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Review

The Role of Genetic Counseling in Gynecological Oncology

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Abstract

***Background*:** Clinical or medical genetics deals with the study and diagnosis of genetic diseases. It is oriented to the formulation of the clinical diagnosis of genetic diseases and genetic counseling to evaluate the possible reproductive risk for the patient and his/her family. The geneticists here play a role in the diagnosis and prevention of some of the diseases occurring most frequently, such as cancer and cardiovascular diseases.

***Methods*:** State-of-the-art through literature review.

***Results*:** Genetic counseling helps consultants make decisions regarding the possibility of developing and/or transmitting genetic diseases, to evaluate the possible choices that can be made once genetic testing has been carried out and its result is known (possible therapies, voluntary pregnancy interruption, etc.). The decision on what to do is always autonomous to the consultants and the doctor or, a qualified professional figure has no role in it. Genetic

testing is an examination that can be done on deoxyribonucleic acid (DNA) as well as on other substances using different techniques.

***Conclusions*:** In doing genetic testing, one should never dwell on one single "suspect" side of the family so as not to generate inappropriate stress and guilt, and not to underestimate the risk of transmission of other (even more serious) diseases on the other hand.

Keywords

Genetic testing; genetic counseling; obstetrics and gynecology; breast cancer; ovarian cancer; endometrial cancer

1. Introduction

With a significant increase in human genetic knowledge in recent decades, genetics has become increasingly important in medical practice [1]. The genetic basis of diseases and response to therapy are rapidly clarified and may soon become part of routine medical practice [2]. Human genetics and molecular testing play an increasingly important role and are integrated into routine obstetric and gynecological practice. Accordingly, the obstetrician-gynecologists are expected to be aware of the progress in the understanding of genetic diseases and of the fundamental principles of molecular testing and genetic screening. In the future, a better understanding of genetic bases of reproductive disorders, common diseases, and cancer, accompanied by improved high-throughput technology for genetic testing will expand testing opportunities and influence treatment options as well as prevention strategies [3, 4]. Given the increasing availability and complexity of genetic testing, it is imperative that the obstetrician-gynecologist or other health practitioner has a complete understanding of the benefits, limitations, and risks of offering specific genetic testing, and the importance of adequate pre-testing and post-testing advice. Obstetrician-gynecologists and other health professionals should determine which test must be offered as the standard in their practices so that similar testing strategies are tendered to all patients. Health practitioners should have procedures in place that ensure timely delivery of testing results to patients. As with any medical practice, expectations pertaining to the performance of genetic testing should be discussed with the patient before the test is ordered. After counseling, patients should have the option to refuse any or all tests. Pre-testing and post-testing counseling should be done in a clear, objective, and non-directive manner, which allows patients enough time to understand information and make informed decisions about testing and further evaluation or treatment. Besides advising each patient on her own personal risk, obstetrician-gynecologists and other healthcare professionals should advise patients on the risk to family members, including their potential to have affected children [5, 6].

Clinical or medical genetics deals with the study and diagnosis of genetic diseases, oriented to the formulation of the clinical diagnosis of genetic diseases and genetic counseling to evaluate the possible reproductive risk for the patient and her family. The geneticist is also called to play a role in the diagnosis and prevention of some of the most frequently occurring diseases, such as cardiovascular disease and cancer. Joseph Adams, who described the genetic transmission of polydactyly [7], William Bateson [8] and Archibald Edward Garrod [9], who described the recessive

transmission of alkaptonuria, are considered founders of this discipline, including Jérôme Lejeune, who first related Down's syndrome, with a chromosomal abnormality, i.e., trisomy 21 (T21), in 1959 and identified abnormality in a fifth chromosomal pair as the cause of "cry of cat" syndrome in 1963 [10], and Victor McKusick who published the first known genes and the related index of diseases in 1966 [11, 12]. Genetic testing procedures now allow prenatal screening for a wide range of congenital defects, including cystic fibrosis and muscular dystrophy. Moreover, the diagnosis of congenital abnormalities during the pre-implantation phase of *in-vitro* fertilization (IVF) is possible by an emerging technique. This is an absolutely safe procedure for the embryo that precedes its implantation in utero and that allows to identify the presence of hereditary diseases in the very early stages of development, when the embryo is still at the blastocyst stage, or 5-7 days after fertilization. At this stage the blastocyst has already differentiated into the embryonic portion (internal cellular mass) and extra-embryonic portion (trophoblast). The biopsy of a few trophoblast cells (<5% of its biomass) has been shown to be safe and does not compromise the development and implantation abilities of the embryo. Therefore, clinicians need a set of criteria as a guide when parents are advised on the possibility, feasibility, and desirability of particular prenatal testing. For example, there are limits to prenatal testing for conditions such as breast cancer gene mutations because affected individuals do not necessarily develop the condition and a cure can be found by the time the condition develops. Moreover, whether parents should receive this information until the child reaches an appropriate age is also debatable. An approach to the development of guidelines is to classify congenital abnormalities based on severity, age of onset, and type (structural-functional versus mental). Through this system, abnormalities that are clearly lethal, leading to a moderate or severe disability with little or no improvement or prospect of cure can be revealed, besides being characterized by early-onset, and/or involve clear mental retardation. This approach is particularly relevant in T21 cases and progressively invasive screening techniques are available to detect this common malformation pattern in humans [13]. Genetic studies are increasingly becoming obstetric and gynecological practices and are considered central for deciphering the genetic basis of complex diseases [14].

Recent developments in molecular biology have significantly aided in progress and information related to the theoretical and clinical work done in the obstetric-gynecological field. Molecular obstetrics and gynecology are therefore the links between the different sections of this field. At present, the molecular understanding of cellular pathways is much better than the direct integration of molecular diagnostics and therapy in routine clinical practice. The use of molecular diagnostics, such as pre-implantation diagnostics or predictive genetic testing, still presents technical problems as well as new, and so far, unclear, social, ethical, and legal implications. To date, the specifics of molecular therapy have not yet met their expectations. Broadly, in obstetrics and gynecology, new molecular discoveries are influenced not only by technical considerations but also by socio-economic and political issues. These include, for example, free access to genetic testing, gene patents, and the financial monopoly over molecular drugs. Therefore, rules must be proposed to potentially integrate the expertise in molecular obstetrics and gynecology in the daily care of patients seeking help or advice [15-17]. Several new genetic tests and a series of recommendations are available for obstetrician-gynecologists. In recent years, screening of low-risk pregnant women has been proposed using methods sometimes called "non-invasive prenatal testing" (NIPT), as well as universal breast-related cancer antigen 1 (BRCA1) and 2 (BRCA2) screening of all women independent of their risk status. After screening, both the proposed

genetic tests raise complicated issues related to predictive value, cost, and consequences for the health care system as well as for the patient. Further, there are significant barriers to the education of physicians in the correct use of this genetic test, and logistical problems in carrying out adequate genetic counseling in the general practice. It is recommended that pregnant women who have been offered NIPT be informed of its advantages and disadvantages compared to standard screening with the warning that a positive NIPT needs to be confirmed by further invasive testing. It is also recommended that population genetic screening of all women for BRCA1 and BRCA2 mutations should not be made until there are complete data on harms, benefits, and cost-effectiveness. Finally, the development of new educational models of genetics for the training of obstetrician-gynecologists is recommended, so that future health care providers are prepared for the opportunities and challenges that genetic testing creates [18].

Genetic counseling is a tool that should help consultants to make decisions regarding the possibility of developing and/or transmitting a genetic disease, and aid in evaluating the possible choices (possible therapies, voluntary pregnancy interruption, etc.) that can be made once the result of genetic testing is known. The decision on what to do is always autonomous to the consultants and the doctor (or in any case the qualified professional figure) has no managerial role. Genetic testing is an examination that can be done on deoxyribonucleic acid (DNA) as well as on other biomolecules using different methods. To summarize, the objectives of genetic counseling are:

1. to verify the correctness of a diagnosis;
2. to ascertain the level of knowledge of the consultants regarding the disease, looking for preconceptions and misinformation; and
3. to provide all necessary information, also about specific associations in support of patients and their families.

Counseling can have various indications:

1. pre-conceptional (having the knowledge of being carriers of a genetic abnormality before planning of pregnancy is better than waiting for it to arrive because it reduces stress and there is more window period to undergo the test and decide);
2. prenatal;
3. screening; and
4. diagnostic;

Counseling is divided into three work phases:

1. the pre-testing phase;
2. the actual test, which can be complex and long, depending on the method used and the suspected pathology; and
3. the post-testing phase, in which the result is evaluated and the patients are asked if they want to be informed about it in the presence of a psychologist, then “what to be done” is discussed, that is, to decide which test can be performed further and whether it is possible to offer the test to other relatives.

The duration of the various phases varies greatly based on the pathology; there are cases in which the test is relatively simple because the defect to be searched is well known and does not require much time because there are not many mutations that cause it. In other cases, the test is long and complex and it takes a long time to be done and evaluated, while, in other diseases the test can be less conclusive on the clinical choice—it is less reliable or there no therapies are

available, as often happens—and this requires a longer pre-testing phase to evaluate the motivation of the patients [19, 20].

1.1 Pre-Testing Interview

In this phase, the important data to ask and to provide to the consultants are:

1. the personal anamnesis of the patient and the family (with the construction of a good family tree for a better representation of how the disease spreads in the family, taking into account abortions, causes of death, and consanguineous unions);
2. the geographic origin and the ethnic group identification of the family (to verify if the ancestors were originally from a genetically isolated area from the outside, for example, small countries);
3. the information on the disease: its mode of transmission, evolution, the existence of therapies or prophylactic measures, etc.;
4. the information on the reliability of testing;
5. the discussion on the consequences of testing if this is positive: What are the advantages of knowing this? Are there therapies or instruments developed in advance that can control the progression of the disease? Are these effective? Can the risk of transmission be controlled? Can it be useful for the other family members? Is the patient able to withstand stress and feelings of guilt given the positive result? What can I do if I do not take the test?
6. informed consent; and
7. the examination of the correct understanding of the given information [21].

1.2 Types of Genetic Testing

Genetic testing can be:

1. diagnostic;
2. identification of healthy carriers;
3. pre-symptomatic (for late-onset diseases the usefulness of the test must be checked);
4. predictive (familial cancers: as above); and
5. medico-legal (e.g., ascertaining or excluding paternity).

While performing the test, one should never dwell on one single “suspect” side of the family; the purpose is not to generate inappropriate stress and guilt, and not to underestimate the risk of transmission of other (even more serious) diseases on the other hand.

2. Genetic Counseling in Gynecological Oncology

2.1 Overview

Cancer can be described as a genetic disease, that is, due to altered DNA, or mutations. Many of these mutations will be accumulated during normal cell division. Some people may inherit abnormal genes, which predispose such individuals to high risk for some malignant neoplasms. These individuals can sometimes be identified as having a family history of affected individuals, some of whom may have an early age of onset or multiple neoplasias. In some of these malignant tumors, specific associated genes have been identified. Hereditary cancers include (but are not limited to) ovary, breast, colon, endometrium, and, to a lesser extent, prostate, skin, and pancreas.

Some of these cancer-predisposing genes are highly penetrant with up to 80–90% of gene carriers who develop the associated neoplasia within 70-year life expectancy. While there is currently no way to correct a mutant gene, early diagnosis, and some chemoprevention techniques are clinically important. Molecular testing for the presence of cancer-predisposing genes is available for many of the hereditary syndromes. Genetic counseling can relieve anxiety in people who fear of being at high risk [22]. The increasing availability of genetic testing has forced women with malignancies of breast, ovary, and colorectal cancer and their physicians to confront new questions regarding screening and prevention [23]. Hereditary cancer syndrome is a genetic predisposition to certain types of cancer, often with a young age of onset, caused by inherited mutations in one or more genes. Commonly seen cases of cancer—such as breast cancer, ovarian cancer, and endometrial cancer—are characteristic of specific hereditary cancer syndromes. The most common hereditary cancer syndromes related to gynecological cancer include hereditary breast and ovarian cancer (HBOC) syndrome, Lynch syndrome, Li-Fraumeni syndrome, Cowden syndrome, and Peutz-Jeghers syndrome. The evaluation of hereditary cancer risk is the key to identifying patients and families potentially at higher risk to develop certain types of cancer. Screening should include, at a minimum, personal cancer history and first- and second-degree relative's cancer history, including description of primary cancer type, age of onset, and family members lineage (paternal versus maternal). Additionally, the ethnic background of a patient can influence her genetic risk. Consultation with a cancer genetics specialist or a physician with expertise in genetics is recommended if the assessment of hereditary cancer risk suggests an increased risk of hereditary cancer syndrome, for an extended collection of genealogical information, risk assessment, education, and counseling, which can lead to genetic testing [24]. Among the many heredo-familial syndromes, the most relevant for absolute frequency and in relation to cancers to which they predispose are those related to high-penetrance gene germline mutations (BRCA, mainly) for breast and ovarian cancers, and those related to mismatch-repair (MMR) gene mutations (particularly, mutL homolog 1 [*MLH1*], mutS homolog 2 [*MSH2*], and mutS homolog 6 [*MSH6*]) for colorectal and endometrial cancers. High-penetrance onco-suppressor genes, *BRCA1* and *BRCA2*, phosphatase and tensin homolog (*PTEN*), and tumor protein 53 (*TP53*) code for a DNA-repair protein involved in the prevention of cellular carcinogenesis. HBOC syndrome includes genetic alteration of various susceptibility genes such as *TP53*, ataxia-telangiectasia mutated (*ATM*), *PTEN* or *MSH2*, *MLH1*, protein homolog 1 (*PMS1*), *PMS2*, *MSH3* and *MSH6*, *BRCA1* and *BRCA2*. Germline mutations of cancer susceptibility genes *BRCA1* and *BRCA2* appear to be the major etiology of HBOC. Family history of subjects affected by these autosomal dominant mutations shows a high breast and/or ovarian cancer incidence, early age at the time of diagnosis, multiple cancers in the same individual (bilateral breast cancer, and breast and ovarian cancer), or unusual cancers (male breast cancer). In particular, *BRCA* gene mutations are more frequently associated with HBOC syndrome, with a risk of breast cancer of 65–85% (up to 70 years of age) and a risk of ovarian cancer of 39–46% and, respectively, of 45–85% and 10–27% in case of in case of *BRCA1* and *BRCA* 2 mutations [25-27]. *TP53* gene mutations are the cause of Li-Fraumeni syndrome, characterized by an increased risk of osteosarcoma, leukemia, brain tumors, adrenal carcinoma, and breast cancer (risk is 18 times greater before 45 years than in the general population). Cowden syndrome, caused by *PTEN* gene mutation, is associated with the increased risk of hamartomas, benign tumors, and breast cancer (lifetime risk of 25–30%) [28]. The mutations in the MMR system, more frequently of *MLH1*, *MSH2*, and *MSH6* genes, resulting in the

so-called "Lynch II syndrome" or hereditary non-polyposis colorectal cancer (HNPCC) syndrome can confer the carriers (up to 70 years of age) the risk of colorectal cancer of 40–60%, the risk of endometrial cancer of 42–60%, and a risk of ovarian cancer of 9–12% [29, 30]. Lynch syndrome, an inherited autosomal dominant cancer susceptibility syndrome, is the most common presentation of hereditary colorectal cancer, which accounts for about 2–5% of all cases of colorectal cancer. More recently, a similar prevalence of endometrial cancers, also due to MMR gene mutations, has been found. Lynch syndrome accounts for 2–3% of endometrial cancers. Significant progress has been made in Lynch syndrome-related colorectal cancer in terms of molecular pathogenesis, risks, genetic basis, and cancer prevention [31]. There has been a growth in the studies exploring new methods of testing germline mutations in the management of gynecological cancers along with the developing therapeutic options and the knowledge of specific genes. The options for systemic therapy are also increasing; for instance, two recent clinical trials (SOLO2 and ARIEL-3) endorsed the use of poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors in the maintenance setting, and pembrolizumab has been approved to treat MMR deficient/microsatellite unstable tumors. Several studies have addressed the resultant growing demand for testing of Lynch syndrome and *BRCA1/2* mutations in endometrial and ovarian cancers, respectively. Finally, various studies have assessed gene and age-specific risk for ovarian cancer, and the role of specific site mutations in *BRCA2* in influencing the length of PARP response, and therefore, the clinical outcome. The use of genomic data to guide therapy choices and determine the outcome is an exciting and unexpectedly expanding field. Addition research grants further support that checking inherited mutations must be a routine part of care in gynecological patients [32].

