A regional population-based hereditary breast cancer screening tool in Italy: First 5-year results

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Abstract

Background: Up to 10% of individuals with breast cancer (BC) belong to families with hereditary syndromes. The aim of this study was to develop an instrument to identify individuals/families at high-hereditary risk for BC and offer dedicated surveillance programs according to different risks.

Methods: The instrument consisted of a primary questionnaire collecting history of BC and ovarian cancer (OC). This questionnaire was applied to women enrolled in...
1 | INTRODUCTION

Hereditary breast ovarian cancer (HBOC) can be defined as a genetic disorder in which breast and ovarian malignant tumors seem to cluster within families. The main factors that suggest a hereditary cancer predisposition syndrome are young age at cancer diagnosis, multiple tumors, bilateral tumors, presence of rare tumors, several cancer-affected relatives, autosomal dominant inheritance and, in some cases, ethnicity. Families with these characteristics should be referred to specialized hospital/centers that offer cancer risk assessment and genetic counseling.

In Italy, most cancer genetic services are largely distributed in the country but they are not regulated by the national health system rules. Therefore, there is limited knowledge regarding the prevalence of HBOC predisposition syndromes in the Italian population, which has already reached more than 60 million people. Moreover, considering the high probability of developing cancer in individuals with hereditary cancer predisposition and the fact that presymptomatic identification of at-risk individuals offers enormous potential for reducing cancer-related risk, a better understanding of the prevalence of hereditary cancer predisposition syndromes in Italy is imperative.

In this context, the goal of this study was to develop a pilot instrument for identifying individuals and families who are at risk for hereditary BC in a regional screening population-based sample from Emilia-Romagna, Italy.
could administer the same questionnaire in the case of positive family history.

2.3 | Primary screening questionnaire

The primary questionnaire was based on typical criteria for hereditary breast and ovarian cancer, that is, young age at onset, bilateral breast cancer (BC), association with ovarian cancer (OC) and relationship with other affected patients. These criteria were already considered as pathognomonic of hereditary breast cancer syndrome by Lynch.\(^\text{16}\) The questionnaire contained a grid that assigned a score from 0 to 2; women who reached the total score of $\geq 2$ were invited to ask for the Spoke evaluation. The grid was adopted since 2000, by the Biosciences Laboratory of Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), in Meldola, identifying 22\% of patients with BRCA1/2 mutations among families with characteristics of hereditary breast and ovarian cancer.\(^\text{17}\) This rate was considered cost-effective as indicated by the ASCO guidelines.\(^\text{18}\)

In addition, a personal or family history of male BC, of BC and OC in the family or in the same patient, of early onset BC ($\leq 35$ years), of bilateral BC at $\leq 50$ years, of non-mucinous and not borderline sporadic OC, of two first-degree relatives affected by BC, of which one arisen at $\leq 40$ years or bilateral, and of triple negative BC ($\leq 60$ years), represented a direct criterion for Hub evaluation. The majority of the primary questionnaires was administered by the radiology technicians at the single unit of the RBCSP, uploading the grid score whenever the patient entered into the mammography room. All questionnaires were collected on a dedicated software program that calculates the score in real time and collects the results on a specific single database for each patient. Also, GPs had the same grid uploaded on their regional electronic health system and autonomously calculated the score when the patient was visited for the first time. The grid was also held by other specialists such as gynecologists, oncologists, and radiologists, but they rarely offered this evaluation to their patients. No informed consent was signed at this time. No central evaluation was performed to calculate the score obtained by different patients.

The questionnaire is shown in Table 1.

2.4 | Spoke model

All healthy women with score $\geq 2$ or patients affected with BC at the age ranging between 36 and 40 years were invited to refer to their own Spoke center. In case of women attending the RBCSP eligible for further assessment, they received a letter with the mammography result and the phone number for calling the own Spoke center. In case of eligibility defined by GPs or other specialists, the appropriate Spoke center phone number was directly given to the patient. Totally 13 centers in Emilia-Romagna were accredited as Spoke centers. At the Spoke Center, either geneticists or oncologists trained in oncogenetic counseling collected information on the cancer family history and drew the pedigree. In both cases a specific informed consent was obtained aimed to receive family history information. The risk of BC was calculated with the Tyrer-Cuzick program.\(^\text{19}\)

