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A targeted approach to genetic counseling in breast cancer patients: the experience of an Italian local project

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ABSTRACT

Aims and background: Patients with hereditary breast cancer (BC) may benefit from genetic counseling and testing for detection of causative mutations, definition of therapeutic and preventive strategies, and identification of at-risk relatives. Italy has few oncogenetic centers and genetic evaluation of all patients with BC is not feasible. Moreover, lack of uniformity in the selection of patients generates inappropriate referral to the geneticist. We designed a model that may represent a reproducible way to select patients at risk for hereditary BC, with the aims of rationalizing access to genetic centers and improving clinical management and surveillance.

Methods: The genetic unit of a Cancer Center and the Departments of Oncology from 2 public Hospitals in Milan were involved in the project. After training sessions at the genetic unit, operators from the 2 hospitals evaluated all patients with BC attending a first oncologic visit, through a specific interview. Patients considered at risk of hereditary BC attended counseling at the genetic unit.

Results: Of 419 patients, 61 (14.5%) were eligible for genetic counseling after the interview. Of these, 46 (10.9%) strictly met testing criteria. Overall, 52 (12.4%) patients underwent genetic counseling and 47 were tested for *BRCA1*/*BRCA2* mutation. After genetic test results, the available options for treatment/surveillance were discussed by a multidisciplinary team, according to the level of genetic risk.

Conclusions: It is possible to improve the process of referring patients with suspected hereditary BC for genetic risk assessment. The application of clinical screening reduced the genetics unit's workload and enabled optimization of time and resources.

Keywords: *BRCA*, Clinical network, Genetic counseling, Hereditary breast cancer

Introduction

Breast cancer (BC) is the most frequent cancer among women worldwide. From 5% to 10% of BC incidence is considered to have a strong inherited component, due to the presence of germline mutation in genes that increase the risk of developing the disease. Thus far, BC genes 1 and 2 (*BRCA1* and *BRCA2*, respectively) are the most common known genes; they are responsible for approximately 20% of familial BC. Mutations in other high-risk genes are less frequent and are present in fewer than 1% of BC families; most other causative genes remain unknown (1). The presence of deleterious mutations of *BRCA1/BRCA2* genes is associated with a higher risk of BC. Breast cancer in carriers is more frequently bilateral, with an earlier age at onset, and in *BRCA1* patients is also more frequently triple-negative. Moreover, *BRCA1/BRCA2* carriers also face an increased risk of ovarian/tubal cancer (OC) (1, 2). Estimation of the lifetime cumulative risk of BC (penetrance) ranges from about 40% to 80%, depending on the type of study. A meta-analysis showed cumulative risk of BC to age 70 of 57% for *BRCA1* mutation carriers and 49% for *BRCA2* mutation

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carriers; the cumulative risk of OC to age 70 was 40% for *BRCA1* carriers and 18% for *BRCA2* carriers (3); increasing penetrance over subsequent birth cohorts was also reported (4, 5).

Preventive options are currently available to women at risk for hereditary BC and OC; measures include intensive surveillance and risk-reducing surgery (6-8). Therefore, the identification of patients and relatives at increased genetic risk is crucial. Several international oncologic societies have proposed guidelines for the identification of patients at risk for hereditary BC, generally based on age at diagnosis, number of affected relatives, multiple tumors, and presence of OC (9-12). Of note, guidelines consider genetic counseling performed by trained genetics professionals to be the standard of care, and eligible patients with BC should be referred to board-certified genetic counselors for genetic risk assessment. Currently, physicians do not always possess appropriate information about hereditary BC and OC; this lack of knowledge generates an inappropriate and growing demand for genetic counseling, which consequently delays access to counseling (13). Genetic counseling should be offered only to women who are suspected to have an increased risk, but the identification of such women and their management remains a challenge (14). Many attempts have been made to help patients easily access genetic counseling, including telephone counseling (15). Moreover, predictive mathematical models to estimate genetic risk, such as BRCAPRO, BOADICEA, Tyrer-Cuzik, and COS models, have been designed to calculate the risk of mutation on the basis of the medical history of a patient's first- and second-degree relatives (5-18). However, the use of these models in clinical practice remains controversial because they still present evident limitations. Therefore, risk prediction using these models in clinical practice should be performed with caution and by trained personnel; in addition, it should be emphasized that the use of these models is not a substitute for genetic counseling (19).

