In the case of familial breast and ovarian cancers, 5-10% of cases may be of hereditary origin. Two major predisposing genes, BRCA1 and BRCA2 are responsible for approximately 30% of families at risk in multiple ethnic populations, and up to 80% of families at risk in isolated populations. Inheritance of mutations in the BRCA1 or BRCA2 genes is done in a dominant manner, each first degree relative having a 50% chance of being a carrier of the mutation.

The consequences of germline mutations in the BRCA genes are the cumulative risks until the age of 80 with a different probability of cancer. Thus in the case of mutations:

- BRCA1: 80-85% risk of breast cancer, 12-40% contralateral breast cancer, 50% ovarian cancer, 8% colon cancer, 6% prostate cancer;
- BRCA2: 80-85% breast cancer, 10-25% ovarian cancer, 7% breast cancer in men, 7% pancreatic cancer, relative risk of 4.65 prostate cancer.

HEREDITARY NON-POLYPOSIC COLORECTAL CANCER - HNPCC

Hereditary non-polyposic colorectal cancers are a very high risk group, including hereditary non-polyposic colorectal cancer (HNPCC or Lynch Syndrome) and familial Adenomatous Polyposis AFP or PAF). In both cases, the cumulative risk of cancer throughout life is very high, with genetic factors playing a key role, and medical monitoring for prevention and surveillance is necessary.

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The genes whose alterations are associated with the existence of HNPCC syndrome belong to the family of DNA mismatch repair genes (DNA), genes involved in controlling the fidelity of DNA replication. The MSH2, MLH1 and MSH6 genes are mainly involved, in descending order of frequency, in 35%, 25% and 15% of cases, respectively. Lynch syndrome is an autosomal dominant type of transmission syndrome. Colorectal neoplasms appear later than AFP and have a less aggressive course. They benefit from microsatellite instability which leads to genetic instability. Because these cases occur at older ages than AFP, differentiation from sporadic cases is more difficult.

The consequences of germline mutations in MMR genes are important, the cumulative risks until the age of 80 years of cancer being 80-90% colon cancer, 9-10% ovarian cancer, 30-60% endometrial cancer, 19% cancer stomach, 18% bile duct cancer, 10% urinary tract cancer. There are other types such as Muir-Torre Syndrome: HNPCC-sebaceous gland tumors or Turcot Syndrome HNPCC and glioblastomas.

ADENOMATOUS FAMILIAL POLYPOSIS - AFP

In the case of this pathology, patients develop hundreds or thousands of colonic or rectal polyps at risk of evolving into colorectal adenocarcinomas. The predisposition is inherited in an autosomal dominant manner with a penetration of almost 100%. The gene located on chromosome 5 is called APC (adenomatous polyposis coli) and is a tumor suppressor gene.

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WHO NEEDS TO COME IN FOR AN ONCOGENETICS CONSULT

COMMON SITUATIONS - autosomal dominant risk

- 3 or more cases in the same familial line;
- 2 or more cases in a small family, or for a mre rare cancer type;
- 1 or 2 cases of cancer in young people;
- More cancers in the same persons.

CONSULT INDICATIONS – Simple situations

- Ovarian cancer in a woman < 60 years old;
- Colon cancer in an individual < 40 years old;
- Breast cancer in a woman < 35 years old;
- Breat cancer in men;
- Medular or basal-like cancer;
- Digestive polyposis;
- Multiple cancers;
- Cancer in a monozygotic twin.

Selection or identification criteria for HBOC patients:

Familial situation	***Coeficient***
BRCA mutation already identified in the family	5
Breast cancer in a woman younger than 30 years old	4
Breast cancer in a woman between 30 and 39 years old	3
Breast cancer in a woman between 40 and 49 years old	2
Breast cancer in a woman between 50 and 70 years old	1
Breast cancer in men	4
Ovarian cancer	3

The indication for consultation, epending on the total score:

- prioritary (score of 5 or upper);
- possible (score between 3-4);
- of low medical utility (score of 2 or lower).