Breast cancer is pathology with a multifactorial etiology, and its development depends on the interaction of different factors, hormonal, metabolic, environmental, and genetic. Most breast cancers are referred to as "sporadic", that is they arise in women without significant family history for this condition (Table 1). A minority of cases (about 15%) are instead called "family tumors" because in each nucleus there is more than one affected component. Finally, nearly 5–7% of breast cancers are considered "hereditary", or due to the presence of variants of DNA constituents that confer a higher risk of cancer development in certain individuals compared to the general population. There are also particular ethnic groups that present a higher risk of hereditary predisposition to breast cancer (e.g., Ashkenazi Jewish women). In the 90s, two genes, *BRCA1* and *BRCA2,* were identified as responsible for this susceptibility, located, respectively on chromosomes 17 and 13. They are responsible for nearly 25% of cases of hereditary breast cancer and nearly 10% of cases of hereditary ovarian cancer. An additional percentage of hereditary tumors is linked to the presence of other gene variants, such as *TP53*, *PTEN*, serine/threonine kinase 11 (*SKT11*), and cadherin-1 (*CDH1*), but these are rarer situations. The remaining cases linked to the presence of different genes mutations but not yet identified include BRCAX (subjects at high risk too with probable but unknown mutation). Finally, genes have been identified that confer moderate-mild risk of breast cancer, although the clinical applicability of genetic screening is still under study. *BRCA1* and *BRCA2* genes are called onco-suppressors and are capable of regulating cell proliferation and repairing any damage in DNA replication. A genetic variant in one of these two genes, able to alter the normal process of protein synthesis or of ribonucleic acid (RNA) splicing, can determine the loss of one of these functions. At the clinical level, an individual presenting a variant of this kind has increased risk of developing breast and/or ovarian cancer, in the course of

her life. The transmission of *BRCA* gene variants is of autosomal dominant type, which is a carrier individual (e.g., who presents such a variant in his/her DNA), can transmit such alteration to the offspring with a probability of 50%, regardless of the child's gender. It is difficult to define the extent of breast cancer risk over the course of life in women carriers of *BRCA1* and *BRCA2* gene variants because studies in this regard have been carried out in different populations, with different approaches (retrospective or prospective), and with variable confidence intervals (CI). However, it is likely to estimate the lifetime risk of breast cancer to be around 60% for *BRCA1* and around 55% for *BRCA2* gene variant carriers. These variants also give rise to increased risk of ovarian/fallopian tube cancer, which is about 59% for *BRCA1* and 16% for *BRCA2* gene variants. They are also responsible for increased male breast cancer risk, equal to 1–5% for *BRCA1* and 5–10% for *BRCA2*. Furthermore, the risk for contralateral breast cancer at least ten years after the first event is also higher in women carriers of *BRCA1* and *BRCA2* alterations compared to non-carrier women (35% vs. 5%), particularly for *BRCA1* gene variant carriers. Finally, some scientific evidence emphasizes increased risk for other types of neoplasms in the presence of *BRCA2* gene variants; *BRCA2* mutations are more associated with pancreatic and prostate cancer than melanoma, gastric, and biliary cancer, but may be associated with all of those and lung cancer. Subjects presenting breast cancer with a hereditary component may present some peculiar clinical features, such as earlier age at diagnosis, bilateral nature of the disease, presence of primitive breast and ovarian cancer, familiarity, and, male subjects with breast cancer among family members. In the *BRCA* gene-linked types, typical biological characteristics may also be present. From the histopathological point of view, *BRCA1* gene-correlated cancer generally appears as a high-grade invasive carcinoma with high mitotic counts and intense inflammatory response. A higher incidence of medullary type aspects is also highlighted. From the immunohistochemical and molecular point of view, most BRCA1 cancers show absence of hormone receptor expression, human epidermal growth factor receptor 2 (HER-2) protein overexpression, or HER2 gene amplification (triple-negative phenotype), high frequency of TP53 protein somatic mutations, and frequent expression of "basal-type" cytokeratins (CK5/6, and CK14). Cancers related to the presence of *BRCA2* gene variants are more similar to sporadic ones. However, they are often high-grade too, with the coexistence of ductal carcinoma in situ (DCIS), and the frequent presence of tubulo-lobular or pleomorphic lobular morphology (Table 2).

Table 1 Breast cancer.

Risk factors	**Protective factors**
• Nulliparity • Early menarche • Late menopause • Obesity (in post-menopause) • Family history • Oral contraceptives (<20 years of age) • Hormonal treatment in menopause	• Early age at first pregnancy (<30 years) • Breast-feeding • A high number of pregnancies • Diet low in calories, saturated fats, refined sugars, and alcohol, and rich in fruits and vegetables, especially cruciferous (cabbage, broccoli, turnips) • Physical activity (30 minutes/day)

Table 2 Classification of breast cancer risk*.

	Risk category		
	General population	**Moderate risk**	**High risk****
The lifelong risk from the age of 20 years	<17%	17-30%	≥30%
Risk in subjects between 40 and 50 years	<3%	3-8%	>8%

*The risk assessment in a secondary and tertiary setting can be improved by using risk assessment tools such as BOADICEA and Tyrer-Cuzick.
**This group includes known genetic mutations (BRCA1, BRCA2, and TP53 genes) and rare conditions associated with an increased risk of breast cancer such as Peutz-Jeghers syndrome (STK11), Cowden syndrome (PTEN), and diffuse familial gastric carcinoma (E-cadherin).

Ovarian cancer is caused by genetic alterations that disrupt proliferation, apoptosis, senescence, and DNA repair. While a vast majority of ovarian cancers are sporadic, due to the accumulation of genetic damage throughout life (Table 3), nearly 15% of cases of ovarian cancer are thought to have a hereditary basis with family history as the strongest risk factor for the development of this disease. Families with multiple cases of ovarian cancer have long been observed. Three distinct hereditary syndromes identified are:

1. HBOC syndrome;
2. HNPCC syndrome; and
3. site-specific ovarian cancer.

Table 3 Ovarian cancer.

Risk factors	**Protective factors**
• Nulliparity • Early menarche • Late menopause • Obesity in adult age • Hormonal treatment in menopause • Family history • Meat/sausage	• Number of pregnancies (≥4 vs. 1) • Breast-feeding • Oral contraceptives • Physical activity • Fish

The mode of inheritance in these families is autosomal dominant with transmission occurring through either the maternal or paternal line. The breast-ovarian and site-specific ovarian cancer family syndromes, which account for more than 90% of familial ovarian cancers, have been linked to the *BRCA1* gene on chromosome 17q. However, there are no simple genetic tests to identify women at high risk of the disease. Therefore, genetic counseling, education, and surveillance with currently available screening techniques should be made available to women at high risk of ovarian cancer by virtue of their family history [33]. In the past, prophylactic oophorectomy has been proposed for women with two or more affected first-degree relatives. Several specific genes involved in ovarian carcinogenesis have been identified, including the *TP53* tumor suppressor gene

and *HER2*/neural (neu) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (*PIC3KA*) oncogenes. Currently, with the identification of the genes responsible (*BRCA1* and *BRCA2*) for most hereditary ovarian cancers, oophorectomy can now be offered specifically to women carriers. Contrarily, non-carriers of these families can be reassured that their risk of ovarian cancer does not increase. The value of oophorectomy in mutation carriers has not yet been demonstrated; however, the benefit may be less than intuitively predicted. First, although lifetime risk of ovarian cancer was initially 60%, recent studies have reported risk in a range of 15–30%. A better understanding of the genetic and/or environmental basis of variable penetrance is needed to enhance our capability to advise women about their risk. Furthermore, after oophorectomy, peritoneal papillary serous carcinoma, indistinguishable from ovarian cancer occurs in some women. The studies that better define the frequency of its occurrence are also necessary to establish the value of prophylactic oophorectomy more firmly. In view of the uncertainty regarding the efficacy of prophylactic oophorectomy, chemopreventive and early diagnostic approaches must be considered as strategies to reduce ovarian cancer mortality in women carrying mutations of ovarian cancer susceptibility genes [34]. To facilitate further clinical and basic research in this field, multidisciplinary hereditary breast-ovarian cancer clinics have been established that offer a wide range of services including *BRCA1* testing, genetic counseling, cancer prevention and treatment [35].

The recent availability of expression microarray has facilitated simultaneous examinations of thousands of genes, and this promises to further extend our understanding of the molecular events involved in ovarian cancer development. This knowledge can be hopefully translated into effective screening, treatment, surveillance, and prevention strategies in the future [36].

Recognizing hereditary ovarian cancer characteristics and appropriately managing women at risk will provide more accurate treatment of the high-risk populations. Women at risk can be identified through genealogical examinations and can receive advice from multidisciplinary genetic oncology clinics; high-risk cases must receive further genetic testing. Risk calculation programs define risk, provide information on disease risk, mutation status, assist in decision-making in clinical options, and the use of genetic testing in the management of high-risk families. While a large number of surrogate preliminary markers have been identified in ovarian cancer genomics, the number of studies is still limited. Several options are available for the management of hereditary ovarian cancer risk, including surveillance, chemoprevention, and prophylactic surgery. In high-risk hereditary ovarian cancer patients, surveillance is not yet accurate. Chemoprevention is currently a controversial topic, as a number of important issues need to be addressed while developing and testing agents for the prevention of ovarian cancer. Prophylactic surgery has been shown to effectively reduce cancer risk and has the potential to substantially reduce mortality associated with ovarian cancer [37, 38]. However, the use of transvaginal ultrasonography (TVUS) and tumor markers (such as cancer antigen 125 [CA-125]), alone or in combination, for early detection of ovarian cancer in women at medium risk has not shown to reduce mortality, besides invasive diagnostic testing (e.g., surgery) raise doubts because of false-positive results (FPR). The patient and her obstetrician-gynecologist should maintain an adequate level of suspicion when potentially relevant signs and symptoms of ovarian cancer are present [39, 40]. In the general population, screening through population-based studies does not necessarily improve early detection or survival. Therefore prevention strategies must be applied to improve results for this disease. Prophylactic surgery reduces risk and risk-reduction salpingo-oophorectomy (RRSO) is the

most effective means of preventing ovarian cancer in a high-risk patient, although risks do not outweigh benefits in medium-risk patients. Other surgical and medical options have unknown or limited efficacy in high-risk patients [41].

Genetic counseling and identification of high-risk families can be essential:

1. in providing the best genetic testing method by explaining the sensitivity and specificity of the method;
2. in offering the opportunity to participate in specific early cancer detection programs (breast [auto-] palpation, ultrasonography, mammography, and magnetic resonance tomography for breast cancer, vaginal exploration, and ultrasonography for ovarian carcinoma);
3. to inform the patient about prophylactic drugs (oral contraceptive pill, chemoprevention [tamoxifen, raloxifene, and aromatase inhibitors]), or surgery (bilateral prophylactic mastectomy and/or oophorectomy); and
4. to provide personalized psychological support.

To meet these broad demands, an interdisciplinary counseling approach (gynecological oncology, human genetics, molecular biology, and psychotherapy) provided by a cancer genetic clinic seems the most appropriate. The participation in predictive genetic testing or the use of preventive or therapeutic options can be elaborately discussed with the subjects. In particular, preventive options are emotionally disturbing for individuals and those with a history of previous cancer. Breast cancer chemoprevention in high-risk women does not seem to be as effective as expected. Nevertheless, the oral contraceptive pill reduces ovarian cancer risk. For prophylactic surgery, several points must be considered, including:

1. individual risk assessment and an increase in life expectancy;
2. value of screening and early diagnostic methods or medical prevention;
3. disease characteristics and prognosis; and
4. anxiety and quality of life.

Decisions regarding these options must be personalized and psychological support must be offered during decision and follow-up period [42]. Lack of information on the effectiveness of screening strategies, chemoprevention, or surgical prophylaxis, and uncertainty regarding penetrance and risk modification have led many experts to recommend that genetic testing for *BRCA1*, *BRCA2*, and other cancer susceptibility genes be performed only in a research setting. However, patients are increasingly demanding access to genetic testing and deserve updated advice on recent progress in the knowledge-base. A primary care physician should focus on identifying women who may be at high risk for cancer for further referrals, allowing the cancer genetics specialist to track medical records, clarify the pedigree, discuss genetic testing, and provide access to the appropriate cancer specialist to discuss risk reduction [43].

In recent years, testing for cancer susceptibility genes has entered the clinical setting. The practicing physician should be familiar with this evolving field of medicine to be able to advise and/or target high-risk patients such as those with a strong personal or family history of cancer [44]. Genetic counseling and testing for hereditary disorders are part of every obstetric-gynecological practice. Family history, ethnicity, and race are regularly evaluated as part of the prenatal evaluation. The discovery of genes responsible for hereditary cancer susceptibility and the wide availability of clinical genetic testing for mutations in these genes have made these and similar evaluations an integral part of the gynecological practice. Guidelines of genetic testing for mutations in *BRCA1*, *BRCA2*, and *MMR* genes responsible for HNPCC syndrome need to be

individualized. As in obstetrics, genetic counseling can provide a critical assessment of family history to help determine the likelihood of a hereditary cancer susceptibility syndrome as well as the adequacy of genetic testing. When screening or prophylactic interventions are prescribed, subsequent clinical recommendations for mutation carriers should consider the patient's age, desire for future pregnancies, and other medical information. Genetic testing for cancer susceptibility can potentially reduce the burden of inherited cancers by saving lives, decreasing medical pathologies, and reducing psychological stress [45, 46]. A thorough assessment of family history remains a fundamental procedure that helps identify patients who are at risk for hereditary cancer. The American College of Obstetrics and Gynecology (ACOG) recommends that all women receive an assessment of family history to examine hereditary risk and that this information is regularly updated. Further, additional follow-up including hereditary cancer testing is advised for patients with an abnormal family history of cancer. Complete profiling for hereditary cancer patients is achieved through multigene panel testing by identifying more health risks than single genome testing. If hereditary cancer is established, patients should be informed about management options, including enhanced surveillance, chemoprevention, and/or surgery. Establishing workflow protocols can help clinicians integrate the assessment of inherited cancer risk into their practice [47]. With the expansion in criteria for BRCA testing, more young women can be identified with a significant risk of breast and ovarian cancers. Fortunately, there is strong evidence to support risk reduction through mastectomy and oophorectomy. However, these surgeries have significant psychological and physical health consequences. For breast cancer, screening with mammography and magnetic resonance imaging (MRI) can be sensible for women who do not want surgery. Here, screening for intraductal papillary mucinous neoplasms (IPMN) with MRI/magnetic resonance cholangiopancreatography (MRCP) is recommended. However, there is no evidence to suggest any efficacy in ovarian cancer screening, and women who choose not to undergo surgery need to have detailed discussion with their clinician about risks and benefits of different management strategies. Women who choose not to do RRSO are recommended biannual CA-125 and TVUS tests. As more women choose to undergo surgical risk reduction, care providers must be able to advise and take care of these women who will face unique health challenges after early surgical menopause [48]. All patients with ovarian cancer should now be tested for *BRCA* 1 and 2 genes, and it increasingly common to first do tissue testing with a reflex and then germline testing if positive.