Some regions of Italy are setting guidelines for the diagnosis and clinical management of hereditary tumors. Although a regional plan involving both patients and the general population has been defined in Emilia Romagna (20), there is no nationwide project underway, unlike in many other nations worldwide. The existing oncogenetic centers are often unable to meet the growing demands of genetic counseling and risk prediction, and disparities in accessing genetic counseling have been recorded.

Hereditary tumors represent a minority of all cancers, and only at-risk individuals who can actually benefit from a thorough assessment of their genetic risk of cancer should be directed to genetic counseling. To better select patients who may benefit from genetic counseling and testing and to avoid inappropriate demand for such procedures, we have defined an approach that uses an initial clinical filter to create effective organization in order to achieve appropriate and targeted management of patients with BC.

Methods

Study design and setting

This project involved the Medical Genetics Unit of the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan (INT) and the Departments of Oncology of 2 Italian hospitals in Milan (Azienda Ospedaliera Fatebenefratelli e Oftalmico and Azienda Ospedaliera Luigi Sacco). The project was submitted and funded by the General Health Directorate of the Lombardy region. The local ethical committees approved the study protocol, and all patients provided informed consent regarding the use of data for research purposes.

The full duration of the project was 30 months, and included 3 major, partially overlapping, phases. The first phase lasted 9 months and was dedicated to the definition of working materials and methods (questionnaires and consent forms) and to the training of involved operators. A dedicated staff (oncologists and study coordinators) from the 2 oncologic departments was selected and trained by INT geneticists. These operators had to become skilled at identifying patients at suspected risk for hereditary BC (who therefore needed to be sent to the Medical Genetics Unit of INT for complete evaluation).

The second phase of the project lasted 20 months, and included the enrollment and selection of patients in order to evaluate eligibility for genetic counseling.

The third and final phase was dedicated to data analysis. The education of dedicated operators continued during the period of enrollment and data analysis, with periodic meetings among oncologists, study coordinators, and geneticists. Personal genetic risk was defined for all patients attending genetic counseling, and an appropriate preventive program was discussed between the geneticist and the multidisciplinary team, according to each patient's needs and level of risk. If risk-reducing measures (i.e., mastectomy and/or adnexectomy) were included, the patient was then referred to a surgeon or gynecologist.

Case selection

All consecutive women with a diagnosis of BC attending the 2 departments of oncology for the first time were interviewed by a trained operator and provided informed consent for the study. Trained operators selected patients who were eligible for subsequent genetic counseling for risk evaluation on the basis of criteria defined by INT (Tab. I). These criteria take into account the number of family cases of BC and OC and age at diagnosis. They are in good accordance with international and widely accepted criteria, and overlap almost completely with BRCA genetic testing criteria (9, 10). During Medical Genetics Unit activity, the global use of these criteria led to a detection rate of pathogenic mutation of *BRCA1* and *BRCA2* genes exceeding 20% (5).

The interview was based on the collection of demographic data and a complete family history of cancer to at least the third degree of kinship. With the help of a trained operator, each suspected eligible patient completed a questionnaire about family history of cancer. Cases considered at risk for familial BC were discussed with a geneticist and then eventually referred for genetic counseling at INT. We also decided to refer patients with borderline eligibility criteria to a geneticist. During genetic counseling, the geneticists evaluated all patients and confirmed their eligibility for genetic testing.