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SELECTION / IDENTIFICATION CRITERIA FOR THE MAIN HERITABLE PREDISPOSITION SYNDROMES

HEREDITARY BREAST AND OVARIAN CANCER - HBOC

General hereditary predispositions for breast and / or ovarian cancer are considered, being used as initial recruitment criteria, the following situations:

- At least 3 cases of epithelial breast and / or ovarian cancer in the same family line, in related persons of grade 1 or 2
- 2 cases of breast cancer in related people of grade 1, if one of the cases was diagnosed up to the age of 40 or if it is bilateral;
- 2 cases of cancer in relatives of the first degree, if at least one of the cases is ovarian cancer;
- 2 cases of breast cancer in relatives of the 1st degree, if at least one of the cases is male;
- Cases of multiple epithelial cancers (bilateral breast or breast + ovarian cancer are considered equivalent to two cases in the same family line.

In addition to the clear situations mentioned above, there are other criteria that may indicate the hereditary predisposition to seemingly sporadic cases, as follows:

- breast cancer in a woman younger than 30;
- any case of medullary histological cancer;
- multiple cancers in a woman younger than 40;
- particular ethnographic origin with an increased likelihood of finding founding mutations, such as Ashkenazi, Icelandic or Polish Jewish origins (note that this criterion has not been used since no

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information is yet available on population in Romania).

Within these criteria, we can distinguish suggestive variations for certain precise predispositions. Thus, families in which there are: BRCA1 mutations are considered "high risk" or "highly suggestive".

- ≥ 2 cases of breast cancer + ≥ 1 case of ovarian cancer, of which one case of cancer before the age of 40 and / or one case of bilateral cancer and the absence of breast cancer in men;
- 2 cases of breast cancer in related women of the first degree, cases declared before the age of 35;
- any case of medullary breast cancer

Families in which there are: BRCA2 mutations are considered "high risk" or "highly suggestive":

- ≥ 3 cases of breast cancer of which 1 case of breast cancer in men;
- ≥ 4 cases of breast cancer reported after the age of 45 and no ovarian cancer.

In addition to these general criteria, specific BRCA1 and BRCA2 criteria were used, as follows:

BRCA1	**BRCA2**
- very suggestive: 3 or more cases of breast / ovarian cancer in women; - suggestive: 3 or more cases of breast cancer in women; - suggestive: suspicion of BRCA neomutations (one	- very suggestive: 3 or more cases of breast cancer in men or women; - suggestive: 3 or more cases of breast cancer in women or pancreatic cancer; - suggestive: suspicion of

case of breast cancer younger than 35, one case of multiple cancer (bilateral breast or breast + other organ), 2 breast cancers in women younger than 45).	BRCA neomutations (one case of breast cancer in persons younger than 35, one case of multiple cancer (bilateral breast or breast + other organ), 2 breast cancers in women younger than 45, isolated breast cancer in men).

HEREDITARY NON-POLYPOSIC COLORECTAL CANCER - HNPCC

The monitoring of HNPCC patients is mainly based on the meeting of 3 criteria defined in 1991 in Amsterdam and revised in 1999:

(1) at least three people with cancers belonging to the low spectrum of Lynch syndrome (colorectal, endometrial, large bowel, urinary tract cancers) histologically proven;

(2) united 2 by 2 by degree 1 of kinship over 2 generations;

(3) at least one of these cancers has been declared before the age of 50.

Exclusion of the diagnosis of familial adenomatous polyposis (classical or attenuated form).

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ONCONGENETICS CONSULT

The genetic risk of breast and / or ovarian cancer is assessed during an oncogenetics consultation. This consultation allows, according to the criteria mentioned above, the identification of individuals with hereditary predisposition to cancer, the establishment of affected personal risks, with the ultimate goal of prolonging the life of the person / patient by optimizing clinical monitoring.

Oncogenetic consultations targeting breast and ovarian cancers were developed in the United States and Western Europe in the early 1990s, immediately after the discovery of BRCA genes. Oncogenetic consultations are aimed at both cancer patients and healthy people with a family history of cancer. The indication for an oncogenetic consultation is based on the identification of familial forms of breast / ovarian / colorectal cancer.