2.5 | Tyrer-Cuzick risk calculation

The Tyrer-Cuzick evaluation collects personal information regarding woman’s age, menarche’s age, height and

| Age at Onset | BC | OC |
|-------------|----|----|
|             | $<40 \text{ y}$ | $40-49 \text{ y} \text{ Bilateral}$ | $40-49 \text{ y Monolateral}$ | $50-59 \text{ y}$ | $\geq 60 \text{ y}$ | Every |
| Woman       | 2  | 2  | 1  | 1  | 0  | 2  |
| Mother      | 2  | 2  | 1  | 1  | 0  | 1  |
| Sister      | 2  | 2  | 1  | 1  | 0  | 1  |
| Daughter    | 2  | 2  | 1  | 1  | 0  | 1  |
| Paternal Grandmother | 2  | 2  | 1  | 1  | 0  | 1  |
| Paternal Aunt | 2  | 2  | 1  | 1  | 0  | 1  |
| Maternal Grandmother | 1  | 1  | 1  | 0  | 0  | 1  |
| Maternal Aunt | 1  | 1  | 1  | 0  | 0  | 1  |
| Relative with MBC | 2  | 2  | 2  | 2  | 2  | -  |
| Cousin (daughter of father’s brother) | 1  | 0  | 0  | 0  | 0  | 1  |
| Nephew      | 1  | 1  | 1  | 0  | 0  | 1  |

Abbreviations: BC, breast cancer; MBC, male breast cancer; OC, ovarian cancer.
weight measurements, parity, previous breast lesions, and menopausal status. Further information with regard to family history of BC or OC in the relatives is also collected. The final calculation provides the 10-year risk and the life-time risk for BC in individual and general population, respectively.

Women with a life-time risk of developing BC at most 1 time more than general population were considered at low risk (LR) and were offered RBCSP. Women with a risk ranging between two and three times more than general population, were considered at intermediate profile and followed with an annual mammogram, associated with ultrasound, in the case of dense breasts since 40 until 45 years and then referred to the RBCSP. Women with a risk more than three times (profile 3 or high) were evaluated for referring to the Hub center with the aim to perform gene test analysis.

This model assessment was chosen among different risk calculators, that is, Gail, Claus, Ford, and manual model. It looked to be likely the most sensitive model to select women at high risk, apart from the lack of male breast cancer family history evaluation.20 However, women who were sent to the Hub center were further evaluated for BRCA1/2 genetic testing according to the Modena criteria.21

2.6 | Hub model

Four regional Hub centers were accounted in Emilia-Romagna. The referral to the Hub centers was proposed in the case of profile 3 at the Spoke evaluation or in the case of direct criteria at the primary screening, as previously mentioned.

At the Hub evaluation, a family history of:

1. Early Onset BC
2. BC and OC in the same patient or in other members
3. Male BC
4. Triple Negative BC at ≤60 years
5. OC not mucinous not borderline
6. Two or more BC in the family with a first-degree relationship each other and young age at onset (≤40 years) or bilateral BC

was considered eligible for genetic testing and the most indicative affected patient in the family was invited to undergo pretest oncogenic sessions, aimed to perform BRCA1/2 analysis. In a period of 3-4 weeks, the BRCA1/2 results were released along with a posttest genetic session. When a positive test was found, relatives of the index case were invited to undergo specific mutation analysis. All positive women already affected or not, were offered a screening protocol with six-monthly breast ultrasound since 18 to 69 years, annual breast MRI since 25 until 74 years, annual mammogram since 35 to 69 years and biennial in the 70-74 years range. In the case of bilateral mastectomy, only breast ultrasound every six months was proposed since the residual cancer risk remains equal to 4%-5% and no guidelines are provided for breast MRI screening utility in this group of women. Breast ultrasound seemed to have a good ratio between cost and effectiveness rather than a solely clinical examination in order to recognize little foci of cancer upon the protheses. For OC screening, a six-monthly transvaginal ultrasound plus Ca.125 marker dosage was proposed, when patients refused to consider the prophylactic oophorectomy or when they were too young to offer. The six-monthly transvaginal ultrasound plus Ca.125 marker dosage was offered on the basis of data obtained by a phase II study in which OC screening performed more frequently than annually with prompt surgical intervention seemed to offer a better chance of early-stage detection in high-risk women.22 In the case of previous OC, only Ca.125 marker dosage every six months was offered.14

However, when criteria or individual disposable for gene testing lacked, a dedicated screening protocol was offered to women with different risk profiles; in the case of high risk (profile 3) it starts at 25 years of age with six-monthly ultrasound until 49, annual mammogram since 35 to 69 years and then biennial until 74 years. For LR and intermediate risk (IR), the screening protocol was described above.14 The surveillance protocol is detailed in Table 2. The process mapping of patients through Spoke and Hub screening procedure is shown in Figure 1.