Lynch syndrome is a hereditary cancer syndrome caused by a germline mutation in a DNA MMR gene, generally *MLH1*, *MSH2*, *MSH6*, or *PMS2*. The most common Lynch syndrome-associated cancers are colorectal and endometrial carcinoma. Identification of women with Lynch syndrome-associated endometrial cancer is important, because these women, their affected siblings, and children are at risk of developing these cancers. However, germline testing of all endometrial cancer patients is not economic, and screening using a young age of diagnosis and/or presence of syndrome-associated family history is underutilized and ineffective. Therefore, most groups now defend cancer tissue testing to screen for Lynch syndrome, with germline testing of women with abnormal tissue testing results. To screen for the stage of this cancer, MLH1, MSH2, MSH6, and PMS2 immunohistochemistry (IHC) is carried out in many clinical laboratories, as IHC is relatively inexpensive and technically more accessible for smaller clinical laboratories. This IHC-based universal testing protocol for Lynch syndrome followed by counseling is now quite common [49].

Although technically more demanding, polymerase chain reaction (PCR)-based tissue testing, plays an important role in identifying these patients. Analysis of MLH1 methylation identifies women with MLH1 loss-related cancer who probably have sporadic endometrial carcinoma and do not need careful surveillance for cancer prevention. High microsatellite instability (MSI) levels have been identified in cancers with positively maintained MMR protein expression. Somatic sequencing of mutated MMR gene, while not currently available in most clinical laboratories, is useful in solving cases in which germline sequencing fails to identify MMR gene mutation. The approach of cancer tissue testing can help identify the majority of women at risk of germline mutations in a Lynch syndrome gene, although not all patients are captured using this approach. A clinical suspect can still play a key role in the accurate identification of a subset of these patients [50]. Molecular studies of endometrial cancer have evolved with the tools available to researchers, such as methods for measuring nucleic acids, protein expression, and their combinations. Today "molecular genetic analysis" implies a wide range of indirect and direct testing methods that produce molecular phenotypes, genotypes, immunotypes, or signatures that were not conceived when histological and biological heterogeneity was first recognized fully [51]. Guidelines recommend immunohistochemical tissue screening for type-I and type-II endometrial cancers in all patients below 70 years of age, and all endometrioid and clear-cell ovarian cancers irrespective of patient's age. If necessary, IHC should be supplemented by hypermethylation testing and/or MSI analysis of tissue MLH1 promotor. Confirmation of Lynch syndrome diagnosis requires molecular genetics examination of the patient's blood to identify germline mutations in MMR genes. This should be performed without previous tissue screening when the Amsterdam II or the Bethesda-revised criteria are met in patients with Lynch syndrome-associated cancer family history. In Lynch syndrome-diagnosed women, the age for prophylactic surgery should be set flexibly based on informed consent [52].

Therefore, the importance of recognition of patients and families with a suspected hereditary predisposition to the development of breast/ovarian/endometrial cancer is evident to be able to place them in appropriate diagnostic-therapeutic programs. The right health professional to identify patients with genetic risk is the general practitioner (GP), often being the family doctor who over the years has followed and registered in his computerized clinical record the health problems of the whole family. In these cases, once GP identifies high genetic risk subjects after careful examination of medical history, he makes aware patients and, after collecting their informed consent, send the data to specific health institutions, which are actively involved in cancer molecular genetics research programs. This framework is quite complex; hence, the optimal clinical management of these patients can be granted only by a team of professionals with integrated skills, who are able to face the problem in an oncological genetic counseling (OGC) program. Thus, during the various OGC phases, continuous and close collaboration between medical oncologists, medical geneticists, senologist and plastic surgeons, gynecologists, radiologists, and psychologists is fundamental and appropriate. If heredo-familial syndrome-related cancers represent a minority (e.g., 5–10% of all breast cancers), the high oncological risk in subjects carrying mutations makes the identification of families crucial, with the provision of adequate genetic advice, including onco-susceptibility genetic testing (on peripheral blood for lymphocyte DNA gene sequencing), to implement disease risk-reduction strategies. Several computerized statistical models (BRCApro, Miriad II, Manchester, Penn II, International Breast Cancer Intervention Study [IBIS], Breast and Ovarian Analysis of Disease Incidence and Carrier

Estimation Algorithm [BOADICEA], etc.) have been developed to analyze genealogical tree and individual history to evaluate the probability of being carriers of BRCA gene mutations. The presence of breast and ovarian cancer, in particular in the same subject, represents, the most significant mutational risk factor, in addition to a young age at diagnosis. Based on the recommendations by the scientific societies (American Society of Clinical Oncology [ASCO], Society of Gynecological Oncologists [SGO], National Comprehensive Cancer Network [NCCN], and International Consensus Conference on Breast Cancer Risk, Genetics, & Risk Management, April 2007), genetic testing is considered indicated with a mutational risk estimate of at least 10% [53-60].

2.2 Recommendations for Oncological Genetic Counseling and Testing

2.2.1 Testing Eligibility Criteria

The identification of *BRCA* genes and their possible etiological relationship with various hereditary cancers has been universally recognized as a milestone in the search for genetic susceptibility to cancer. While the female carriers of *BRCA* gene mutations have increased risk of developing breast or ovarian cancer and, to a lesser extent, colon cancer, male carriers are at increased risk of developing breast, colon, or prostate cancer. Although genetic testing promises possible pre-symptomatic determination and treatment of women genetically susceptible to cancer, current data reveal some dilemmas and uncertainties regarding our ability to interpret test results and offer effective management options. Moreover, with the introduction of new information, several complex ethical, legal, and social issues have been raised, which also necessitate further research on the most effective use of this genetic information and formulation of appropriate strategies for clinical management [61]. It is appropriate that genetic testing for the identification of hereditary cancer risk be limited only to carefully selected subjects according to well-defined methods because of their complexity and related clinic-prognostic, psycho-social, ethical and legal, and economic implications. The following are therefore the suggested criteria to identify the patients and/or the families to whom the genetic analysis is proposed due to suspected predisposition to breast and/or ovarian/tubal cancer, e.g., specific BRCA testing access criteria:

1. affected individuals without family history:
    a. breast cancer at ≤36 years;
    b. breast cancer and ovarian cancer, at any age;
    c. bilateral breast cancer at ⩽50 years;
    d. breast cancer with triple-negative histology at ⩽50 years;
    e. male breast cancer, at any age; and
    f. ovarian (or tubal) cancer at ⩽50 years or high-grade serous carcinoma, at any age;
2. affected individuals with family history:
    a. individuals affected by breast cancer at <50 years and with family history:
        i. one family member affected by breast cancer at ⩽50 years;
        ii. one family member affected by bilateral breast cancer, at any age; and
        iii. one family member affected by ovarian (or tubal) cancer, at any age;
    b. individuals affected by breast cancer at >50 years and with family history:
        i. two family members affected by breast/ovarian cancer, at any age; and

c. individuals affected by ovarian/tubal cancer:
   i. one family member affected by ovarian (or tubal) cancer, at any age; and

3. healthy individuals with family history comprising:
   a. one family member affected by:
      i. breast cancer ≤36 years;
      ii. breast cancer + ovarian cancer, at any age;
      iii. bilateral breast cancer ≤50 years;
      iv. breast cancer with triple-negative histology ≤50 years;
      v. male breast cancer, at any age; and
      vi. ovarian (or tubal) cancer ≤50 years or high-grade serous carcinoma, at any age;
   b. two first-degree affected members of the family or who have developed breast cancer at ⩽50 years;
   c. one first-degree affected member of the family or who have developed breast cancer at ⩽50 years + one first-degree family affected member or who have developed bilateral breast cancer, at any age;
   d. one first-degree affected member of the family or who developed breast cancer at ⩽50 years + one first-degree family affected member or who developed ovarian (or tubal) cancer, at any age;
   e. two first-degree affected members of the family or who developed ovarian (or tubal) cancer, at any age;
   f. three first-degree affected members of the family or who developed breast or ovarian cancer, at any age; and
   g. in any case, healthy or sick subjects who have one family member with the ascertained pathological variant.

Notes:

1. The characteristics must be present either in the maternal or in the paternal side; the affected relatives in the two branches do not add-up;
2. the affected family members must be first-degree relatives; for instance, in the paternal branch, paternal aunts, paternal grandmother, and cousins (daughters of father's brother) are considered from the genetic point of view as first- and not second- or third-degree relatives; and
3. in situations where it is difficult to collect information on family members (relatives who died at early age or never known), in families with few relatives (single children and single children parents), or in families with many male subjects, genetic testing can be considered even if the eligibility criteria are not absolutely fulfilled.

Cases in which the patient decides, for any reason, not to carry out genetic testing, the formulation of cancer risk can be carried out *a priori*, based on the provided clinical data. In this case, it is necessary to explain to the patient the limits associated with this evaluation, fundamentally linked to individual variability, to the presence of presumed but not identifiable security risk factors, and to the frequent imprecision or lack of reliable family history data. Suggested criteria to identify people to be sent to OGC for suspected genetically determined predisposition to breast and/or adnexal cancer are:

1. early-onset (breast cancer at <35 years; ovarian cancer at <50 years);
2. onset in the same patient or presence in the same family, both breast and ovarian cancer;

3. male breast cancer (especially characteristic of *BRCA2* mutation); and
4. a high number of first- and second-degree relatives affected by breast or ovarian cancer, all occurred in the same line of inheritance (maternal or paternal).

Eligibility criteria for genetic (*BRCA1*-2) testing are (Figure 1):

1. two or more first-degree relatives with the onset of breast cancer before the age of 50;
2. two or more first-degree relatives with the onset of bilateral breast cancer at any age;
3. two or more first-degree relatives of which one with bilateral breast cancer and one with breast cancer ensuing before the age of 50;
4. three or more first-degree relatives with the onset of breast cancer at any age;
5. two first-degree relatives, one with breast cancer before 50 years and the other with ovarian cancer at any age;
6. two first-degree relatives with ovarian cancer at any age;
7. sporadic cases (e.g., without apparent familiarity) of men with breast cancer;
8. sporadic cases (without apparent familiarity) of women with concomitant breast and ovarian cancers; and
9. sporadic cases (without apparent familiarity) of women with onset of breast cancer before 30 years of age.

(Note: first-degree relatives: parents, children, brothers, and sisters; second-degree relatives: grandparents, uncles, nephews).

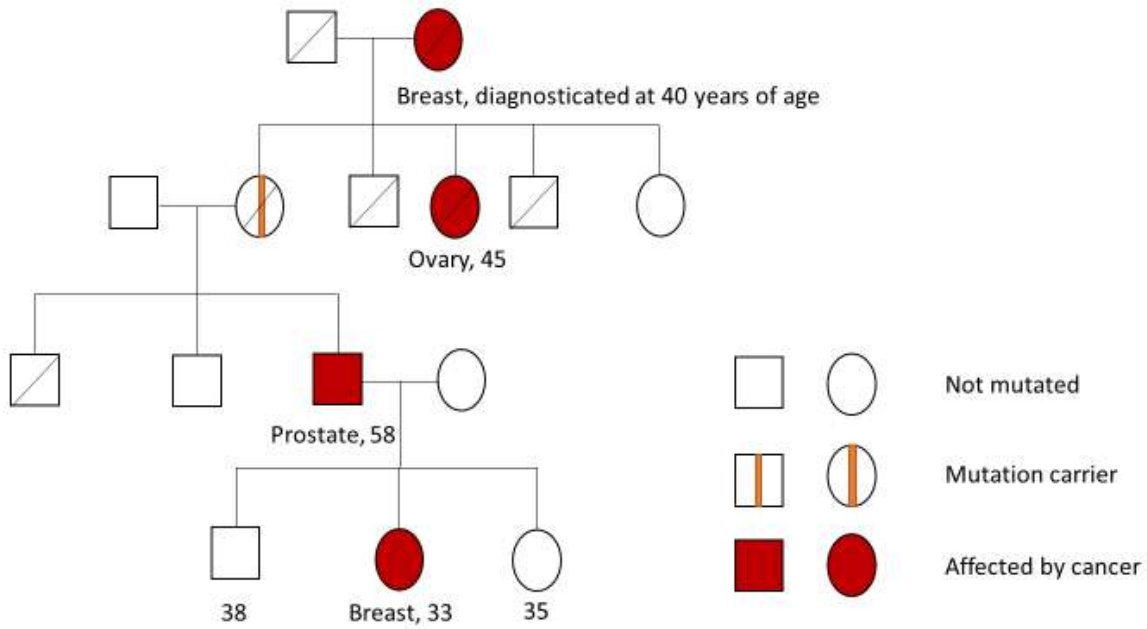

Figure 1 Example of a family with a high genetic risk for breast and/or ovarian cancer.

To summarize, recommendations for OGC and testing are the following:

1. HBOC syndrome:
   a. breast cancer with synchronous/metachronous ovarian/tubal/peritoneal cancer or bilateral/double ipsilateral breast cancer;

b. early-onset breast cancer (at ⩽40 years or ⩽50 years + one close relative [first-second-third degree] with breast cancer at ⩽50 years);
c. breast cancer or ovarian/tubal/peritoneal cancer (at any age) with two or more close relatives (first-second-third degree) with breast cancer (at any age);
d. breast cancer (at ⩽50 years) and one close relative (first-second-third degree) with ovarian/tubal/peritoneal cancer or male breast cancer (at any age);
e. ovarian/tubal/peritoneal cancer (at any age) and one close relative (first-second-third degree) with breast cancer (at ⩽50 years) or ovarian/tubal/peritoneal cancer (at any age);
f. ovarian/tubal/peritoneal cancer (at any age) or breast cancer (at ⩽50 years) in ethnic groups at high risk such as Ashkenazi Jews, Icelanders, Swedes, Hungarians, etc.;
g. known BRCA mutation in one close relative (first-second degree); and
h. medullary/pseudo-medullary or triple-negative (estrogen receptor [ER], progesterone receptor [PR], and HER-2) breast cancer;

2. HNPCC syndrome:
   a. endometrial or colorectal cancer, according to the Amsterdam criteria [62]:
      i. at least three relatives of the same line with HNPCC-associated cancer;
      ii. the first-degree relative affected by one of the other two;
      iii. at least two successive affected generations; and
      iv. HNPCC syndrome-associated cancer diagnosed at <50 years;
   b. endometrial and synchronous or metachronous colorectal or ovarian cancer, one of which diagnosed at <50 years;
   c. endometrial or ovarian cancer with synchronous/metachronous colorectal cancer or other HNPCC syndrome-associated cancer (at any age);
   d. endometrial or colorectal cancer in the first-degree relative or at least two close relatives (first-second degree) with HNPCC syndrome-associated cancer diagnosed at <50 years;
   e. endometrial or colorectal cancer with evidence of MMR defect (MSI or loss of immunohistochemical expression of MLH1, MSH2, and MSH6 genes); and
   f. MMR genetic mutation in close relatives (first-second degree).

2.2.2 Oncological Genetic Counseling

OGC is a communication process that takes place through multidisciplinary teamwork. During various interviews, the issues concerning humanitarian, scientific, methodological, surveillance, and changes in lifestyle habits are faced. It is therefore important that pre- and post-testing interviews for OGC take place at separate times compared to the other routine visits, given the sensitivity and peculiarity of the covered topics. The subject is indeed informed of the possibility of having herself a genetic oncological problem, which could be already present in her family and be transmitted to the offspring. She is also informed of the meaning of “genetic predisposition”, and its short- and long-term consequences (in terms of therapy), and needs to be supported on making the best choices for herself, starting from the possibility of deciding whether to make genetic testing, up to the choice of carrying out prophylactic surgical interventions. Providing genetic information and counseling can be complex and time-consuming. The genetic counseling service is offered by the people certified by the American Board of Medical Genetics and Genomics (ABMGG). These include trained genetic counselors with Master’s Degree, physicians

who have completed special training in clinical genetics, nurses with special skills in genetics, and support staff. A team approach is needed to provide patients with comprehensive genetic counseling services [63].