Oncogenetic consultation is required when the presence of a highly penetrating genetic disease is suspected based on clinical criteria (eg rare cancers, neoplasms in the same

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patient, breast cancer in men) or family aggregation (eg. 3 people with cancer in the same family). The consultation is addressed to the patient diagnosed with cancer at risk of family aggregation but also to his relatives. If the presence of a genetic mutation is identified, the next step is to compile the genetic tree. It allows the identification of all subjects at potential risk of being carriers of that mutation.

The oncogenetics consultation is performed only after obtaining the informed consent of the patient or his legal representative. After the preliminary evaluation of the patient's file by the medical oncologist, the medical consultation is individual and is performed by a multidisciplinary team. Following the consultation, the patient is offered the result of the molecular diagnosis, if he wants to know the result, and a series of prophylactic measures and / or an alternative of personalized periodic follow-up.

Reconstruction of the family history (family history) is a key element in assessing the notion of hereditary risk, a notion that, once retained, triggers the beginning of oncogenetic investigation and the search for constitutional mutations in syndromes without phenotypic expression. For the reconstruction of the family history, all relatives with or without cancer are reviewed, over at least 3 generations (where possible), and the diagnoses are confirmed by clinical and histopathological documentation. The family history allows the oncogenetician to evaluate the multifactorial origin or, as the case may be, the hereditary predisposition with significant penetration of the case (s) of cancer in the family. In order to optimize genetic testing, specific recruitment criteria must be met, as mentioned above. In this context, it is initially recommended to test the person most likely to be the carrier of a deletional germline mutation, a person called "index case" and who is most often affected by cancer. A second person in the family will also be tested in the first

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phase, recruiting an index case or, if this is not possible, a very close relative. Statistical methods developed to calculate the probability of detecting a mutation according to family and personal characteristics are for example the Myriad II model *[Marroni et al., 2004]* or BOADICEA method *[Antoniou et al., 2004]*.

Most often, individuals susceptible to hereditary predisposition to cancer are referred for oncogenetic consultation by the family doctor or another specialist. It happens, however, that this approach is individual and results from the information disseminated in the media. The oncogenetic investigation includes two meetings / discussions (oncogenetic consultations) with the patient in question (index case) or, when this is not possible, with a close relative.

The patient is informed both on the right to refuse to be communicated the result, on total anonymity, but also on:

- the relevance of a positive or negative result;
- the importance of this result for the rest of his family;
- intellectual property rights in terms of test results.

Depending on the preliminary results of the tests, the patient may be asked for a second and a third independent blood sample, in order to complete the examination of the genetic characteristics or to confirm any probative results. These additional collections may also be performed at the patient's home.

Throughout the assessment, the interdisciplinary team remains at the patient's disposal for additional information or for the introduction of new elements within the family.

The patient has the right at any time to decide to stop or suspend medical procedures.

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The first meeting has three stages:

Stage I – Meeting the oncologist/oncogenetician

- interpretation of the family tree with regard in particular to cases of cancer or other diseases of potential importance;
- the medical diagnosis and the results related to this diagnosis;
- exploring family illnesses;
- medical advice for prevention, detection, monitoring and genetic counseling;
- the decision to start, or not, the molecular genetic investigation (examination of genetic characteristics) by blood collection. This decision may be delayed, depending on the need for additional information, the constraints on participation in the evaluation of other family members, or the presentation to a multidisciplinary oncogenetics group.

Stage II – Meeting the oncogenetician counsellor

- drawing a genealogical tree (family history) as accurately as possible;
- specifying the family structure on the genealogical tree - the identity of each family member, age, status vis-à-vis cancer pathologies;
- collecting various family information, especially those related to cases of cancer or other diseases of potential importance, age at the diagnosis of pathologies and their location;
- informing the family about the mechanisms of heredity and risk factors in cancer;
- informing the family about the oncogenetic investigation.