Genetic counseling

Counseling comprises advising women about their risk of BC and what they can do about it, including the possibility of

TABLE I - Eligibility criteria for suspected hereditary breast/ovarian cancer

Regardless of family history, patients with:
- Breast cancer <36 y
- Breast cancer plus ovarian cancer at any age
- Breast cancer in male patients at any age
- Ovarian cancer ≤45 y
- Bilateral breast cancer ≤50 y

Patients with breast or ovarian cancer at any age with first-degree relatives with:
- Breast cancer <36 y
- Breast cancer plus ovarian cancer at any age
- Breast cancer in male patients at any age
- Ovarian cancer ≤45 y
- Bilateral breast cancer ≤50 y

Families (patient included) with:
- Two first-degree relatives[a] with:
  - Breast cancer ≤50 y
  - Breast cancer ≤50 y and bilateral breast cancer at any age
  - Breast cancer ≤50 y and ovarian cancer at any age
  - Breast cancer ≤50 y and male breast cancer at any age
  - Bilateral breast cancer at any age and ovarian cancer at any age
- Two first-degree relatives[a] with ovarian cancer at any age
- Three first-degree relatives[a] with breast cancer at any age

[a]First-degree relatives, and/or second-degree relatives if related by a male individual; maternal and paternal branch of the family should be considered separately; affected relatives must be first-degree and belong to the same branch of the family.

genetic testing. Women who undergo testing regarding *BRCA1* and *BRCA2* genes potentially face 3 issues: identification of a mutation that increases the risk of BC (pathogenic mutation), identification of a variant of unknown clinical significance (UV), or the absence of mutations and UV. Taking into account the actual limitations of genetic testing, the second and third types of results do not exclude a residual genetic risk because other BC- and OC-predisposing genes are mostly unknown.

BRCA1/BRCA2 gene mutation testing consisted of direct sequencing and multiplex ligation-dependent probe amplification to examine all coding exons, corresponding splice sites, and gross rearrangements of both genes.

Risk management

Once the genetic oncologic risk was defined, a multidisciplinary team (geneticist, oncologist, and surgeon) discussed the best therapeutic approach for each individual patient. Figure 1 shows a flowchart of the patients' course.

All proportions of patients (i.e., eligible patients as a fraction of total patients) are expressed as percentages, and a 95% confidence interval (95% CI) is provided for each.

Results

The initial phase of this project started in March 2010, with learning sessions to train 4 oncologists and 2 study coordinators

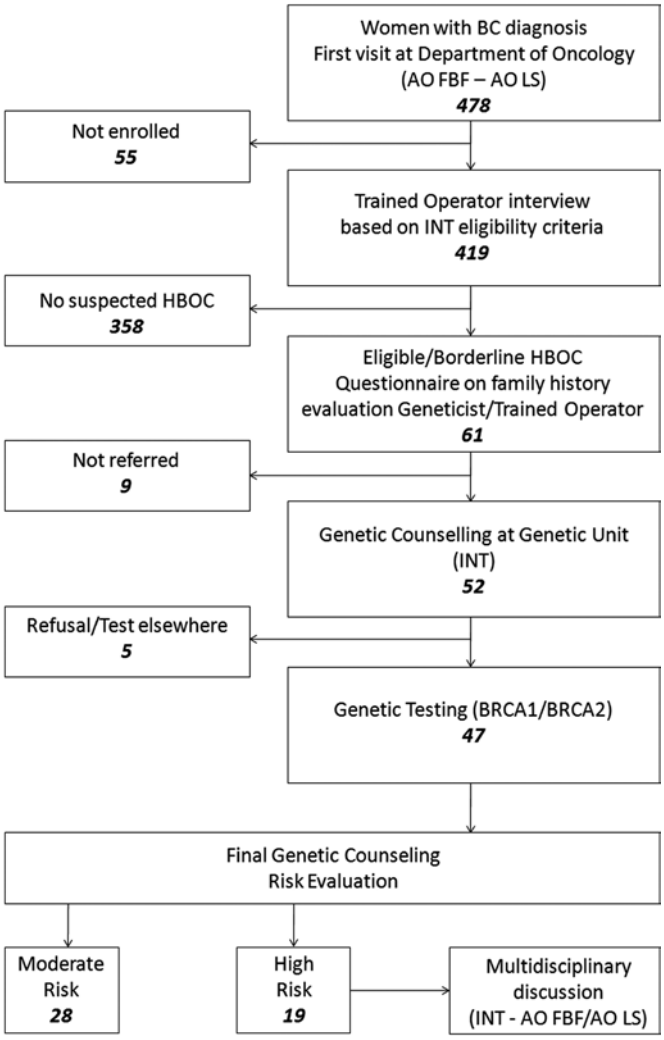

Fig. 1 - Flowchart of the patients' course. AO FBF = AO Fatebenefratelli & Oftalmico; AO LS = AO Luigi Sacco; BC = breast cancer; HBOC = hereditary breast/ovarian cancer; INT = Istituto Nazionale Tumori.