2.2.3 Preliminary Phase (Sending to Oncological Genetic Counseling)

In view of the importance of OGC, in identifying the population with higher risk to develop an oncological pathology, it is mandatory to raise awareness of the whole medical class to this issue, beyond each one's specific specialization. Only a small number of subjects affected by neoplasia will need genetic-oncological evaluation and therefore it is necessary to know how to recognize cases that really need this approach. Cancers attributable to a determined genetic predisposition, in fact, represent only a minor number of all neoplasms, and it is desirable that only those individuals who can actually benefit from it, or those in whom clinical utility is undisputed, both in preventive and in therapeutic terms, are addressed to OGC. In fact, currently, while the incidence of cancer is continuously growing and media underline the possibility of prevention, the condition in which the patient or her family request to generate the discussion is more frequent. However, it is important to highlight that in most of these cases there is no appropriate indication to initiate genetic investigations. Foremost, it is important to inform the specialist clinicians and the GP who, in the preliminary phase of risk assessment, aimed at sending the patient to OGC, that it is not necessary to collect the information on the complete genealogical tree of the patient, but the primary information concerning the closest relatives (first degree) and age of occurrence of reported cancers is sufficient to provide first general orientation. Second, it is worth recommending that while addressing to OGC, the physician must also consider physical and psychological conditions, as well as an interpersonal relationship of the patient at that particular moment of her life, and of her motivation to undertake this program. Given the strong prognostic/therapeutic and psychological implications that may arise from genetic evaluation, it is indeed fundamental that the decision is shared primarily with the patient herself, appropriately informed of all the possible implications, always respecting the guidelines agreed at the national and international levels as per the criteria of evidence-based medicine (EBM).

2.2.4 Pre-Testing Phase (First Oncological Genetic Counseling Interview)

The first OGC interview (pre-testing phase) constitutes a specialized medical act aimed at:

1. reconstructing the personal and familial oncological anamnesis, also considering the most distant generations (up to the third degree of relationship, both from the maternal and from the paternal side);
2. reviewing the available clinical documentation of the patient and of the other family members affected by cancer;
3. evaluating the *a priori* probability to find a genetic predisposition. In some second-level OGC, statistical calculation models for the prediction of the risk of disease and of the *a priori* probability of BRCA gene alteration (e.g., Gail, Claus, Cuzick-Tyrer, BRCApro, BOADICEA) are used. These models give almost similar results, even if the "high-risk" threshold cannot be defined. In fact, some centers use a threshold of >10% to start with genetic testing, while others use a higher value. Therefore, these models are not currently the commonly used ones to initiate genetic testing;

4. checking the appropriateness of the request of genetic analysis, in accordance with the selection criteria proposed by the individual centers based on national and international guidelines;
5. proposing genetic analysis and illustrating the possible result;
6. explaining the implications of the result on surveillance, prophylactic surgery, and chemoprevention;
7. explaining the possible implications for the other family members (modality of any alteration found by the test);
8. discuss the potential psychological impact (fear, anguish, and doubts) associated with the execution of genetic analysis and therefore the possibility of availing psychological support both in the pre- and in the post-testing phases; and
9. explaining how to perform genetic analysis and the time required for reporting the result.

At the end of the interview, if the patient decides to undergo this analysis, she proceeds to sign the informed consent, which must necessarily cover all the aspects discussed during the consultation and be clear enough so that the patient can understand it in every part. Informed consent must be countersigned by the person who requests the analysis and a copy must be given to the patient.

3. Genetic Testing in Gynecological Oncology

3.1 Definition and Purpose

Genetic testing refers to the clinical analysis of DNA, RNA, chromosomes, proteins, metabolites, or other gene products. It is performed to highlight genotypic, karyotypic, or phenotypic markers associated with several human heritable diseases. In assessing the hereditary predisposition to cancer, genetic testing can be distinguished into:

1. Diagnostic testing: It allows diagnosing or confirming clinical suspicion in an affected person by studying the role of an alteration of a gene under investigation in the onset of oncological pathology.
2. Predictive testing: It identifies the presence of a genetic alteration associated with an increased risk of developing certain pathology in still asymptomatic subjects.

“Cascade testing” refers to genetic counseling and testing in blood relatives of individuals who have been identified with specific genetic mutations. Testing protocols and other interventions can save lives and improve the health and quality of life of these family members. Obstetricians and gynecologists should know the eligibility for cascade testing and should use all available resources to ensure that cascade testing is offered and conducted in a timely manner. Despite the obvious health benefits for specific populations and individuals, obstetricians and gynecologists should be aware of the potential challenges associated with cascade testing and the options can help patients overcome these obstacles. Moreover, these obstacles could be overcome with the awareness and participation of the health care provider in local and state initiatives to improve the implementation of cascade testing. Resources (available within federal and state agencies, professional societies, and advocacy and community groups) are critical to the successful implementation of cascade testing [64].

3.2 Procedures and Methods of Analysis

The identification of a hereditary predisposition to the development of breast/ovarian cancer is based on resting for constitutional DNA variants. The biological sample predominantly utilized for the analysis is peripheral blood. A study on genes associated with a higher risk of development of breast cancer compared to the general population has been performed. The two most involved genes in the predisposition to the development of breast cancer are *BRCA1* and *BRCA2*, alterations in which could explain approximately one-third of hereditary breast cancer cases. Furthermore, there are other known genes that confer a high risk of breast cancer (*TP53*, *PTEN*, *CDH1*, and liver kinase B1 [*LKB1*]); however, the presence of variants in such genes is extremely rare. It has recently been discovered that cell-free micro-RNA (miRNA) circulates in the body fluids of healthy and patients of ovarian cancer, suggesting that it could serve as a new diagnostic marker. Despite the high ribonuclease levels in several kinds of body fluids, most of the circulating miRNAs are packaged in microvesicles, exosomes, or apoptotic bodies, and bound to RNA-binding proteins, such as Argonaut 2, or lipoprotein complexes, and are therefore highly stable. Cell-free miRNA signatures are known to be similar to those from the originating tumor cells, indicating that circulating miRNA profiles accurately reflect tumor profiles. As miRNA dysregulation is known to be involved in ovarian cancer tumorigenesis, cell-free miRNA circulating in body fluids, such as serum, plasma, whole blood, and urine, may reflect not only the existence of ovarian cancer but also tumor histology, stage, and patients' prognosis. Several groups have successfully demonstrated that serum or plasma miRNAs are able to discriminate ovarian cancer patients from healthy controls, suggesting that the addition of these miRNAs to current testing regimens may improve the accuracy of diagnosis of ovarian cancer. Furthermore, recent studies have revealed that changes in cell-free circulating miRNA levels are associated with the condition of cancer patients. Discrepancies in study results owing to the lack of an established endogenous miRNA control for the normalization of circulating miRNA levels, as well as different methods of extraction and quantification, are the pitfalls that are required to be solved before clinical application. There is still a long way to go; however, before this could be achieved, further evidence would be required to use circulating cell-free miRNAs not only as biomarkers but also as potential therapeutic targets for ovarian cancer in the future [65].

3.3 Choice of the Case to be Submitted to Genetic Testing

Selecting the index case is one of the most important factors to correctly classify familial genetic risk. The outcome of genetic testing for assessing the oncological risk has indeed different consequences and purposes depending on the patient undergoing this investigation. Therefore, to maintain test reliability, it is of fundamental importance to start the analysis from the subject with *a priori* higher predisposition to genetic alteration (e.g., early age of onset of breast or ovarian cancer, bilateral breast cancer, male breast cancer). The latter (defined as "index case") could be the subject that comes to OGC or one of her relatives, selected by careful review of the provided documents. In certain situations where selecting the index case is difficult (e.g., owing to the absence of at least one living affected family member, lack of cooperation of the selected family member, fear to undergo the test, disinterest, geographical distance), the analysis could be proposed to another person, even unaffected. Furthermore, the re-evaluation of cancer history could verify the presence of criteria for the proposal of other genetic investigations.

3.4 Characteristics of Laboratory for Interpretation of Genetic Testing

The results of genetic testing should be clinically interpreted in the laboratory where this investigation is performed. Clinical utility of genetic testing is indeed strongly related to the correct interpretation of identified variants that must be provided by the laboratory in a clear manner with specific technical/bibliographic references. The analysis of the *BRCA* gene must be performed in certified laboratories that have defined *a priori* all analysis programs, from the request forms to sample treatment, type of used technology, and reporting process. Since the mutational spectrum of *BRCA* genes is extremely heterogeneous, it is indispensable to have the expertise in the laboratory to interpret any result obtained from genetic analysis. Each laboratory must comply with the guidelines of scientific societies or those of the various international consortia to interpret the laboratory data. For example, in 2014, guidelines to interpret oncological genetic testing results were published by the Italian Society of Human Genetics (SIGU) in collaboration with the Italian Medical Oncology Association (AIOM) [66]. In 2015, the Evidence-based Network for the Interpretation of Germline Mutant Allele (ENIGMA) consortium, which deals with the study and interpretation of variants of uncertain significance (VUS) in *BRCA* genes and other breast cancer susceptibility genes, put forward the classification criteria for *BRCA* gene variants, to which the laboratories can refer [67]. The process of classifying variants is very complex and is based on several lines of evidence, including molecular characteristics of the variant, laboratory data concerning the functionality of protein products, tests to highlight alterations of the splicing or expression processes, epidemiological data and co-occurrence of the variant with other ones with known pathological significance, and correlation with the phenotype of the index case. Furthermore, informatic platforms are being utilized, through silico prediction programs to evaluate the effect of the variant on the protein structure/function and on the splicing process. Moreover, the presence of the identified variant could be verified in the available databases, to evaluate its frequency and possible interpretation. Despite following these procedures, it is not always possible to successfully interpret in the clinical practice. The most common variant classification system, published by the International Agency for Research on Cancer (IARC) group [68] and the ACMGG in collaboration with the Association for Molecular Pathology (AMP) [69], classifies variants into five categories:

1. benign (class 1, probability to have clinical significance < 0.001);
2. probably benign (class 2, the probability to have a clinical effect between 0.001 and 0.049);
3. VUS (class 3);
4. probably pathological (class 4, probability of being causative between 0.95 and 0.99); and
5. pathologic (class 5, probability of being causative > 0.99).

Classes 4 and 5 are variants that involve the adoption of screening and preventive measures for the high risk and the possibility of the extension of the test to the family. In class 3, follow-up is organized on the basis of family history and other risk factors. In classes 1 and 2, the probability that the variants are related to the onset of cancer is extremely low.

3.5 Result and Management

During post-testing OGC, the multidisciplinary team, composed of medical specialists with integrated skills, informs the patient of the outcomes and the relative risk (RR), the associated clinical-psychological implications, along with different medical/surgical options for therapy and

follow-up, and the possibility of involving family members. In fact, the objective of post-testing OGC is to provide the patient with all indications to make her aware of any future decision. Moreover, the importance of keeping in touch with the OGC center for subsequent diagnostic examinations and/or for research reasons must be explained.

Results of genetic testing are:

1. "positive" test: The analysis identified a pathological or probably pathological variant, that is associable with high oncological risk. This result confirms the involvement of the *BRCA* gene in the onset of the neoplasm in an affected subject and verifies the presence/absence of this variant in affected/healthy family members. Moreover, it changes or augments the prevention protocols in the patient and her family members. These protocols, however, must be kept in consideration with the oncological situation in progress (disease outcome). Subjects with pathological variants have an increased risk of developing breast/ovarian cancer throughout their life; however, they are not necessarily destined to get affected. This risk is not, in fact, quantifiable in the individual subject as it does not exclusively depend on the established variant but also on the concomitant presence of other factors not known to interfere with the genetic component.
2. "non-informative" or "non-conclusive" test: The analysis did not allow to identify any variant. In this case, it is not possible to exclude the possibility of predisposition to cancer development in other genes not known or currently under study or the presence of variants in non-explored zones of the gene (intronic regions, promoters, etc.). In fact, despite the selection of the index case in the most correct way and the familial *a priori* oncological risk being extremely high, most outcomes of *BRCA* genetic testing fall within this branch, owing to the genetic heterogeneity of the disease. Consequently, cancer risk assessment and clinical-instrumental prevention measures can be established based on personal and family cancer history. It is important that a contact between the subject with non-informative testing and the OGC center or the laboratory where she underwent the test remains so that, if there were any significant changes in family history, which is always dynamic, or there were updates at the genetic level, it would be possible to review the familial situation and propose new investigations.
3. VUS: This represents the outcome with the most difficult clinical management. The analysis of the *BRCA* gene allows identification of a variant to which, at the current state of knowledge, it is not possible to associate a certain clinical meaning, and therefore oncologic risk, owing to lack of experimental data and genetic/epidemiological information. To interpret this result, the competence of the laboratory, which has to justify this finding in the report, is extremely important. Delivery of a VUS result must be performed by a specialist who is able to interpret the data provided by the laboratory. The management of patients with VUS is based on evaluating the oncologic anamnesis of the subject who underwent the test and of the familial *a priori* oncologic risk. Although the extension of the analysis to family members for clinical purpose is not indicated, it could be useful for research purpose (e.g., for segregation analysis).
4. "negative" test: The pathologic variant identified in a family member was not found in the subject who underwent the test. In this case, if the subject is healthy, the result shows her risk of developing breast and ovarian cancer to be similar to that of the general population and involves great psychological benefit. However, there are situations that limit the

interpretation of a negative result. This is the case of tests performed in subjects with a grade of relationship far from the index case. If the subject with a negative result is affected by breast cancer, she is defined as "phenocopy" as it is not possible to exclude that her illness is related to other genetic factors than the identified variant in the family or that it depends on multifactorial causes (sporadic cancer). Moreover, there is the possibility of phenocopies among first-degree relatives of subjects affected by a mutation; however, the occurrence is uncommon. In situations where the index case is represented by a healthy subject, the complete result of *BRCA* testing is informative only if the variant with pathological meaning is identified. If no variant is identified, the interpretation is more complex: the result could, in fact, be a true negative, or the index case has not inherited the variant possibly present in the affected untested family member or indeterminate, as the *BRCA* gene variants may not be present in the family.

The benefits of testing for those who have already had cancer are:

1. to know more exactly their own genetic risk and further risks that may result from the mutation in addition to the previous pathology; to know if other organs are at risk, and what clinical-instrumental surveillance is appropriate in addition to normal oncological follow-up.
2. if one of the known (BRCA1/2) mutations is present, family members (children, siblings, and parents) should know their genetic status, that is they will know if they have inherited the same mutation (50% probability).
3. to adhere to national primary and secondary prevention protocols for the high risk (Figure 2).

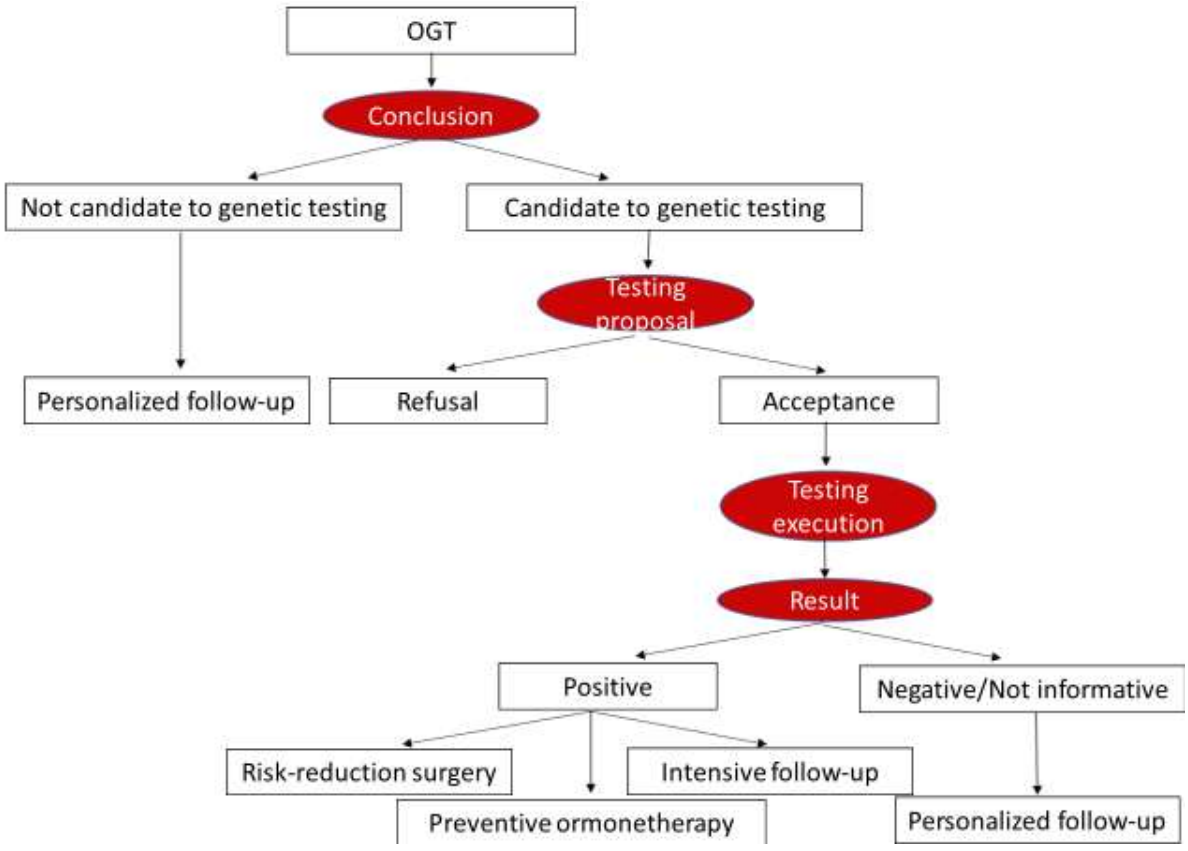

Figure 2 Management of the patient with suspected breast cancer inheritance.