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Stage III - Collecting a blood sample

- at the proposal of the consulting doctor, after the patient signs an informed consent form;
- bringing to the patient's knowledge the fact that the laboratory analysis can have a variable duration of time, due to the complexity of the studied genes and the lack of preferential localization of the deletional mutations;
- does not require the patient to have an empty stomach before this;

The second meeting:

- it can be requested by the patient, by the doctor who directed it, or justified by the oncologist according to new elements, useful in the oncogenetic monitoring of the family;
- the patient is contacted when the final results are centralized. He is free to refuse to be informed of the results of the examination of genetic characteristics, this decision not being irreversible;
- during the consultation, carried out by the oncogenetic counselor and the oncologist / oncogeneticist, the patient is informed of the complete results, regardless of their nature, as well as the implications that these results may have on the patient and his family;
- the family result of molecular genetics is brought to the attention of one of the family members studied, most often the member with whom the evaluation began. That information is communicated by the patient to the other members of the family, who can

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each benefit, upon request, from an oncogenetic consultation;

- the individual result of molecular genetics is brought to the attention strictly to the receipient, respecting as far as possible the generational order. This communication is carried out within a strict confidentiality: no result is communicated to another person (including doctors) than the patient himself. The outcome of other family members is not disclosed. The information circulating within the family is transmitted by those persons according to their own wishes. The prevention and detection measures are then adapted to each member of the family, depending on the risk diagnosed and specified to those persons by the oncologist.

Începând cu prima consultație dar și pe parcursul derulării etapelor consultului oncogenetic, pacientul și familia acestuia pot, în orice moment, să se întâlnească cu un psiholog.

MOLECULAR DIAGNOSTIC AND THE RELEVANCE OF THE RESULT

Genetic testing is currently possible for a variety of genetic syndromes. Within a Department / Center of Oncogenetics, the molecular diagnosis can be made for familial breast and ovarian cancers, familial adenomatous polyposis or non-polyposis colorectal cancers, being possible the extension of the test base for other hereditary cancers as well.

Genes involved in hereditary predisposition to cancer and the risks involved:

- HBOC - BRCA1 and BRCA2 genes
- HNPCC - MMR (MSH2, MLH1, MSH6) genes
- AFP – APC gene

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Oncogenetic molecular diagnosis is made by complete sequencing of exonic regions and intron / exon junctions, using the technique dideoxy – Dye Terminator (Sanger Sequencing).

The steps required for a molecular diagnosis are:

1. DNA Extraction
2. Mutational-screening (reccurent mutations)
3. PCR increase of the regions of interest
4. Purrification of PCR products
5. Amplicon sequencing
6. Purrification of sequencing products
7. Cappilary electrophoresis
8. Results interpretation

Difficulties in molecular diagnosis are caused by:

1. Very large genes (thousands of nucleotides), numerous exons

2. Thousands of different mutations already identified

3. Approximately 100,000 nucleotides to "read" in a BRCA test

4. Numerous benign polymorphisms in the analyzed genes

5. Approximately 50% of the identified sequence variants are pathogenically uncertain (unclassified variants)

6. Numerous false-positive / false-negative situations

Following the molecular test, 5 categories of results can be obtained:

1. **True positive:** the tested individual has the mutation that was tested;

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2. True negative: the individual tested does not show the mutation identified in the family; the risk of cancer is equivalent to that of the general population;
3. **Negative:** the cancer patient has been tested for a certain mutation but the result is negative and family aggregation is due to common exogenous risk factors;
4. **Non-informative:** no specific mutation is identified although there is an aggregation of a cancer within the family. This situation occurs when the mutation is found in a gene other than the one tested. Although cancer appears to be hereditary, no specific mutation can be identified;
5. **Variant of unknown significance:** a variant of the gene sequence is identified, but it is not known whether this is a normal or a pathological variant. Correlations with epidemiological and clinical data may suggest its significance.