in the departments of oncology of the 2 general hospitals in Milan. During such meetings, the geneticist team explained with theoretical and practical sessions how to administer the questionnaire in order to evaluate patients' eligibility for a genetic test. Two meetings (one meeting for each department of oncology) were organized to present the project to other specialists involved in the management of high-risk patients, including geneticists, oncologists, surgeons, gynecologists, and radiologists.

From July 2010 to February 2012, 478 patients with diagnosed BC attended a first oncologic visit in one of the 2 departments of oncology. Of these, 419 (87.7%, 95% CI 0.84-0.9) were enrolled and participated in the project, and were interviewed by a trained operator. The other 55 patients (12.3%, 95% CI 0.096-0.156) were not enrolled in the study for the following reasons: refusal to provide informed consent, difficult geographic accessibility, seeking a second opinion only, and metastatic disease at diagnosis. Based on the selection criteria (Tab. I), a total of 61 of 419 patients (14.5%,

95% CI 0.115-0.183) were considered eligible for genetic counseling. Of these, 46 patients (10.9%, 95% CI 0.083-0.143) strictly met eligibility criteria, while the eligibility of 15 (3.6%, 95% CI 0.022-0.058) for genetic counseling and testing was considered borderline. Nine patients did not attend genetic counseling because of disease progression, refusal, or prior evaluation at other genetic centers.

Therefore, 52 patients were examined by the geneticist (12.4% of all patients enrolled in the project, 95% CI 0.096-0.159). In 47 cases, blood samples were obtained for the detection of germline mutations of *BRCA1* and *BRCA2* genes (4/52 patients rejected the procedure, and in one case the patient had already been tested elsewhere). Of the 47 tested patients, 7 (14.9%, 95% CI 0.074-0.277) had a pathogenic mutation in *BRCA1* or *BRCA2* gene, and 6 (12.8%, 95% CI 0.059-0.252) presented a variant of unknown significance in *BRCA1* or *BRCA2* gene. No *BRCA1/BRCA2* mutations were observed in the remaining 34 (72.3%, 95% CI 0.582-0.831) cases.

In 12 cases, although a pathogenic mutation of *BRCA1* or *BRCA2* was not detected, patients were classified as at high genetic risk of hereditary BC/OC because of a strong family history of cancer. Therefore, globally 19/47 patients (40.4%, 95% CI 0.276-0.547) were considered at high genetic risk. After a multidisciplinary discussion, targeted management (mastectomy versus lumpectomy + radiotherapy, close surveillance, and risk-reducing surgery for BC and OC) was discussed with each of these patients. The patients were therefore re-referred to their oncologists for follow-up and treatment. Enrolled patients were generally compliant and appreciated the availability of genetic counseling, although at a different center.

Discussion

Although BC is common, hereditary BC is not. Medical oncogenetics units are not widespread in every country, and oncogenetic counseling is not actually recommended to all patients with BC (9-12, 14). Therefore, the challenge is to identify patients who need to be referred and are most likely to benefit from oncogenetic counseling and testing. In fact, identification of patients with an increased risk for hereditary BC allows more tailored screening and further preventive interventions, as well as the involvement of family members in order to identify who has inherited familial risk. The project described in this article shows that it is feasible to provide initial clinical screening for the genetic assessment and analysis of patients with BC referred to the departments of oncology of 2 major hospitals in Milan. Through the proposed approach, only strictly or borderline eligible patients were referred for additional genetic counseling. Specifically, only 10.9% of patients enrolled in the study were selected, and this percentage increased to 14.5% when borderline eligible patients were included. These data may be considered in accord with those widely reported in the literature, since familial BC accounts for approximately 5%-10% of all BC cases (1, 2). Furthermore, the performance of this initial clinical screen by oncologists instead of geneticists resulted in a significantly reduced workload for the Genetics Unit of the National Cancer Institute of Milan, as well as the subsequent proper optimization of time and resources. This approach has allowed departments of oncology without a genetics unit to be able to guarantee proper genetic counseling to eligible patients with BC. It should be pointed out that genetic counselling is a long-term process; it is time-consuming, and patients with hereditary BC represent only a small fraction of all patients with BC. Therefore, oncogenetics units are not necessary in all oncology departments. A well-organized network of oncogenetics units/oncologic departments could be sufficient to cover the entire health care demand.