3.6 Methodology

Genetic testing to establish the presence of any DNA mutation corresponding to *BRCA1* and *BRCA2* genes involves extremely complicated and sophisticated analyses that should be performed only by centers with proven experience. At such centers, the procedure involves an initial evaluation of the specific risk of the patient with the reconstruction of the "oncological pedigree" and of the probability of mutation through computerized statistical models (e.g., BRCApro); therefore, if eligibility criteria are met, genetic testing is performed. The analysis is normally performed on genomic DNA purified from a peripheral blood sample, with prior patient's informed consent, to establish the presence of possible DNA mutations, corresponding to *BRCA1* and *BRCA2* genes. It is important to emphasize that in a high-risk family, the first subject to be submitted to the test must be one of the family members with previous anamnestic cancer; subsequently, if one of the known mutations is present, it will be possible to extend the research to healthy first-degree relatives. The result of the first tested family member is available only after 6 to 12 months, lesser than that for relatives (about 1 month), as we already know where to look for the mutation in that specific family. There is currently no evidence that justifies the execution of *BRCA1* and *BRCA2* genetic testing before 18 years of age. It is therefore advisable to wait for the children to reach this age and decide autonomously and consciously whether to undergo genetic analyses.

The methodology for conducting genetic testing has undergone several changes in the past few years. Technically, the most commonly used methodology is the Sanger sequencing of the whole coding region and of the exon-intron junctions of *BRCA1* and *BRCA2* genes, supplemented by the Multiplex-Ligation Probe Amplification (MLPA) technique, to identify large genomic rearrangements (duplications or deletions of exons or parts of them). Recently, the clinical use of a new technology called "next-generation sequencing" (NGS) is being evaluated, which could analyze several cancer susceptibility genes simultaneously. Moreover, this procedure has shorter execution times and lower costs. Disadvantages are fundamentally related to the fact that in the panel of genes available on the market, certain genes are included for which epidemiological studies that have verified their penetrance; however, their incidence in the various populations and their effective clinical utility have not yet been determined. The number of VUS has been identified in relatively poorly studied genes and therefore difficult to interpret; however, their interpretation could be possible through NGS. To simultaneously study the susceptible genes in different types of cancer, it is essential that OGC forecasts a specific *a priori* diagnostic program for each pathology that can be investigated. In the informed consent for NGS, it must be possible that the patient could deny the consent for the analysis of some genes. Regardless of the analysis technique it uses, the laboratory must state its sensitivity, specificity, and limits in the report [70].

3.7 Other Susceptibility Genes for Development of Breast Cancer

The number of reports investigating disease susceptibility based on low-penetrance and high-frequency single nucleotide polymorphism (SNP) carriage has increased recently. Evidence is accumulating that defines specific individual variations in breast cancer susceptibility. Genetic variations in the metabolism of estradiol and xenobiotics and in genes involved in cell-cycle control have been described as significant factors for breast cancer susceptibility, with variations depending on ethnic background and co-factors such as smoking and family history of breast

cancer. In short, the highest level of evidence to date linking SNP and breast cancer stems from nested case-control studies within the prospective Nurses' Health Study (NHS). These data establish seven SNPs—human progesterone B-receptor (hPRB) +331 guanine/adenine (G/A), androgen receptor (AR) cytosine-adenine-guanine (CAG) repeat, aromatase cytochrome P450 (CYP) 19 thymine-thymine-thymine-adenine (TTTA) 10, CYP1A1 *Moraxella* spp. isoschizomer (MspI), vitamin D receptor (VDR) *Flavobacterium okeanokoites* (FOK) 1, X-ray repair cross-complementing protein 1 (XRCC1) arginine-194-tryptophan (Arg194Trp), and XRCC2 arginine-188-histidine (Arg188His)—as small but significant risk factors for spontaneous, non-hereditary breast cancer. Furthermore, a meta-analysis of literature data establishes the type 1 transforming growth factor-β receptor (TGFBR1)*6A, Harvey rat sarcoma (HRAS) 1, glutathione S-transferase Pi (GSTP) isoleucine-105-valine (Ile105Val), and glutathione S-transferase mu M1 (GSTM1) SNP as low-penetrance genetic risk factors for sporadic breast cancer. The clinical consequences of such increased risk may involve detailed patient instructions regarding general measures of breast cancer prevention, such as low-fat diet, body mass index (BMI) optimization, exercise, and alcohol and long-term hormone replacement therapy (HRT) avoidance, and participation in breast cancer screening program in the age group of 50 to 70 years. Specific surgical or pharmacological interventions, such as prophylactic mastectomy and oophorectomy or prophylactic tamoxifen intake are not indicated based on SNP analysis at this time [71].

In addition to *BRCA1* and *BRCA2* genes, other high-penetrance genes are known to cause syndromes with a higher risk of breast cancer as compared to the general population. These include TP53, responsible for Li Fraumeni syndrome, PTEN, responsible for Cowden syndrome, CDH1, responsible for widespread hereditary gastric cancer, and STK11, responsible for Peutz-Jeghers syndrome. Specific data collected during OGC, such as the presence of other neoplasms besides breast/ovarian cancer in the patient and/or in her family, the presence of specific skin lesions (e.g., trichilemmomas or lipomas), or breast cancer histological examination indicative of lobular histotype, for example, are elements that may suggest the specialist regarding the possible proposal for further genetic insights. Pathological variants identified in these genes are extremely rare. However, their presence can involve increased risk for neoplasms in other sites in addition to the breast (e.g., uterus, thyroid, stomach, and sarcomas) in different age groups, or can make tissues more sensitive to radiant treatments (less ability to repair radio-induced cell damage). It follows that in these cases the activation of an oncological prevention/treatment plan is more complex and less standardized and that the emotional impact is more significant because oncological risk may involve several organs in patients at different ages (even in childhood). Therefore, the usefulness of such tests must be evaluated on the basis of their clinical impact on the individual and the support provided by the team to take care of several problems linked to a possible positive outcome. At the international level, the NCCN guidelines report indications and clinical management of TP53 and PTEN genetic testing [72]. There are other genes with moderate penetrance for breast cancer development: partner and localizer of BRCA2 (*PALB2*), *ATM*, Fanconi anemia complementation group M (*FANCM*), and RecQ helicase-like (*RECQL*). The extent of cancer risk associated with these has not yet been defined or evaluated. However, some of these genes are included in the panels used for NGS. Moreover, communication of the result to the patient is extremely complex owing to the absence of reliable data on the association between variants and cancer risk.

3.8 Reporting Modalities

The results of genetic testing may be of considerable importance to patients, their parents, and the most remote family members. Clinical therapy and surveillance, reproductive decisions, and genetic diagnostics in family members, including prenatal diagnosis, are based on these findings. Therefore, the genetic testing reports should provide a clear, concise, accurate, completely interpretative, and authoritative answer to the clinical question. The need to harmonize genetic testing reporting practices has been recognized by the External Quality Assessment (EQA), providers and laboratories. The ESHG Genetic Services Quality Committee has generated reference guidelines for genetic disciplines (biochemistry, cytogenetics, and molecular genetics). These guidelines provide assistance on reporting content, including result interpretation [73]. In addition to providing useful data to identify the subject in analysis and to the laboratory that performed the test, the reports of genetic analyses must contain the information indicated below, necessary for the correct interpretation of test result:

1. nature of the analyzed biological material (DNA, RNA, or other).
2. origin/tissue of the analyzed material (in particular, it must be specified if the tissue is normal or neoplastic).
3. date of collection of the biological material in question.
4. gene/genes object of the analysis.
5. examined genetic regions.
6. used methods and their analytical sensitivity.
7. reference genetic sequence (using genetic databases reference code numbers).
8. description of the observed alterations with respect to reference sequences, using the nomenclature established by the international guidelines of the Human Genome Variation Society (HGVS) [74].
9. description of the functional meaning of the identified alteration according to the variant's classification scheme (five points) and its correlation with the patient's phenotype.
10. indication of which variants are not indicated in the report (e.g., common polymorphisms and benign variants, i.e., little or no clinical meaning).
11. citation of literature data to support the interpretation of analysis results (literature data and consulted databases).

4. Surveillance Measures and Prevention Strategies

Surveillance of high-risk subjects should be modulated primarily based on mutation type, age, and lifestyle (e.g., age of menarche and menopause, early assumption [<18 years] of oral contraceptive pill, obesity, etc.). Moreover, controls should be calibrated in relation to mammary gland personal structure (breast density). The proposal of a clinical surveillance protocol for subjects at high family risk considers the following fundamental points:

1. Age of onset of breast cancer is progressively moving toward the younger age of the population. This cancer currently represents 41% of all neoplasms identified in women before 50 years, which is just in the age range in which screening programs are difficult to implement and always debated.

2. Risk of exposure to ionizing radiations (e.g., mammographic examination) is higher in the younger population. Pathological variant carriers could have higher susceptibility owing to a decreased capacity to repair radio-induced cell damage.
3. Mammogram sensitivity in "dense" breasts, characteristic of younger age, is reduced.
4. Some histological features typical of *BRCA*-related breast cancers are high cell proliferation speed and low differentiation grade.

For all these reasons, it is believed that subjects at high family risk require an intensive surveillance protocol, even taking into consideration the suggestion for more expensive diagnostic techniques in both "economic" and "risk" terms, meant as FPR increase (e.g., use of breast MRI). The proposed surveillance protocol for these subjects is as follows:

1. between 18 and 25 years: self-examination every 3–4 months and senological visit.
2. between 25 and 30 years: six-monthly clinical visit, six-monthly breast ultrasonography, and annual MRI.
3. between 30 and 35 years: six-monthly clinical visit, six-monthly breast ultrasonography, annual MRI, annual digital or very low dose mammography (overall average glandular dose <4 milli Grays [mGy] = only oblique), and six-monthly gynecological examination + TVUS and CA-125 marker dosage.
4. between 35 and 50 years: six-monthly clinical visit, six-monthly breast ultrasonography, annual digital or low dose mammography (overall average glandular dose <8 mGy), annual MRI, and six-monthly gynecological examination + TVUS and CA-125 marker dosage.
5. over 50 years: six-monthly clinical visit, annual standard mammography, breast ultrasonography (based on the radiologist's advice), annual MRI, and six-monthly gynecological visit + TVUS and CA-125 marker dosage.

Nonetheless, evidence on the utility of human epididymis protein 4 (HE4) marker related to CA-125, for the early identification of ovarian cancer in patients at risk, is insufficient. In male carriers of BRCA1/2 gene mutation, there are no pre-set instrumental surveillance protocols. The most effective tool is self-examination once every month. Guidelines of the National Operative Force on Breast Cancer (FONCaM) recommend surveillance of subjects at risk. Diagnostic anticipation for patients with genetic mutations must start at the age of 25 or at least ten years before last cancer in the family (e.g., if a mother was diagnosed with cancer at 30 years, senological control for the daughter must be initiated when she is 20 years old), due to the increasing probability of cancer in the following generations. The proposed monitoring protocol involves:

1. Prior to the age of 25 years: clinical examination + six-monthly breast ultrasonography;
2. Between 25 and 34 years of age: clinical examination + six-monthly breast ultrasonography + annual MRI with gadolinium contrast medium (X-ray mammogram is preferable after 35 years of age; however, for radiological needs, it can also be performed earlier with only a single projection and dose <4 mGy);
3. Between 35 and 54 years of age: clinical examination + six-monthly breast ultrasonography + annual MRI with gadolinium contrast medium + annual X-ray mammogram (instrumental surveys on annual cadence can either be carried out at the same time or alternatively every six-months);
4. Between 55 and 69 years of age: clinical examination + six-monthly breast ultrasonography + annual X-ray mammogram;
5. After 70 years of age: clinical examination + X-ray mammogram every two years;

6. Depending on mutation and age: annual/six-monthly gynecological examinations with TVUS and CA-125 control (dosage must also be continued after eventual oophorectomy since islands of ovarian tissue can be present in the peritoneal membrane, which justifies the impracticality of total risk elimination); and
7. For BRCA1-2 subjects in particular: annual cutaneous nevi and oropharynx inspection + anticipation of colonoscopic control [or at least fecal occult blood test (FOBT)] at 40 years + prostate examination in males beginning at the age of 40 years [75].

Recommendations of the International Consensus Conference on Breast Cancer Risk, Genetics, & Risk Management include:

1. Medium/moderate risk: Relative risk 1-5 (general female population; females with premature menarche, nulliparity, late menopause, HRT, obesity, smoking, alcohol, and second or third-degree relative with breast cancer): validated oncological screening which includes senological/gynecological visit and annual mammography between 40 and 50 years of age, depending on the nation, and, preferably, continuous till life expectancy >5 years.
2. High risk: Relative risk 1-5 [lobular carcinoma in situ (LCIS); atypical ductal hyperplasia (ADH); atypical lobular hyperplasia (ALH); and females having two first-degree relatives with breast cancer, but without mutation]: senological/gynecological examination every six months and annual mammography (starting from 40 years or 5–10 years before the earliest age of onset of breast cancer in the family, continuously) ± RI [high false-positive rate (FPR) and scarcity of screening data]; transvaginal pelvic ultrasonography every six months ±CA-125 dosage (from 25–30 years or 5–10 years before the earliest age of onset of ovarian cancer in the family); and subset of patients eligible for chemoprevention (tamoxifen before menopause and tamoxifen or raloxifene after menopause); and
3. Very high risk: Relative risk >10 (known or probable BRCA, PTEN, or TP53 mutation, or personal history of breast or thoracic wall irradiation <30 years): senological/gynecological examination every six months and mammography + MRI every six months alternatively (from 40 years onwards or ten years before the earliest age of onset of breast cancer in the family, continually) + transvaginal pelvic ultrasonography every six months ±CA-125 dosage (from 25–30 years or 5–10 years before the earliest age of onset of ovarian cancer in the family); and subset of patients eligible for chemoprevention (tamoxifen before menopause and tamoxifen or raloxifene after menopause) or RRSO and mastectomy, though the latter is not commonly recommended.

The NCCN surveillance strategies in BRCA mutation carriers are:

1. Monthly self-examination of the breast starting from 18 years of age;
2. Senological visit every six months starting from the age of 25 years;
3. Mammography and annual breast MRI from 25 years of age;
4. Prophylactic mastectomy (on an individual basis);
5. RRSO at 35–40 years or at the end of the reproductive cycle (on an individual basis);
6. Transvaginal pelvic ultrasonography every six months and CA-125 dosage (from 35 years onwards or 5–10 years before the earliest age of onset of ovarian cancer in the family); and
7. Chemoprevention.