The identified sequence variants are classified as follows:

1. **Neutral** - non-pathogenic (common polymorphisms)
2. **Probably neutral**
3. **Variants with pathogenicity / unknown significance** (UV - Unclassified Variant)
4. **Probably pathogenic**
5. **Pathogenic** (deleterious mutations)

Errors that may occur in molecular diagnosis:

1. Errors due to handling
   - contamination
   - mixing od samples
   - coding errors
2. False-positives
   - identifying a mutation that does not exist
   - “overestimation ” of a UV

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3. False-negatives
   - failure to identify an existing mutation
   - "overestimation " of a UV

PERSONALIZED ONCOGENIC SURVEILLANCE PROGRAM (PSOP)

The consequence of detecting such a mutation is the oncological recording of the subject and the application of primary, secondary or tertiary prevention measures, such as:

- **Adaptation / modification of medical or surgical therapeutic measures** (eg exclusion of menopausal hormone replacement therapy)
- **Different application of screening and early diagnosis measures** (onset at a young age, high frequency, special tests)
- **Individualized application of preventive measures:** bilateral ovarectomy, bilateral mastectomy, thyroidectomy, ablation of polyps, use of contraceptives.

SOLUTIONS AVAILABLE FOR HBOC CASES

- **Preventive surveillance -** Breast cancer (BRCA)
  - Clinical examination of the breasts at 6-12 months;
  - Annual mammography / MRI starting from the person turns 18.
- **Preventive Surveillance -** Ovarian Cancer (OVCA)
  - Annual dosing of CA-125 serum from the age of 25;
  - Gynecological examination at 6 months, Transvaginal ultrasonography annually.
- **Lifestyle change -** diet, alcohol, etc.

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- **Chemoprevention** (BRCA & OVCA)
  - Tamoxifen, oral contraceptives
- **Bilateral prophylactic mastectomy**
  - Reduces the risk of BRCA by >90%
- **Bilateral prophylactic ovariectomy**
  - Reduces OVCA risk by >95%
  - At pre-menopause, reduces the risk of BRCA by ~ 50%.

We recommend the application of the following screening algorithm for breast cancer and its adaptation to patients at genetic risk:

Legend: AEX – autoexamination, EXF – physical exam, IRM – magnetic resonance imagistics, LCIS – carcinoma.

Risk	Age years	AEX	EXF	Mammography	IRM
NORMAL					
	20-40	+	1-3 years	-	-
	≥ 40	+	6-12 months	annualy	
HIGH					
LCIS, ADH,ALH		+		annual after diagnostic	-
BRCA + familial risk		+		annually, starting 10 years earlier than the youngest relative but not earlier than 25 years	annualy

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Mantlle field irradiation	< 25	+	annualy		-
	>25	+	6-12 months	annually after 8 years of healing	annualy
5-year risk of invasive breast cancer ≥ 1.7%	>35	+	6-12 months	annualy	-
Risk> 20% of developing breast cancer during life calculated by BRCA PRO or BOADICEA models		+	6-12 months	annualy	annualy

The genetic test finds its full utility if the result highlights a deletional constitutional mutation. The test can be implemented immediately for other family members, much faster, and a negative result for the latter has the merit of reliably eliminating the notion of hereditary risk of cancer. In the case of a positive result, for a patient or a relative who has a mutation, it is of the utmost importance that the doctor informs the patient of the risks compared to a normal individual in the general population.

The role of the doctor is also to advise the patient on the different detection and prevention strategies that can be implemented, so that the patient chooses the strategy best suited to his case. Currently, there are 3 types of strategies:

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- **Intensive surveillance**– Early clinical and mammographic examinations are recommended for women once a year starting from the age of 30. Given the low sensitivity of mammography, especially in young women whose breast tissue is denser, this examination should be performed even twice a year. In terms of sensitivity, the MRI technique is more advanced (71-100%) than mammography (36-42%), while the specificity of the two techniques is similar (95%). In the long term, the optimal strategy would be to perform more frequent screening, combining the use of mammography and higher resolution MRI techniques. Regarding ovarian cancer, an endovaginal pelvic ultrasound is recommended coupled with a gynecological examination and serum CA125 dosing, once every 6 months from the age of 35 years.