2.7 | Genetic testing

Genetic testing for identifying BRCA1 and BRCA2 mutations included the Next Generation Sequencing (NGS) on the entire codifying sequence and the Multiplex Ligation Polymerase Analysis (MLPA) for rearrangements of BRCA1/2 gene. The variants were divided, according to the ENIGMA classification, in five classes: C5 and C4 were considered as positive results and carriers were followed as previous reported. In the case of C3, C2, and C1 results, the screening was based on the risk profile defined by the Tyrer-Cuzick risk model. For the C3 classes, a customized pipeline for variant calling was questioned every month in order to find an eventual reclassification.

3 | RESULTS

3.1 | Primary screening questionnaire

From January 2012 to December 2016, among 660 040 women participating in the RBCSP, 659 747 women answered the questionnaire, whereas 293 (0.04%) refused to
compile the same. Totally, 22,289 women (3.5%) received the letter and were invited to refer to the own Spoke center. By dividing all women in quintiles for age from 45 to 74 years, 8,518 of those invited to call on the Spoke evaluation ranged between 45 and 49 years (38.2%). Detailed information on classes of age, number, and percentage of patients referred to the Spoke center by RBCSP can be found in Table 3.

### 3.2 | Spoke evaluation

Among all, 22,289 women were referred to the Spoke by the RBCSP, only 5,615 (25.2%) phoned for having a Spoke evaluation. All requests were held in about 2 weeks. In addition, 2,258 (19.4%) women were referred by GPs and 3,794 (32.5%) by specialists to the Spoke centers, with the remaining women (48.1%) coming from RBCSP. Women referred by GPs were, in about one-quarter of cases, younger than 35 years of age (560/2,258, 24.8%), whereas specialists identified more patients in the age 40-44 years (887/3,794, 23.4%). Totally, 11,667 women arrived at the Spoke centers. Among those, 330 refused to complete the assessment, and the remaining 11,337 women were evaluated. Totally, 4,627 women evaluated were considered eligible for the Hub referral (40.8%), whereas 6,710 (59.2%) had an IR or LR profile. Data on source, age and risk profile are reported in Table 4.

Among all 11,667 women who made an appointment at the Spoke center, 1,400 (12%) were very young (<35 years), 2,570 (22%) ranged between 35 and 44 years of age, whereas 7,697 (66%) were aged from 45 to 74 years. Out of 3,970 women aged less than 45 years, 2,449 (61.7%) were sent at the Spoke Center by specialists, 1,472 by GPs (37.1%) and 49 by RBCSP (1.2%).

### 3.3 | Hub evaluation

Out of 4,627 women assessed as HR (profile 3), only 2,815 (60.8%) accepted the Hub evaluation. The most proportion of women eligible for the Hub evaluation was identified by GPs (1,205/2,241, 53.8%), followed by specialists (1,768/3,684, 48.0%) and finally by RBCSP (1,654/5,412, 30.6%) as shown in Table 5.

Additionally, following the seven criteria considered as enough for the Hub referral at the primary questionnaire, 2,739 women were sent directly, without the Spoke assessment. Totally, 5,554 women received a Hub evaluation. In 2,342 cases (42.2%), a genetic test was performed, whereas 3,212 (57.8%) women did not meet criteria for BRCA1/2 analysis. Five hundred and forty-four women (23.2%), resulted BRCA1/2 mutation carriers. As expected, among BRCA1/2 mutated women, the highest rate of mutations was found in very young women, aged less than 30 years (35%); the positive rate decreased until 18% in women ranging between 55 and 59 years. Women without mutation ascertained were classified as having profiles 1, 2, or 3 according to the previous Tyrer-Cuzick risk calculation. Table 6 reports data on women who underwent a genetic test. The number of patients along the process mapping is depicted in Figure 2.