Various risk models are available to estimate the likelihood of genetic mutations. These include the Ontario Family History Assessment Tool, the Family History Screen-7, the Referral Screening Tool, the Pedigree Assessment Tools, and the Manchester scoring system. More complex risk models, such as Tyrer-Cuzik, BRCAPRO, BOADICEA, and COS, have also been developed (5, 16-18, 21). Although these models generally feature sensitivity exceeding 85%, results from clinical trials are controversial and their use in clinical practice varies widely (14). Therefore, as previously stated, they cannot function as a substitute for genetic counseling (5, 19). Appropriate risk assessment remains of fundamental importance to properly refer high-risk patients for additional genetic counseling, DNA testing, and risk-reducing strategies. Moreover, according to guidelines, oncogenetic counseling performed by trained genetics professionals is the ethical standard of care and testing without appropriate counseling must be avoided (9, 10).

In this scenario, the correct selection of patients who may benefit from genetic counseling and further management is fundamental, considering the low frequency of *BRCA1* and *BRCA2* gene mutations. In our project, within the first oncologic screening visit, a preliminary investigation of personal and family history was used as a filter to properly address the patients to a geneticist, and only 12.4% of patients with BC underwent genetic testing. Although the detection rate recorded in our study was only 14.9%, the number of cases analyzed was too small, and we emphasize that in the entire sample of families screened at INT, the criteria allowed a detection rate of at least 20%. However, nongenetic clinicians require correct and intensive training. In our project, oncologists were adequately trained to assess genetic risk following defined criteria, and collaboration between the departments of oncology and the INT Medical Genetic Unit was encouraged in order to build an effective path for high-risk patients. A recent survey of 1197 general practitioners and 1223 breast surgeons from the United Kingdom, the Netherlands, France, and Germany was conducted to assess behaviors of nongenetic health professionals towards at-risk patients and to verify their efficacy as gatekeepers regarding further genetic counseling (22). Interestingly, the study revealed great variability in clinicians' decisions, probably due to the lack of shared guidelines. Of note, the majority of general practitioners and breast surgeons stated that they would provide genetic risk assessment, without referring high-risk patients for proper genetic counseling. Moreover, a failure to correctly assess family history of the paternal line was evident in many cases. The outcome of the study highlights the need for adequate education regarding the use of risk assessment tools for clinicians who lack specific expertise in genetic assessment. Another survey conducted among Japanese gynecologic oncologists showed that although the majority of them

paid attention to hereditary BC, fewer than 1 in 5 doctors were able to provide counseling, 1 in 10 doctors provided printed information to high-risk patients, and 1 in 7 doctors recommended a visit to the department of genetics (23). Interestingly, the recommendation of genetic counseling and performance of genetic testing were dependent on whether an oncogenetics department was present in the institution. These data reflect the relative rarity of oncogenetics departments and the effect on decision-making by clinicians, who could fail to refer high-risk patients for genetic counseling. Our study demonstrated that this situation can be overcome through the creation of a network of geneticists and BC specialists.