- **Profilactic surgery** – alternative prevention interventions to intensive clinical surveillance may be proposed. For women at risk, this decision requires deep personal reflection, most often accompanied by a multidisciplinary framework, because prophylactic surgery is an irreversible mutilating gesture that can significantly affect the quality of life of the woman concerned and the image of her own femininity. However, the radical version of prophylactic surgery remains the most effective attitude for reducing the risk of cancer. Bilateral prophylactic mastectomy has been shown to reduce the risk of breast cancer by 90%, while prophylactic ovariectomy reduces the risk of ovarian cancer by 96%, the latter also having a protective role on breast cancer (reducing the risk by 53%). in pre-menopausal women). However, ovariectomy does not eliminate the risk of extra-ovarian cancer, which is why menopausal women with BRCA mutations are recommended to have a prophylactic annexectomy. These interventions should be discussed on a case-by-case basis

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in multidisciplinary meetings, given that, on the one hand, breast cancers do not occur in all BRCA mutants, and on the other hand, interventions do not completely suppress the risks associated with these cancers.

- **Chemoprevention** – is another alternative method of prevention, based on hormone therapy, which has been the subject of numerous studies and continues to be evaluated. It is about prevention through the use of Selective Estrogen Receptor Modulators (SERMs), a new class of therapeutic molecules that target estrogen receptors. These molecules have anti-estrogenic activity in the breast and bones (tamoxifen, raloxifene), but can also generate, in the case of first-generation molecules, agonist side effects in other organs (for example, in the endometrium in the case of tamoxifen). Other hormonal modulators, such as aromatase inhibitors, are being tested. This type of molecule has a protective effect in cancers with estrogen receptors, but does not benefit from any effect on cancers in the absence of these receptors, a very common case observed in tumors associated with BRCA mutations.

Patients with Lynch syndrome are candidates for prophylaxis of endometrial and ovarian cancer by total hysterectomy with bilateral salpingo-oophorectomy. Periodic colonoscopic evaluation is done at an interval of 1-2 years, starting from 20-25 years or 2-5 years earlier than the youngest member of the family with cancer. In certain situations, upper digestive endoscopy may be recommended at an interval of 2-3 years, starting with the age of 30-35. Depending on the character of the adenomas, their location, the patient's status, his option, endoscopic polypectomy, segmental colectomy or total colectomy with ileo-rectal anastomosis may be proposed. A

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daily dose of 600mg aspirin can reduce the risk of colon cancer.

Patients with a mutation in the APC gene are monitored periodically by repeating colonoscopy at 2-3 years intervals. The periodicity of the test is adjusted according to the number, size, characters of the polyps. In addition to monitoring, risk reduction strategies such as colectomy or proctocolectomy may be proposed given that the risk of cancer reaches 100% at age 50 and that the highest incidence of occurrence is in the third decade of life.

PSYCHOLOGICAL SUPPORT IN THE PERSONALIZED ONCOGENETIC SURVEILLANCE PROGRAM

Oncogenetic counseling and testing are intra-family experiences faced by the individual and his family members, which sometimes involve difficult-to-manage medical decisions, such as: complex ethical, legal and psychosocial issues.

Individual and family psychological counseling is aimed at developing models of adaptation and integration for the best possible management of oncogenetic risk, aiming at a high level of quality of life of the individual and his family.

In the specific context of oncogenetics, the psycho-oncologist has a very different role from the one he assumes in a "classic" psycho-oncological consultation. Far from representing the traditional "psychologist" who engages in an open discussion whose goal was to promote the spontaneous expression of the patient's mental needs and try to find an answer with tools specific to the psychotherapist, the psycho-oncologist assumes, in the context of an approach in oncogenetics, a specific role and adapted to each case.

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In the case of the oncogenetic approach, the psychological repercussions can be significant and the place of the psychologist is very useful and important within the medical team. The basic variables that influence a person's decision, at a psychological level, to get involved in the genetic testing and counseling process are: risk perception, expected benefits or limitations of genetic testing, psychological general stress, or prognosis of a cancer diagnosis at a time of life, lack of confidence in emotional reactions when faced with negative events, the level of expectations of family support and communication within the family.