Recommendations of the American Cancer Society (ACS) surveillance for patients with Lynch/HNPCC syndrome [76]: Annual check for the early diagnosis of endometrial carcinoma through endometrial biopsy starting from the age of 35 years. To improve survival in women with

endometrial cancer, the strategies beyond initial treatment must be worked upon. Although the majority of women are diagnosed at the early stage of the disease and are cured with surgery alone, there is still a subgroup with advanced and high-risk early-stage disease in whom the life expectancy might be prolonged with the addition of chemotherapy. IHC will help identify those women with Lynch syndrome who would benefit from more frequent colorectal cancer surveillance and genetic counseling. If they are diagnosed with colorectal cancer, it implies an important therapeutic inference. Lastly, because majority of women survive their diagnosis of endometrial cancer, they remain at risk for breast and colorectal cancer, therefore these women should be counseled regarding the screening of these cancers. These three interventions will contribute to improving the overall survival of women with endometrial cancer [77].

4.1 Primary Prevention

A healthy lifestyle based mainly on weight control, varied and balanced diet, regular physical activity, oral contraceptives assumption after 20 years of age, and abstention from smoking and alcohol abuse are the indispensable and unavoidable conditions for cancer prevention and should be adopted by both, affected and healthy women with genetic variants. Genetic tests showing the positive result or the presence of class 4 or 5 genetic variant in an affected woman before primary cancer surgery allows planning of the time and interventional modalities. Breast surgery in affected patients with proven genetic variants suggests some issues on the type of intervention proposed. The presence of a genetic variant is a sign that both breasts are at high risk of the disease, even if it is not predicted with certainty. In case of an ongoing disease, it would be reasonable to suggest a radical intervention (unilateral mastectomy) rather than a conservative intervention to the patient and propose surgery for the contralateral breast afterward. This time period must be utilized to evaluate prognostic factors for the earlier disease and to give the patient time to understand the changes taking place in her body. Choosing a contextual double radical intervention, however, needs to be discussed with the patient in a comprehensive manner, taking into account her psychological state and the discomfort caused by news of the presence of a genetic variant. The patient must be counseled and explained how her self-image shall be modified and all the factors correlated to it. Conservative intervention followed by sentinel lymph node (SLN) biopsy/axillary lymphadenectomy and radiotherapy is always available, in spite of the fact that the first scientific data concerning juvenile breast tissue susceptibility to radiation has come up. On the contrary, situations where high genetic risk has been recognized but the test is not available, it is advisable to obtain the result before the intervention (Italian or foreign structures capable of providing a reliable result in time for surgery are available). At the same time, it is imperative that the patient is promptly addressed to an Oncological genetic counseling program (OGC program), even if she will have to make a choice in a short time, in order to grant a responsive informed consent suitable for her situation. Primary breast cancer prevention in subjects with an ascertained genetic variant can be implemented by two distinct types of interventions that can, however, be considered complementary: prophylactic surgery, better defined “risk-reduction” surgery (mastectomy and salpingo-oophorectomy), and chemoprevention.

4.1.1 Prophylactic Surgery

Prophylactic surgery is possible in well-selected cases and also when strongly preferred by the patient, both for the breast {(mastectomy) with a risk reduction of 90% (because of the possibility of the presence of residual breast tissue after the intervention) which arrives to 95% if associated with oophorectomy [Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) Study]} and the ovary [(bilateral RRSO including Fallopian tubes until their insertion on the uterus) from the age of 40 years and beyond, and once the pregnancy desire is finished, with a risk reduction of 98%]. Ovarian surgery, consequently, also serves in breast cancer risk reduction. Psychological counseling must always be proposed in the decision-making phase and should be included even post-intervention. Breast surgery should preferably be carried out at a center with proven cancer experience for the need of a team comprising breast surgeons and plastic surgeons who are well versed with the anatomic-pathological consideration in knowing BRCA-related aspects, examination of appropriate sections including the removed healthy tissues to highlight possible occult cancers [78].

Risk-Reduction Mastectomy. The most effective and lasting therapeutic strategy in the prevention of the onset of contralateral breast cancer in affected females and healthy females with a genetic predilection for breast cancer is risk-reducing mastectomy. With this method, risk-reduction in the onset of breast cancer is about 90%, reaching 95% if Risk-Reducing Salpingo-Oophorectomy (RRSO) is also performed. Its role, however, is still debated for multiple reasons including psychosocial motivation; insufficiency of evidence on its actual effectiveness in terms of global survival in both, women with previous neoplasm and healthy women; and the awareness that most breast cancers nowadays are curable with conservative surgeries. In women already affected with breast cancer, the role of contralateral prophylactic surgery versus conservative surgery has been evaluated in several studies. A meta-analysis of 10 trials has highlighted that ipsilateral cancer risk is higher in women with BRCA1 or BRCA2 genetic variants undergoing conservative surgery than in women without ascertained genetic variants to a median follow-up >7 years (RR 1.5, $p = 0.003$). It was also found that the risk for contralateral cancer increased if the first tumor had arisen at an early age (RR 3.56, 95% CI 2.50–5.08, $p < 0.001$). Instead, in terms of global survival, there is no adequate evidence to support the effectiveness of contralateral prophylactic mastectomy [79]. Heemskerk-Gerritsen et al. in 2015 carried out a study on more than 500 BRCA-mutated females affected by breast cancer, subjected to conservative surgery alone versus contralateral prophylactic surgery. At a 15-year follow-up, an assessment confirmed significant advantages in terms of global survival in patients who opted for contralateral prophylactic surgery. Benefits are higher in the younger patients (<40 years), particularly in those with good prognosis (1–2 grading, positive hormone receptors, and non-candidate to adjuvant chemotherapy). Further research shows that while prophylactic mastectomy, RRSO, and contralateral mastectomy are surely able to reduce breast cancer risk, bilateral mastectomy alone is not associated with decreased risk of death in all cases [80].

According to the European Society of Breast Cancer Specialists' (EUSOMA) criteria, this intervention should grant remarkable results in at least 75% of the cases, asymmetry in not more than 20% cases, minor complications (infections and small areas of necrosis) and capsule contracture in not more than 10% of all cases. The indication for SLN biopsy does not find the general consensus. The evident benefits of mastectomy include effectiveness in completely

reducing breast cancer risk, even if not to zero, in reducing disease anxiety and, in some cases, aesthetic improvement of the pre-existing situation. Yet, the potential disadvantages must not be overlooked: it is a major surgery; the cosmetic result, even if performed by very skilled and capable surgeons, can dissatisfy expectations as it may not allow full restoration of the original form and function; it may consequently cause drastic, traumatic and irreversible changes in the tissues; early and/or late complications may arise (e.g., superinfections, capsular retraction, insensitivity of the area, asymmetry, evident scars), possible offspring lactation would not be possible, and psychological and relational discomfort with the partner could arise. It must be stressed that there are also some conditions in which mastectomy is not indicated such as non-informative genetic testing, class 1–2–3 VUS result, or unavailability of tests; Munchausen syndrome and major psychological/psychiatric disorders; higher operating risk than the obtainable benefits; unrealistic woman's expectations; and disease outcome. Therefore, to minimize these implications, correct surgical approach is mandatory and the patient must make a firm and conscious choice. For this purpose, adequate psychological and multidisciplinary support is necessary, both in the course of the decision-making phase and in times after the intervention. It may be reasonable to obtain from the patient an informed consent that includes all the previously reported issues [81].

Risk-Reduction Salpingo-Oophorectomy (RRSO). Women with BRCA1 and BRCA2 genetic variants have a higher risk (about 60% in patients with BRCA1 and 20% in patients with BRCA2) of developing an ovarian/tubal cancer compared to the general population. The most frequent histotype in mutated patients is high-grade serous carcinoma, which represents one of the most aggressive ovarian cancers. Till date, no tools or biomolecular markers identifying early ovarian cancer have been developed and, therefore, it is indispensable to discuss, as part of the prevention program, RRSO intervention, which may reduce cancer risk from 95% to 98%. It is also not possible to completely eliminate cancer risk since ovarian tissue islands may persist in the peritoneal membrane. Furthermore, if RRSO is performed in the pre-menopausal age, it reduces breast cancer risk to about half in both, BRCA1 and BRCA2 genetic variants. In contrast, RRSO entails important implications from the reproductive and hormonal point of view, such as infertility and early menopause. In this regard, oocyte cryopreservation may be opted. Study protocols advise salpingectomy (as adnexal cancers in mutated BRCA patients originate in the tubes) in the first place and later, oophorectomy, in order to delay menopause. For these reasons, it is necessary to consider and discuss thoroughly with the patient, all the involved risks and benefits before making a final conscious decision. Any suspected ovarian lesion must be characterized according to the International Ovarian Tumor Analysis (IOTA) criteria [82]. In the course of execution of RRSO, both ovarian/tubal CIS and invasive cancers have been identified. Although there are some recent studies that have shown the presence of high-grade serous endometrial carcinomas in patients with BRCA1 genetic variants, this information is yet to be verified. Therefore, no indications for prophylactic hysterectomy in such patients exist.

To summarize, the standards for RRSO must entail:

1. age $\geqslant$35 years;
2. BRCA gene mutation;
3. good life expectancy;
4. multidisciplinary discussion (including psychological consultation);
5. knowledge regarding provisional oncological protection; and

6. post-surgical psychological support.

A meta-analysis, involving 346 studies from 1999 to 2007, reports 79% reduction in ovarian/tubal cancer risk and 51% reduction in breast cancer risk [83]. At the same time, a prospective cohort study (RRSO, n = 188; surveillance, n = 478) suggested 95% reduction in ovarian/tubal cancer mortality and 90% reduction in breast cancer mortality [84, 85].

4.1.2 Chemoprevention

Since the end of the1970s, different molecules, both natural and synthetic, have been used in various experimental clinical protocols to evaluate their efficacy, in terms of prevention, in particular subgroups of patients: healthy people at a high risk of cancer development, subjects with precancerous lesions, and patients at a risk of developing second cancer during the follow-up of the preceding one. Healthy subjects at high familial risk, in whom the opportunity to use such molecules can effectively constitute a legitimate preventive strategy, represent a unique target in this regard. Literature reports that about 90% of the BRCA1 genetic variant-related breast cancers are unresponsive to endocrine therapy; on the contrary, 80% of BRCA2 genetic variant-related breast cancers are hormone-sensitive. Some chemoprevention studies have evaluated the protective effect of different molecules known as Selective Estrogen Receptor Modulators (SERM), such as tamoxifen and raloxifene, for breast cancer prevention. A meta-analysis of 2013 analyzed cases from nine randomized controlled trials (RCT), comparing SERM assumption versus placebo in women without breast cancer, confirmed 38% reduction in overall cancer incidence (more evident in the first five years) against significantly increased risk for thromboembolism [odds ratio (OR) 1.73, 95% CI 1.47–2.05] [86].

Tamoxifen, a well-known drug employed in adjuvant therapy for hormone-responsive cancers, has been extensively studied in different types of patients, including healthy high-risk women and patients with Ductal carcinoma-in-situ (DCIS). Four Phase III studies have reported the most significant results: National Surgical Adjuvant Breast and Bowel Project Prevention-1 (NSABP P-1), Royal Marsden, Italian Study of Prevention with Tamoxifen, and IBIS 1. The first study registered tamoxifen, in 1998 by the Food and Drug Administration (FDA), as a preventative drug for women categorized as high risk for breast cancer by the Gail model. The study confirmed 49% ($p < .00001$) risk reduction in invasive breast cancer, 50% ($p < .002$) risk reduction in non-invasive cancer, and 69% risk reduction in hormone-responsive cancer, in general. No significant reduction in the incidence of cancers unresponsive to hormone therapy was observed. On the other hand, the drug provoked an increased incidence in endometrial cancers and thromboembolic events in postmenopausal females [87]. In the second trial, data at a median follow-up of 20 years were published. There was not established any substantial risk reduction in breast cancer throughout the treatment phase, except for the post-therapy phase [88]. At the same time, the Italian study that randomized healthy hysterectomized women to tamoxifen versus placebo verified in the two groups, at a median follow-up of 11 years, comparable breast cancer incidence in patients subjected to bilateral oophorectomy and in women at low risk of hormone-sensitive cancer, while it reported a reduction in its incidence in high-risk women treated with tamoxifen (RR 0.24, 95% CI 0.10–0.59). Also, the group of patients treated with tamoxifen in this trial developed side effects (hot flushes, genital/urinary disorders, hypertriglyceridemia, thromboembolic events, and cardiac arrhythmias) more frequently compared to the placebo group [89]. The IBIS 1 study, at a median

follow-up of eight years, substantiated constant, additional, preventive effect of tamoxifen [90]. Therefore, today there is evidence that tamoxifen is able to minimize the risk of hormone-responsive breast cancers. The evidence published in Italy has not been considered sufficiently significant so as to point out the preventive role of this drug.

The Multiple Outcomes of Raloxifene Evaluation (MORE) and the subsequent Continuing Outcomes Relevant to Evista (CORE) studies were the first to evaluate raloxifene as a preventive drug for breast cancer. Both studies, at a follow-up of eight years, confirmed 66% reduction in the incidence of invasive breast cancer [hazard ratio (H) 0.34, 95% CI 0.22–0.50] and 76% reduction in the hormone-sensitive varieties (H 0.24, 95% CI 0.15–0.40) in the treatment group [91,92]. Subsequently, the Study of Tamoxifen and Raloxifene (STAR), a large primary prevention trial in high-risk postmenopausal women according to the Gail model or previous LCIS, compared tamoxifen versus raloxifene hypothesis. At a median follow-up of six years, the trial highlighted raloxifene short-lived efficacy in the prevention of invasive breast cancer, although with lower toxicity spectrum, in terms of uterine neoplasms and thromboembolic episodes [93]. In 2013, therefore, the guidelines by National Institute for Health and Care Excellence (NICE) in Great Britain recommended tamoxifen as a preventive drug for five years in healthy women of any age but at a high risk of breast cancer and/or of raloxifene in the same post-menopausal patients [94].

In addition to SERM, different molecules have been used and are still being studied in chemoprevention trials. Aromatase inhibitors, for example, extensively used in the treatment of patients already affected with breast cancer, were evaluated in two major chemoprevention studies in high-risk postmenopausal women, the Mammary Prevention 3 (MAP.3) and IBIS II: the first validated an annual risk reduction rate of 65% with a spectrum of acceptable toxicity, while the second showed, after a median follow-up of five years, an incidence of breast cancer of 2% in the anastrozole group versus 4% in the placebo group (H 0.47, 95% CI 0.32–0.68, $p < 0.0001$). Side effects, in particular on the musculoskeletal and vascular apparatus, occurred more frequently in the group undergoing therapy [95, 96].

Fenretinide, or N-(4-hydroxyphenyl) retinamide (4-HPR), a synthetic retinoid, is another molecule of viable interest in breast cancer chemoprevention. It exerts a marked anti-proliferative effect on the epithelium of the mammary gland. Veronesi et al. conducted a Phase III study in 2972 patients with a history of breast cancer (stage I), who have undergone any adjuvant medical therapies, randomized to fenretinide 200 mg/day for five years versus observation. The analysis, at a median follow-up of eight years, established a significant reduction in both, local recurrences and ovarian cancer incidence, in pre-menopausal women and those undergoing treatment. The 15-year follow-up results proved the effectiveness of the drug in pre-menopause, with a 38% global reduction in second cancer incidence, more evident in females less than 40 years of age (reduction of 50%), both for ER-positive and for ER-negative cancers [97]. However, the main limitations to the use of this drug in chemoprevention include toxicity, particularly at the mucocutaneous level (dryness and desquamation), hepatic (enzymatic alterations) level, biochemical (hypertriglyceridemia) level, and visual (delayed adaptation to night-time vision) level, as well as the need for simultaneous use of a contraceptive owing to its potential teratogenic effect. In 2011, a Phase III RCT with fenretinide 200 mg/day for five years versus placebo was carried out in 20 to 46-year-old females, either at high genetic risk or BRCA-mutated; nevertheless, the trial was terminated in early 2016 due to inadequate enrolment. In conclusion, the use of fenretinide as a preventive drug, considering the lack of reliable data on its efficacy, is

not indicated in the international guidelines, at present. The use of oral contraceptives has been indicated in different studies, as a protective means against the onset of ovarian cancer in patients with BRCA genetic variants. Contrasting data, instead, concerning the onset of breast cancer have emerged, especially in relation to the commencing age of postulation. It should, however, be stressed that chemoprevention cannot be viewed as an alternative to primary prevention, at present, rather, as a complementary therapy. In summary, chemoprevention relies on tamoxifen, aromatase inhibitors, and fenretinide, as reported in controlled studies [European Institute of Oncology (IEO)], the latter has a higher efficacy in young healthy women with ascertained mutation or a likelihood of >20% mutation (Figure 3 and Figure 4).