In Emilia Romagna (another region of Italy), a project with a different design has been conducted (an approved regional protocol). All women who undergo screening mammography or ask for information from general practitioners/specialists complete a grid that defines their risk level according to National Institute for Health and Care Excellence guidelines. Women with a risk level ≥2 are referred to a breast unit for a brief initial genetic counseling session; from there, only women with a risk level of 3 are referred to a genetic unit for additional genetic counseling, and for genetic testing if confirmed to be eligible. Only a small proportion (567/182,915, 0.31%) of the screened population was referred to genetic counseling; of those referred, approximately 40%-60% were considered eligible for genetic testing (20). Considering costs and the limitations of genetic testing (i.e., most predisposing genes are unknown), genetic testing of an at-risk family must begin, whenever possible, from an affected index case. In fact, affected women are more likely to carry a mutation than healthy family members. Consequently, if the evaluated woman is healthy, affected family members have to be recruited to start family genetic testing. Conversely, our project was conducted directly on patients with BC, and relatives were subsequently involved.

A major issue for patients is anxiety related to the susceptibility to hereditary BC. Thus, even if they have not had any genetic testing or tested negative for *BRCA1/BRCA2* mutations, many patients may request more aggressive surgery or chemotherapy in the face of uncertain clinical indications in order to reduce their anxiety about recurrence (24, 25). In this context, the proper selection of patients with BC for additional genetic evaluation is even more important.

Schwartz et al (26) conducted a randomized trial of in-person versus telephone-based genetic counseling and reported that counseling can be effectively and efficiently delivered by phone in order to increase access and decrease costs. However, they subsequently reported that the overall increased access should be considered in light of the possibility that this may also lead to lower rates of testing among a subgroup of high-risk women (27). In fact, considering different cultural and ethnic background, not all women are suitable for telephone-based counseling. The information derived from risk communication requires a careful approach.

Notably, a model like the one we propose includes the possibility that, if necessary, genetic counseling and testing could be completed in a short period of time after BC diagnosis and could offer some patients the choice to modify subsequent surgical decisions. As Cortesi et al (28) have shown, genetic counseling and testing at the time of BC diagnosis, instead of after surgery, modifies the patient's attitude toward risk-reducing mastectomy in *BRCA* mutation carriers, increasing the rate of bilateral prophylactic mastectomy instead of conservative surgery and radiotherapy. In any case, numerous questions remain unanswered regarding the optimal management of BC risk in *BRCA1/BRCA2* mutation carriers, and careful evaluation of the positive and negative effects of the available options is needed (14, 29).

In conclusion, a good network between the departments of oncology of general hospitals and medical genetic units was effective in properly referring patients with high-risk BC for additional genetic counseling. The correct selection of potential mutated patients is recommended, especially if genetics units that offer genetic testing are few and widespread throughout a nation. A proper path for genetic evaluation in patients with BC may reduce unnecessary genetic counseling. We encourage collaboration among different specialties and institutions to improve clinical practice. Additional studies are required to better explore the effectiveness of an initial oncologic screening for genetic counseling in BC and its large-scale feasibility, in order to validate these preliminary findings.

Disclosures

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Conflict of interest: None.

References

1. Lalloo F, Evans DG. Familial breast cancer. Clin Genet. 2012;82(2):105-114.
2. Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015;33(4):304-311.
3. Chen S, Parmigiani G. Meta-analysis of *BRCA1* and *BRCA2* penetrance. J Clin Oncol. 2007;25(11):1329-1333.
4. Evans DG, Shenton A, Woodward E, Lalloo F, Howell A, Maher ER. Penetrance estimates for *BRCA1* and *BRCA2* based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. BMC Cancer. 2008;8(1):155.
5. Berrino J, Berrino F, Francisci S, et al. Estimate of the penetrance of BRCA mutation and the COS software for the assessment of BRCA mutation probability. Fam Cancer. 2015;14(1):117-128.
6. Couch FJ, Nathanson KL, Offit K. Two decades after BRCA: setting paradigms in personalized cancer care and prevention. Science. 2014;343(6178):1466-1470.
7. Robson M, Offit K. Clinical practice. Management of an inherited predisposition to breast cancer. N Engl J Med. 2007; 357(2):154-162.
8. NCCN Clinical Practice Guidelines. Breast Cancer Risk Reduction. Available at: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed September 3, 2015.
9. NCCN Clinical Practice Guidelines. Genetic/Familial High-Risk Assessment: Breast and Ovarian. Available at: http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed September 3, 2015.
10. FONCAM. Linee guida carcinoma eredo-familiare: Donne ad alto rischio per carcinoma mammario familiare: sorveglianza e trattamento. Available at: http://www.senologia.it/images/pdf/carcinoma%20eredo-familiare.pdf. Accessed June 21, 2014.