The psychological impact on the individual can be influenced by various factors such as: anxiety problems, misunderstanding of medical information or family problems that may occur in various stages of the Personalized Oncogenetic Surveillance Program, during the development of family history (genetic tree preparation), in the waiting period for the test result, when finding out the result of the oncogenetic test, when choosing the implementation of the oncological prevention recommendations.

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- ***The first psycho-oncological interview*** is the right opportunity for the psychologist to review the motivations of the subject underlying the genetic approach. The psychologist has the opportunity to explore the subject's representations of cancer, especially in relation to the often loaded family history, as well as the level of information, as well as the integration of information about the subject in the first meeting with the geneticist. This meeting then addresses, in a way that the patient notices the risk, his ability to anticipate the test result, his desire to transmit the information received to the family, and moreover, open communication within the family. It evokes the psychological consequences of the genetic risk situation, as well as the possible risks of psychopathological decompensation related to this situation.
- ***The second meeting with the psychologist within the Personalized Oncology Surveillance Program*** - If a mutation is identified and the subject must consider the various possibilities of surveillance or preventive surgery, consultation with a psycho-oncologist is mandatory in case of a decision to perform a prophylactic mastectomy and strongly recommended in case of decision to perform a Prophylactic ovariectomy - for example - allow weighing the advantages and disadvantages of each option, checking the subject's ability to anticipate his own reactions to different possible scenarios and evoking the psychological situation towards himself as well as his family.

In fact, the whole family must also be taken into account. Who will inform the other family members and who will motivate them to participate in this process? What is the way of communication or derelation within the family? What are the family's beliefs and values regarding health and the medical, curative and preventive approach? There are as many questions to which the healthy person or the patient together with the psychologist find the most appropriate answers for

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himself and his family. Special attention needs to be paid to the situation of a previous experience of the family facing cancer as well as its interactions with those who care for those suffering from this disease.

Sharing or retaining information about health, disease, genetic susceptibility, can sometimes be understated by feelings of pressure from other family members to take the test. The current state of health of the family members as well as the status of the relationships (divorce, marriage, mourning) can provide indications on the opportunity to perform the test, or, conversely, to provide a period of reflection.

Personalized Oncogenetic Surveillance Program is a delicate process insofar as, on the one hand, we have collected a set of complex information that is provided, information that requires an understanding of the notion of risk, along with all its difficult implications, and on the other hand, it is sensitive information, both for the person requesting an oncogenetics consultant and for those close to him.

The psychological reactions observed in the field of oncogenetics are distributed, as in the other fields of psycho-oncology, on a theory of continuity that starts from "normal" reactions, such as sadness or latent anxiety, to severe psychopathological decompensation reactions, such as it would be the episode of structured depression or psychotic depersonalization. At the same time, we can talk about a number of psychological reactions that are frequently observed in the person taking an oncogenetic approach: anxious concerns about cancer and the risk of cancer, with critical moments (eg when the woman reaches her mother after being diagnosed with cancer), feelings of vulnerability (which can lead to an overestimation of her personal risk), fear of death and aggressive cancer treatments (often by identifying with family members who have been treated or have died as a result of breast, ovarian, or colon cancer),

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feelings of isolation and misunderstanding from loved ones that could lead to social and emotional withdrawal behavior, guilt of transmitting the disease, but also shame or worry, etc.

It is essential to identify significant states of sadness. In addition to mental suffering - which will not be taken into account if it has been the subject of a prior assessment - the state of despair can lead to various additional difficulties, once the oncogenetic approach has started: non-adherence to medical supervision procedures, difficulties in making a decision and to assume the role of messenger of his own family.

The multidisciplinary approach proposed in this context aims to facilitate the understanding of the risk of genetic predisposition as well as the possibilities of medical management of this risk, without generating inappropriate anxiety. Geneticists and clinicians will transmit information in a progressive manner, knowing the difficulty of providing complex information in an emotional context burdened by the existence of a family or personal history.

The aim of this communication is to improve the perception of the risk of developing the disease as well as the knowledge of relevant genetic aspects in this context, without aggravating the emotional concern, favoring the clear choice between different options, such as making the decision to test and then cope with the consequences of its outcome.