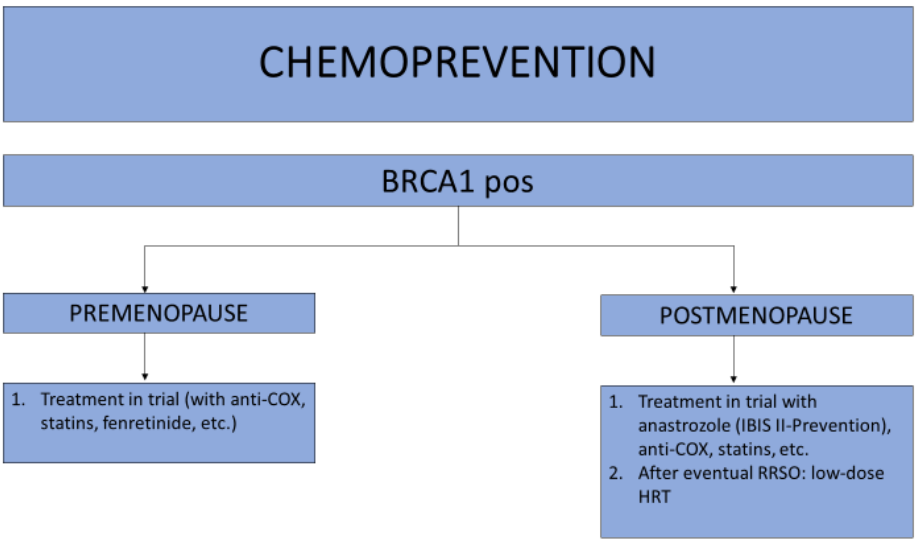

Figure 3 Subjects at a high risk of familial-hereditary breast cancer (though, not affected) (from F.O.N.Ca.M. guidelines, 2008).

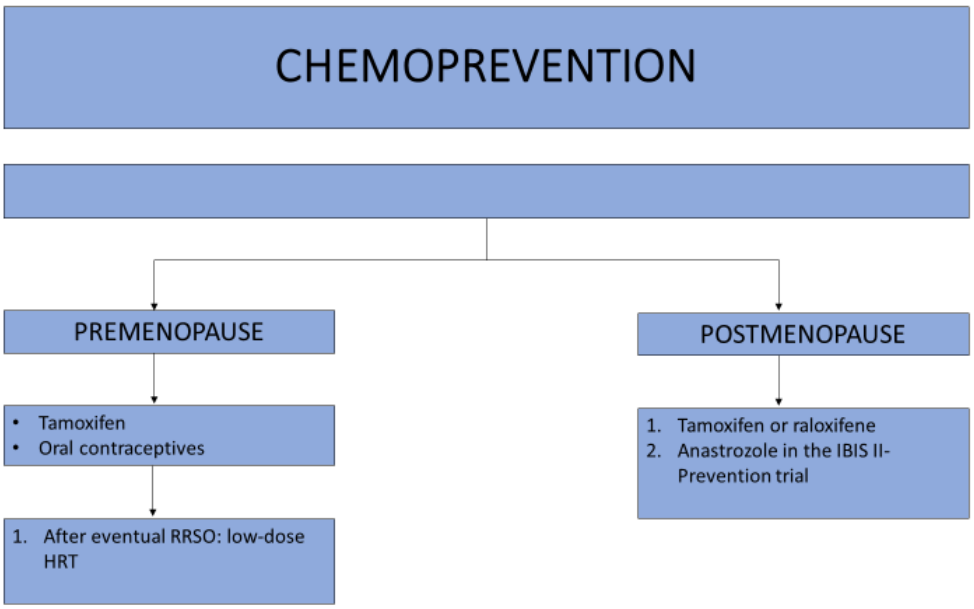

Figure 4 Subjects at high risk of breast cancer (though, not affected) (from F.O.N.Ca.M. guidelines, 2008).

Chemoprevention trials, using oral contraceptives and retinoids, would be essential in determining whether these drugs are advantageous in selected populations. Further work will be indispensable in understanding the mechanism of action of oral contraceptives in the prevention of ovarian cancers and if this protective effect would be maintained in the high-risk population or not. The results of the Milan study have proved to be promising for the retinoids in ovarian cancer prevention and would be employed in chemoprevention trials, both, alone and in combination with oral contraceptives, to determine any additive effects with the use of these drugs. Till date, only little is known about the pre-invasive modifications in ovary so as to predict women at risk of developing ovarian cancer. Nowadays, high-risk women can be identified by genetic counseling and testing, although ultrasound and serum markers are the only modalities available for the evaluation of these women. Research is now focused on discovering tools for evaluating women, especially those at a high risk of ovarian cancer, in order to better understand the neoplastic process in the ovary and. consequently, identify these women prior to the development of advanced ovarian cancer. The current ongoing research is also focusing on understanding chemoprevention for ovarian cancers so that women can receive the optimal chemo-preventive agent as soon as being diagnosed as a high-risk group. Prognosis of the advanced disease is so poor that early diagnosis and chemoprevention are the only methods, at present, to appreciably enhance survival in epithelial ovarian cancer [98].

4.2 Secondary Prevention

4.2.1 Medical Treatment in BRCA Genetic Variant-Affected Patients

The treatment of patients with genetic variant-related breast cancer to date does not differ from the one adopted in the general population. Most BRCA1-related cancers present a typical picture, characterized by high grading, ER- and PR-negativity, and the absence of HER-2 amplification. These characters typically outline aggressive cancers. However, at present, the prognosis of these cancers does not appear insignificant compared to sporadic ones, and consequently, a more aggressive therapeutic conduct, based only on the presence of high family risk, is not indicated.

PARP Inhibitors and Platinum-Derivatives Chemotherapy. In the last few years, PARP inhibitors, molecules that utilize the incapacity of cells to correct injury due to DNA repair gene mutations, inducted by chemotherapeutics, in particular, platinum derivatives, have been studied. Among these, olaparib (Lynparza) was recently accredited by the Italian Drug Agency (AIFA) as monotherapy for the maintenance treatment of patients with platinum-sensitive recurrence of high-grade serious epithelial ovarian carcinoma, Fallopian tube carcinoma, or primary peritoneal carcinoma, and BRCA-mutated (germline and/or somatic mutation), which respond (complete or partial response) to platinum-based chemotherapy. Therefore, at first instance, if genetic testing is requested for therapeutic purposes, it is essential to consider that the eventual positivity has repercussions on other family members. Moreover, the efficacy of PARP inhibitors in breast cancer is still under study. It has higher efficiency in triple-negative cancers, independent from the presence of BRCA mutation. Although well-tolerated by the patient, the long-term side effects of these drugs are unknown. Recently, it has been highlighted that the use of chemotherapy in a neoadjuvant phase with platinum derivatives can extend the response rate in patients with BRCA-mutation.

DNA repair deficiencies have become the target of PARP inhibition as a successful therapeutic strategy in ovarian cancer. Hereditary ovarian cancers are derived from germline mutations in BRCA1, BRCA2, or different essential genes in the homologous DNA repair recombination process. Sporadic ovarian cancers may acquire a phenotype of homologous recombination deficiency, additionally through various other mechanisms. Recent research has found PARP inhibitors to target ovarian cancers with homologous recombination deficiency selectively. There are eight PARP inhibitors at multiple stages of clinical development, four of which are actively studied in Phase III ovarian cancer studies. In December 2014, the first PARP inhibitor, olaparib, was authorized for ovarian cancer patients with two distinct clinical indications in Europe and the United States (US). Ovarian cancer has, thus, become a model for successful translation of targeted therapy against DNA repair deficiencies in cancer [99].

5. The Role of the Psychologist in Oncological Genetic Counseling

A review of the psycho-social oncology literature indicates the scarcity of psychological services available in early detection programs, yet there is an increase in awareness of the need for psychosocial distress in women whose mothers had cancer. The explosion of information transmitted through the news media to the public about breast and ovarian cancer, their early detection, and genetic susceptibility should heighten the sensitivity of the scientific community to the apprehensions of women who are first-degree relatives of women with these cancers. Through psycho-social assessment and evaluation, it has been observed that life cycle events, unresolved episodic grief, cognitive adaptation to loss, and interpersonal relationships contribute to the importance of total care and medical responsibility of the gynecologic cancer patient. Psycho-social counseling suggests the necessity of continual intervention to address women's increased anxieties about gynecological cancers. Particular attention should be given to the psychological needs of vulnerable subjects in disease-screening programs. Medical providers of early detection screening should rigorously explore the psycho-social aspects of early detection and provide the appropriate intervention to meet women's needs [100]. A positive result of genetic testing makes the woman more aware of her risk condition planning. The issues that can emerge in people who receive communication on genetic cancer risk are:

1. the worry of getting or recurrence of cancer;
2. the fear of diagnostic tests;
3. the fear of being able to transmit or have transmitted the mutation responsible for the onset of the disease to the offspring;
4. the sense of responsibility toward the involved partner; and
5. the difficulty of planning one's future.

These reactions are not only closely related to the content of the received communication but also the type of personality and the perception of the individual risk. In other words, the occurrence of risk involves the need to properly process the received information to allow the implementation, as much as possible, of adaptive behaviors to the uncertainty generated by the diagnosis itself. Psychological counseling is the technique that is best suited to provide accurate and clear information, ensuring adequate psychological support to the person. It aims to:

1. favor a good relationship between the treating team and the patient, so that the personal value of the latter can be strengthened independently from the feeling of being sick to the sense of control over life events, and decision-making autonomy;
2. create the conditions for the individual to use genetic information in a significant personal way, reducing psychological stress and increasing the personal sense of control; and
3. promote the integration of genetic information in her personal and family history as well as her individual choices.

Firstly, to avoid anguish and to help deal with the possible inheritance properly, genetic testing must be preceded by an individual, couple, or familial oncological counseling, to make the patient understand that having this type of mutation does not mean to inherit cancer, but only an altered mechanism of defense. BRCA1-2 genes are onco-suppressor genes with autosomal dominant-type of transmission. Therefore, an individual, be it male or female, carrier of an alteration (mutation) in one of these genes, has a 50% risk of transmitting it to the offspring, independent of their sex. Normally, these genes should re-adjust the DNA breaks; however, one of their changes that results in non-functioning only increases the risk for the cell to turn cancerous, having no mechanism of repair. It is estimated that during a lifetime, a BRCA1-2 mutation carrier has a 60–80% probability to develop breast cancer (compared to 10% of non-mutated subjects). BRCA1 carrier also has a 40–45% risk to develop ovarian cancer and around 20% for the BRCA2 mutation. In addition, male subjects carrying these mutations (in particular BRCA2) present a slight increase in breast cancer incidence, but minimal compared to women because of the small number of breast cells usually present in males.

Conversely, prostate cancer risk is increased with a more precocious appearance compared to the general population. In both, the sexes of these families, the risk for colon, pancreas, oropharyngeal district, and melanoma is also high. Based on these considerations, the importance of recognition of patients and/or families with suspected genetically determined predisposition to the development of breast and/or adnexal cancer is evident, whose management can be guaranteed only in the context of a medical care multidisciplinary team that includes the collaboration of GP, oncologist, geneticist, psychologist, surgeon, and radiologist, in order to address, in the most adequate way, the clinical and psychological issues of predisposed individuals. Finally, it is important to stress to these patients that multiple factors always cause cancer, and genetic predisposition alone is not enough to give rise to it, for which environmental issues and lifestyles are also important.

During the whole OGC program, it is crucial to promote the expression of thoughts, fears, and personal experiences related to the treated topics. Reassuring a woman about the normality of her health will allow her to understand the situation and gradually restore the sense of control over her life. During pre-testing consultation, a psychologist's presence provides support in the information and communication process; in fact, it is essential that the patient fully understands the meaning of what is proposed. The treated topics (illness, health, procreation, and death) have substantial emotional value and have significant psychological repercussions that can prevent the total understanding of the contents itself. It is essential to enrich useful elements for better knowledge of the diagnostic and therapeutic procedures, inform about the various existing options, as well as discuss and analyze the meanings and consequences for each of the possible alternatives for the woman and/or her family.

Furthermore, psychological counseling following pre-testing consultation may be necessary when the decision to undergo the test may be difficult (e.g., in young subjects). In the post-testing restitution phase, the patient must be helped to have a realistic perception of her risk situation, to put in place adequate implementing adaptation strategies to plan her own life, taking into account the information received and the changes that can be made necessary. Generally, it has been found that

1. negative testing is associated with anxiety-distress reduction;
2. positive testing is related to high anxiety-distress levels, but only for short term (1–2 years), then levels are normalized; persistence of high levels occurs in subjects already afflicted by psychological or psychiatric problems; and
3. prophylactic mastectomy is the most effective means of reducing anxiety-distress.

Psychological counseling may be necessary:

1. When the patient is involved in complex decision processes concerning specific aspects of genetic diseases, such as prevention choices (particularly, when the individual opts for mutilating preventive interventions), reproductive choices in risk situations, or the option of sharing her risk condition with other family members. Psychological counseling has the objective to assess the perception of the risk of the disease, the emotional impact of the therapeutic proposal (surgery), the expectations, the capacity of adaptation, and the analysis of personal and social resources; and
2. in subjects who have suffered numerous deaths in the family due to the genetic nature of the pathology.

Although tendentious counseling interventions are conducted individually, it is possible to activate an intervention involving the couple or the entire family, when problems emerge such as:

1. the decision to procreate or to adopt a child;
2. difficulties in the relationship between the person and the partner linked to the sense of responsibility and fault and also to the change of one's image;
3. previous complicated familial dynamics among the components of the families belonging to the same genealogical tree, which prevent the passage of genetic information; and
4. Finally, a psychologist's role can be also useful for staff training; in fact, the clinician that manages communications with high emotional content may need specific training.

6. Guidelines

The latest NICE guidelines updated from 2004 [102] and 2006 [103], on the classification of familial breast cancer and the assistance of high-risk people [101], provide new recommendations for women and men with new or previous breast cancer diagnosis who have a family history of breast and ovarian cancer, not considered in earlier versions [104]. NICE guidelines are based on the systematic review of the best available evidence and explicit considerations on health intervention cost-effectiveness. When evidence is limited, recommendations are based on the experience of the group that produced the guidelines like Guidelines Development Group (GDG) and on standards of good clinical practice.

6.1 Information and Support to Patients

It includes providing patients with personalized information, including local and national support services and organizations.

6.2 Initial Evaluation without History of Breast Cancer in the Primary Care Setting

When a subject without a history of breast cancer presents breast symptoms or manifests concerns for family members with breast cancer, to adequately assess her risk, it is essential to collect the family history of first and second-degree relatives, thus allowing appropriate classification and assistance. Accurate information on cancer diagnosis in family members should be obtained like age at diagnosis, neoplasms location, multiple neoplasms (including any cases of bilateral disease), and Jewish ancestry. Specialist advice to assess breast cancer risk should be requested if the person meets at least one of the following criteria:

1. a first-degree family woman diagnosed with breast cancer at <40 years of age;
2. a first-degree family man diagnosed with breast cancer at any age;
3. a first-degree family member diagnosed with bilateral breast cancer and primary neoplasm diagnosed at <50 years of age;
4. two first-degree relatives or one first-degree relative and one second-degree relative with a breast cancer diagnosis at any age;
5. one first- or second-degree family member diagnosed with breast cancer at any age and one first- or second-degree family member diagnosed with ovarian cancer at any age (at least one of them must be first-degree); and
6. three first- or second-degree family members from the same branch diagnosed with breast cancer at any age.