11. Evans DG, Graham J, O'Connell S, Arnold S, Fitzsimmons D. Familial breast cancer: summary of updated NICE guidance. BMJ. 2013;25;346:f3829.
12. Balmaña J, Díez O, Rubio IT, Cardoso F; ESMO Guidelines Working Group. *BRCA* in breast cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2011;22(Suppl 6):vi31-vi34.
13. Wideroff L, Vadaparampil ST, Greene MH, Taplin S, Olson L, Freedman AN. Hereditary breast/ovarian and colorectal cancer genetics knowledge in a national sample of US physicians. J Med Genet. 2005;42(10):749-755.
14. Nelson HD, Pappas M, Zakher B, Mitchell JP, Okinaka-Hu L, Fu R. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med. 2014;160(4):255-266.
15. Sutphen R, Davila B, Shappell H, et al. Real world experience with cancer genetic counseling via telephone. Fam Cancer. 2010;9(4):681-689.
16. Antoniou AC, Pharoah PD, McMullan G, et al. A comprehensive model for familial breast cancer incorporating *BRCA1*, *BRCA2* and other genes. Br J Cancer. 2002;86(1):76-83.
17. Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes *BRCA1* and *BRCA2*. Am J Hum Genet. 1998;62(1):145-158.
18. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004;23(7):1111-1130.
19. Varesco L, Viassolo V, Viel A, et al. Performance of BOADICEA and BRCAPRO genetic models and of empirical criteria based on cancer family history for predicting *BRCA* mutation carrier probabilities: a retrospective study in a sample of Italian cancer genetics clinics. Breast. 2013;22(6):1130-1135.
20. Sassoli De' Bianchi P. Finarelli AC, Baldassarri B, et al. Rischio eredo-familiare per tumore della mammella: il programma della Regione Emilia-Romagna. Available at: http://win.gisma.it/atti/torino2013/poster/sassoli_poster_gisma_2013.pdf. Accessed June 21, 2014.
21. Antoniou AC, Easton DF. Risk prediction models for familial breast cancer. Future Oncol. 2006;2(2):257-274.
22. Nippert I, Julian-Reynier C, Harris H, et al. Cancer risk communication, predictive testing and management in France, Germany, the Netherlands and the UK: general practitioners' and breast surgeons' current practice and preferred practice responsibilities. J Community Genet. 2014;5(1):69-79.
23. Tanabe N, Shikama A, Bando H, Satoh T, Shimizu C. A survey of the practice patterns of gynecologic oncologists dealing with hereditary cancer patients in Japan. Fam Cancer. 2014;13(3):489-498.
24. Katz SJ, Morrow M. Contralateral prophylactic mastectomy for breast cancer: addressing peace of mind. JAMA. 2013;310(8):793-794.
25. Meiser B, Butow P, Friedlander M, et al. Psychological impact of genetic testing in women from high-risk breast cancer families. Eur J Cancer. 2002;38(15):2025-2031.
26. Schwartz MD, Valdimarsdottir HB, Peshkin BN, et al. Randomized noninferiority trial of telephone versus in-person genetic counseling for hereditary breast and ovarian cancer. J Clin Oncol. 2014;32(7):618-626.
27. Butrick M, Kelly S, Peshkin BN, et al. Disparities in uptake of *BRCA1/2* genetic testing in a randomized trial of telephone counseling. Genet Med. 2015;17(6):467-475.
28. Cortesi L, Razzaboni E, Toss A, et al. A rapid genetic counselling and testing in newly diagnosed breast cancer is associated with high rate of risk-reducing mastectomy in *BRCA1/2*-positive Italian women. Ann Oncol. 2014;25(1):57-63.
29. Borreani C, Manoukian S, Bianchi E, et al. The psychological impact of breast and ovarian cancer preventive options in *BRCA1* and *BRCA2* mutation carriers. Clin Genet. 2014;85(1):7-15.