The model of making a medical decision based on information, shared between the clinician and the patient, applies particularly in this context. In fact, it responds to a situation of choice between several options: the choice of whether or not to perform a genetic test, whether or not to know the result of this test, whether or not to transmit the information received, immediately or later, to family members; a choice that, in fact - and this is undoubtedly one

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of the most complex decision-making situations - involves opting for simple supervision or surgical prevention in order to reduce the risk of developing cancer. On these different points, and especially if there is uncertainty about the benefit / risk ratio of any of the decision-making alternatives, it is essential that the patient be involved in a direct way, helping him to shed light to his values and preferences after a good understanding has been verified and the choice to be made has been made.

The approach in oncogenetics reveals a multidisciplinary process that associates geneticists, genetic counselors, oncologists, clinical specialists and psycho-oncologists, for better answering the three main dimensions:

- education (need for information),
- help in taking a decision and
- psychological support (helping adaptation).

Regular exchanges of views between professionals will allow the gathering of information and perceptions into a common whole in order to better understand the expectations, values, choices of consultants and possible psychological difficulties.
This process is intended to be the guarantee of an approach that aims at the patient's respect and autonomy in making his decision. To be accepted, monitoring must prove safe, as well as a reversal of the "side effects" balance, with the result that the survival and / or quality of life of the individual concerned is improved.
In *technical terms*, this means reducing mortality through early detection, the most effective therapeutic action being prevention.
In *human terms*, this means that the information received by the person determines the adoption of those behaviors that allow early detection of the disease and better management of

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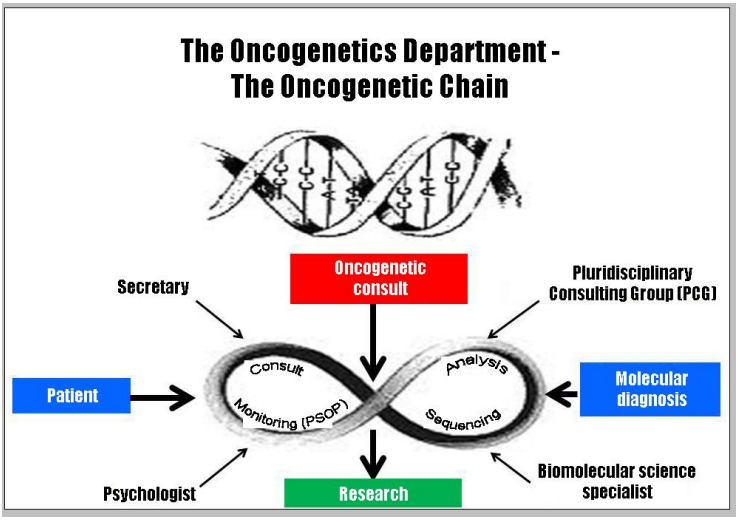
the changes it can bring to the life of the individual, so that the quality of life is as good as possible.

ONCOGENETICS DEPARTAMENT – SCOPE AND OBJECTIVES

SCOPE - Multidisciplinary assessment of patients and their families who are at risk of hereditary or familial cancer and who require investigation by a diagnostic test of molecular genetics.



OBJECTIVES

- Identification of target groups of patients at risk (breast / ovary, colorectal, endocrine), through meetings of the Multidisciplinary Advisory Group (GCP).

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- Oncogenetic consultation - in-depth training of specialists in the field of oncogenetics.
- Molecular diagnostic test - analysis by molecular biology of genetic risk factors.
- Comparative epidemiological study on cancer risk factors in the Romanian population.
- Implementation of oncogenetic monitoring of at-risk patients and their families, through the **Personalized Oncogenetic Surveillance Program (PSOP)**.

MULTIDISCIPLINARY ADVISORY GROUP (GCP)

- Oncogenetician
- Oncogenetics consultant
- Geneticist
- Psychologist
- Oncologist
- Gynecologist
- Gastroenterologist
- Endocrinologist
- Epidemiologist
- Surgeon
- Specialist in radiology and imaging
- Histopathologist
- Molecular biology specialist - responsible for diagnosis
- Bioethics specialist

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