When more family members are involved, all must belong to the same branch. People who do not meet these criteria have breast cancer risk similar to the general population. As a consequence, they must only be reassured and do not require specialist advice.

6.3 Identification of Gene Carriers with or without History of Breast Cancer

To identify the people to be sent to a specialized genetic clinic, in addition to their family history if available in a secondary care setting, a documented reliability method to calculate the probability that the person is BRCA1/BRCA2 gene carrier (e.g., BOADICEA and the Manchester score) should be used [105, 106]. The possibility of genetic testing of people who are ≥10% likely to be combined BRCA1/BRCA2 gene mutation carriers should be offered at accredited centers [107]. Family members with a personal history of breast or ovarian cancer should ideally be genetically tested. However, it is also possible to test healthy subjects if the affected family member is not available. The treatment of newly diagnosed breast cancer patients may be different if it is a familial form; however, there is no evidence from clinical trials that supports the execution of genetic testing within four weeks of a breast cancer diagnosis. Genetic testing should be performed in subjects eligible to be sent to the geneticist during the initial phase of their disease or thereafter at any time. Rapid access to genetic testing (within four weeks of breast cancer diagnosis) should be provided only in clinical trials. Potential risks and benefits of genetic testing should be discussed, addressing the probability of detecting a mutation, the implications

for the individual and her family members, and the implications resulting from VUS identification or failure to find the mutation. Considering that the evolution of knowledge will improve the identification of familial breast cancer, families with an uncertain genetic diagnosis should be informed that in the future, they can be re-evaluated for further investigation.

6.4 Breast Cancer Surveillance

Women with a family history of breast cancer, with or without a personal history of breast cancer, and according to specialized assessment having moderate to high risk and decided not to undergo preventive mastectomy, can benefit from radiological surveillance. Digital mammography and breast MRI must be performed according to recommended standards. In high-risk women (with known BRCA or TP53 gene mutation, or with >30% probability of being mutation carriers), MRI screening has higher cost-effectiveness than mammography. The possibility to perform MRI in women aged 30–49 years, with or without a personal history of breast cancer, if they are BRCA1 or BRCA2 mutation carriers or to women who are >30% likely to be BRCA gene carriers, should be offered every year. The possibility to perform mammography every year should be provided to women:

1. between 40 and 49 years with moderate breast cancer risk;
2. between 40 and 59 years with high breast cancer risk but with ≤30% probability of being BRCA or TP53 mutation carriers;
3. between 40 and 59 years with >30% probability of being BRCA carriers; and
4. between 40 and 69 years with a known BRCA mutation.

Women aged <30 years or women at any age with known TP53 mutation should not undergo mammography. Routine ultrasonography in women at moderate or high risk of breast cancer should not be performed, except in cases where MRI surveillance is not feasible (e.g., claustrophobia) or when mammography or MRI findings are difficult to interpret [108].

6.5 Risk Reduction Strategies in Women without History of Breast Cancer

HRT and oral contraceptive use can increase breast cancer risk. Women aged 35 and older with a family history of breast cancer should be informed that the use of oral contraceptives increases breast cancer risk, regardless of the increase of absolute risk due to age. Risks and benefits of oral contraceptives should be discussed with women BRCA mutation carriers: on the one hand, a potential increase of breast cancer risk at <40 years of age; and on the other hand, reduction of ovarian cancer risk throughout life. Women with a family history of breast cancer who are evaluating or already taking HRT should be informed of the increased risk of breast cancer associated with the type and duration of this therapy. Recently, some clinical trials have shown a significant reduction in breast cancer risk with tamoxifen and raloxifene. Although cost-effective, both drugs increase thromboembolic risk, and tamoxifen can cause endometrial cancer. After risk assessment by the specialist, women without a breast cancer history and do not have an increased risk of thromboembolic disease or endometrial cancer should be:

1. prescribed tamoxifen for five years, if they are not yet in menopause and at high breast cancer risk;
2. prescribed tamoxifen for five years, if they are in menopause, at high breast cancer risk, and hysterectomies;

3. prescribed tamoxifen or raloxifene for five years, if they are in menopause, at high breast cancer risk, and with a preserved uterus;
4. considered for tamoxifen for five years, if they are not yet in menopause and at moderate breast cancer risk over the next ten years;
5. considered for tamoxifen for five years, if they are in menopause, at moderate breast cancer risk over the next ten years, and without uterus/hysterectomies; and
6. Considered for tamoxifen or raloxifene for five years, if they are in menopause, at moderate breast cancer risk over the next ten years, and with a preserved uterus.

6.6 Risk-Reduction Strategies in Women with Family History of Breast or Ovarian Cancer

As more women with a higher risk of an inherited gynecologic cancer are identified, clinicians are challenged to counsel them on risk-reduction strategies. Women with increased risk of breast or ovarian cancer due to their family history may consider surgery among the risk-reduction options. Women with a new breast cancer diagnosis may have different surgical options than those without a family history of breast cancer. Risks and benefits of preventive mastectomy should also be discussed with women with suspected or known BRCA1, BRCA2, or TP53 mutation. Interventions of preventive and reconstructive mastectomy must be performed by a surgical team specialized in breast cancer and reconstructive surgery. Risks and benefits of bilateral RRSO should be discussed with women suspected or with known BRCA1, BRCA2, or TP53 mutation, including the benefits of reducing breast and ovarian cancer risk and adverse effects of surgically-induced menopause. Benefits and risks of HRT after oophorectomy in women aged $\leqslant$50 years without breast cancer diagnosis should also be discussed with the patients. Although recent studies show the potential for ovarian cancer surveillance strategies, there is no definitive evidence that surveillance leads to a stage shift or a reduction in mortality. Recent studies support the following conclusions: first, oral contraceptive use reduces ovarian cancer risk without significant increase in breast cancer risk, second, RRSO leads to a reduction in ovarian cancer, breast cancer, and overall mortality in women who are carriers of BRCA1 and BRCA2 mutations, and third, “ovarian cancers” associated with BRCA mutations actually include Fallopian tube and peritoneal cancer and may have a precursor lesion in the Fallopian tube thus suggesting removing the Fallopian tube to reduce ovarian cancer risk. Considering the interplay between the hormonal impact of ovarian function on breast cancer risk, as well as the risk reduction associated with oophorectomy, and the effect of early menopause on other health outcomes, an integrated multidisciplinary approach is required to aid in the highly complex decisions faced by women with high risk of developing inherited gynecological cancers [109-112].

6.7 Potential Obstacles and Implementation

Lower thresholds recommended for genetic testing will increase the number of referrals to the accredited medical genetic centers; however, according to the GDG, the infrastructure should be able to meet the demands. In May 2016, the Division of Cancer Prevention (DCP), the Division of Cancer Control and Population Sciences (DCCPS), and National Cancer Institute (NCI), convened a workshop to discuss a conceptual framework for identifying and genetically testing previously diagnosed but un-referred patients with ovarian cancer and other unrecognized BRCA1 or BRCA2 mutation carriers to improve the detection of families at risk for breast or ovarian cancer. The

concept, designated as “Traceback”, was initiated by the recognition that although BRCA1 and BRCA2 mutations are frequent in women with ovarian cancer, such women have not been tested, especially if their diagnosis presaged changes in testing guidelines. The failure to identify mutation carriers among probands thus represents a lost opportunity to prevent cancer in unsuspecting relatives through risk-reduction intervention in mutation carriers and to provide appropriate reassurances to non-carriers. The Traceback program could offer a valuable opportunity to reach families from different racial, ethnic, and socio-economic groups who historically have not sought or been offered genetic counseling and testing and thereby contribute to a reduction in health disparities in women with germline BRCA mutations. The workshop assembled international experts in genetics, medical and gynecological oncology, clinical psychology, epidemiology, genomics, cost-effectiveness modeling, pathology, bioethics, and patient advocacy to identify factors to consider when undertaking a Traceback program to achieve an interdisciplinary perspective [113-115].

6.8 Recommendations for Future Research

The GDG has identified the following priorities:

1. to develop and validate models to calculate the probability of being gene carriers that include additional data, such as cancer molecular pathology and prevalence of mutations concerning ethnic groups;
2. to determine the benefits and risks of rapid access to genetic testing for subjects newly diagnosed with breast cancer, evaluating both, the optimal model for delivery and organization, clinical efficacy and cost-effectiveness of such an innovation, clinical outcomes and patients’ feedback;
3. to define the risks and benefits of screening with MRI versus mammography in women >50 years of age with a personal history of breast cancer; studies should plan subgroup analyses based on breast density;
4. to conduct RCT to compare the efficacy and cost-effectiveness of aromatase inhibitors versus tamoxifen in reducing breast cancer incidence in women with a family history of breast or ovarian cancer; and
5. to compare the clinical and psychological outcomes in women undergoing preventive mastectomy versus those who do not [116].

7. Conclusions

The epidemiological data support the existence of two discrete manifestations of hereditary carcinoma: HBOC syndrome and HNPCC syndrome. HBOC syndrome, an inherited cancer-susceptibility syndrome, is characterized by multiple family members with breast cancer, ovarian cancer, or both. Based on the present understanding of the origin and management of ovarian cancer and for simplicity, it is also referred to as fallopian tube cancer and primary peritoneal cancer. Clinical genetic testing for gene mutations allows more precise identification of women at high risk for inherited breast and ovarian cancer. For these individuals, screening and prevention strategies can be instituted for risk reduction. Obstetrician-gynecologists and gynecological oncologists play a significant role in identifying patients with increased risk of inherited cancer syndromes. If an obstetrician-gynecologist or other care provider does not have the necessary

knowledge or expertise in cancer genetics to counsel a patient appropriately, referral to a genetic counselor, gynecological or medical oncologist, or other genetics specialists is considered. Thus awareness of the biological and familial risk factors is useful and can assist navigating the follow-up of the patients and families for these complex disorders. Large national and international cohorts continue to collect data of women with known BRCA1/2 mutations or high risk in an attempt to understand better the genetic risk, risk modifiers, impact on the quality of life or screening, testing, and risk reduction strategies. More genes that confer varying risks of breast cancer, ovarian cancer, and other types of cancer are being discovered, along with new technologies for genetic testing. The Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) has also begun to identify other genetic modifiers of BRCA1/2 risk and cancer cluster regions in an attempt to individualize site-specific cancer risk and prevention strategies. The Gynecological Oncology Group (GOG) has initiated a long-term follow-up study to the GOG 199 protocol, which will continue to enhance the understanding of the patient decisions, impact on the quality of life, and other genetic factors responsible for cancer initiation and progression. These are invaluable resources with massive datasets that require extensive analyses, which will continue to rapidly expand our present knowledge and management of women with hereditary cancer syndromes [117, 118].

Breast cancer is the most common neoplasm in women. The cumulative risk of the disease is 10% up to 80 years of age. A family history of breast and ovarian cancer is a significant risk factor. About 5–10% of all breast cancer cases and 25–40% of these patients under 35 years of age have a hereditary origin. BRCA1/BRCA2 mutation is responsible for 3–8% of all breast cancer cases and 30–40% of familial cases. In addition, 10% of ovarian cancer patients have a genetic predisposition. About 80% of families with ovarian cancer history have BRCA1 mutations, while 15% have BRCA2 mutations. Women at risk can receive counseling from interdisciplinary cancer genetics clinics, while high-risk women should undergo genetic testing. Risk-calculation programs can define the risk and assist in decision making for genetic testing and clinical options. The latter requires information on disease risk and mutation status. Chemoprevention is currently a controversial topic, while oral contraceptives can be considered for reducing ovarian cancer risk. Prophylactic mastectomy and bilateral oophorectomy are the only proven options that lead to risk reduction, but naturally, affect the patient's physical integrity. It is still unclear whether early cancer diagnosis is individually beneficial; however, it is the least invasive option for the patient. Although hereditary breast cancer has different pathological characteristics and BRCA mutation is an independent negative prognostic factor; currently, there are no particular therapeutic guidelines. Moreover, without adjuvant hormone therapy or chemotherapy, overall survival in BRCA mutation carriers is reduced. Chemotherapeutic regimens that particularly involve platinum are useful in hereditary breast cancer treatment [119].

The majority of HNPCC families are linked to one of four genes encoding MMR proteins. Molecular analyses demonstrate that genetic screening for germline transmission of a defective allele of one or another of these genes is now possible in high-risk individuals. With ovarian cancer being an important health issue, it is necessary to design reliable screening tests to detect defective, inherited, or somatic alleles in individual carriers. However, to date, most progress is demonstrated in high-risk patients with a family history of the disease. The ramifications of such research may impact a variety of complex scientific, clinical, legal, ethical, and psychosocial issues. Thus, genetic counseling is required for a thorough understanding of these issues with a cautious

approach to most effectively meet the individual needs of the patient population. In addition to current treatment modalities, positive results may indicate the need for increased clinical surveillance, prophylactic treatment, and genetic counseling of patients on an individual basis. These are among the management options that may be appropriate for some genetically predisposed, asymptomatic women. The identification of BRCA1/BRCA2 mutations in women with ovarian cancer, in fact, allows accurate predictive genetic testing of their at-risk relatives, thus providing them early detection and risk reduction strategies. In the case of women with recurrent, progressive ovarian cancer, the window of opportunity for genetic testing is limited. While these situations pose unique challenges, they also present a significant opportunity to benefit the patient and her family. Finally, it will be intriguing to see whether the technology can be made reliable enough to benefit not only high-risk individuals but also the general population. Further research is needed on the most effective use of this genetic information in formulating counseling and clinical management strategies. Also, attention should be directed toward the provision of genetic counseling and testing during the end of life care [120-122].

Since BRCA1 and BRCA2 genes have been discovered in relatively recent times (1994–95), prevention and monitoring strategies are under continuous review and improvement. However, it is good to underline that we are unaware of the real effectiveness of the close surveillance programs in reducing morbidity and mortality in women at risk from these cancers. More precise information may be generated in the future from research and specific RCT results, including GP database contribution. It is desirable, in the GP setting, the development of a computerized algorithm based on numerous factors (age, family and personal history, alcohol consumption, smoking, and suspicious symptoms) with good predictive power to discriminate and identify patients with the highest risk. Testing execution is subjected to OGC which should not be directive toward the implementation of genetic analysis. We must also emphasize that almost all breast, endometrial, colon, and ovarian cancers should undergo testing and subsequent counseling. The index case must be the individual with the highest genetic risk in the family, and the laboratory must provide clinical interpretation of the genetic testing. Management of the result of genetic analysis must be delegated to a multidisciplinary team composed of specialists with integrated skills. Only genetic testing that highlights a genetic variant implies intensive surveillance protocol and deliberation on breast and ovarian prophylactic surgery measures. Indeterminate or VUS-indicative testing indicates a surveillance protocol based on the personal and familial oncological history. Prophylactic surgery is the most effective measure in reducing the risk of developing breast/ovarian/Fallopian tube cancer.

Chemoprevention cannot be currently considered an alternative to primary prevention, but rather a complement. Finally, it is good to remember that the organization of centers where OGC is performed is variable between and within a region. This depends on the local health care organization and available resources. In Italy, in areas like Emilia-Romagna, all breast cancer screening programs are defined at the regional level, and high-risk patients must not pay for genetic testing or the successive clinical-instrumental testing. Similarly, recently in Lombardy, patients who are carriers of a genetic variant have obtained health ticket exemption. It should be emphasized that since 2015, the D99 exemption code has been introduced, which permits free access to the surveillance program for healthy women at high risk because they are BRCA gene mutation carriers. Therefore all issues related to individuals with genetic variants should be understood and made explicit to all health operators to have the possibility of intervention on the

economic resources to target inherited breast cancer, as well as the related human, psychological, genetic, and management issues [123-142].

Author Contributions

Ciro Comparetto and Franco Borruto contributed equally to this work, Florence Dupré is a consultant.

Competing Interests

The authors have declared that no competing interests exist.

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