### 4 | DISCUSSION

Our model is an effective tool to identify individuals/families at risk for BC, in a population-based sample. In fact, nearly all women attending the RBCSP, with the exception of 293 cases (0.04%), compiled the primary questionnaire, also taking into account the change of family history along time. This
multistep tool, proposed by a healthcare staff, provides more awareness about hereditary BC than a recently developed nurse navigator approach, by which a low participation of screening patients requesting HBOC education and evaluation occurred (9%).

Hoskins et al. previously validated a tool for each case of BC or OC arbitrarily selected, weighting more points for patients with features associated with a higher probability that a BRCA mutation is present: early age of BC diagnosis, OC diagnosis, male BC in the family. The authors analyzed a total of 3906 women without a personal history of BC presenting for a screening mammogram at a community hospital, identifying 86 (2.2%) women with a family history indicative of a high probability (>10%) that a BRCA mutation was present. The percentage of at-risk families was superimposable to our selection model in which 22 289 (3.5%) women were eligible for a secondary screening step.

FIGURE 1 The flowchart of patients through the Spoke and Hub screening procedure. BC, breast cancer; GP, general practitioner; HR, high risk; IR, intermediate risk; LR, low risk; RBCSP, Regional Breast Cancer Screening Program
An added value of this multistep process has been provided by GPs and specialists involvement. A recent systematic review on 40 studies published between 1996 and 2017, has evaluated the effects on patients of genetic cancer risk assessment in general practice.30 A variety of testing and screening tools were available for genetic cancer risk assessment in general practice, principally for breast-ovarian, but GPs often reported low knowledge about hereditary cancers even if, time along, they were increasingly interested. In our experience too, the lowest percentage of women sent to the Spoke evaluation, came from GPs (19.4%) with respect to specialists (32.5%) and RBCSP (48.1%). However, GPs and

### Table 3
Women refer to Spoke evaluation by RBCSP according to the age

| Total No | Age | % |
|----------|-----|---|
| 8518     | 45-49 | 38.2 |
| 3836     | 50-54 | 17.2 |
| 2856     | 55-59 | 12.8 |
| 2511     | 60-64 | 11.3 |
| 2354     | 65-69 | 10.6 |
| 2214     | 70-74 | 9.9 |
| 22 289   | All   | 100 |

### Table 4
Characteristics of women arrived at the Spoke centers

| Age | GPs | Specialists | RBCSP | Total | % | Refuse | LR | IR | HR |
|-----|-----|-------------|-------|-------|---|--------|----|----|----|
| <35 | 560 | 840         | 0     | 1400  | 12| 32     | 237| 424| 707|
| 35-39| 403 | 722         | 0     | 1125  | 9.6| 26     | 191| 365| 543|
| 40-44| 509 | 887         | 49    | 1445  | 12.4| 35     | 309| 453| 648|
| 45-49| 246 | 432         | 1832  | 2510  | 21.5| 96     | 835| 663| 916|
| 50-54| 214 | 369         | 1153  | 1736  | 14.9| 48     | 612| 423| 653|
| 55-59| 140 | 234         | 861   | 1235  | 10.6| 28     | 458| 260| 489|
| 60-64| 100 | 146         | 743   | 989   | 8.5 | 26     | 409| 234| 320|
| 65-69| 65  | 102         | 599   | 766   | 6.6 | 30     | 339| 180| 217|
| 70-74| 21  | 62          | 378   | 461   | 4   | 9      | 210| 108| 134|
| Total| 2258| 3794        | 5615  | 11 667| 100| 330    | 3600| 3110| 4627|

Abbreviations: HR, High Risk; IR, Intermediate Risk; LR, Low Risk.

### Table 5
Characteristics of women assessed at the Hub centers

| Age | GPs | Specialists | RBCSP | Total | Hub referral % |
|-----|-----|-------------|-------|-------|----------------|
| <35 | 556 | 289         | 52.0  | 909   | 52.0          | 52.0  | 776   | 443  | 57.1  | 2241 | 1205  | 53.8 |
| 35-44| 812 | 418         | 51.5  | 1552  | 45.0          | 1320  | 651   | 49.3  | 3684  | 1768  | 48.0 |
| 45-74| 0   | 0           | 0     | 48    | 39.6          | 5364  | 1635  | 30.5  | 5412  | 1654  | 30.6 |
| Total| 1368| 717         | 52.4  | 2509  | 47.5          | 7460  | 2729  | 36.6  | 11 337| 4627  | 40.8 |

### Table 6
Characteristics of women underwent BRCA1/2 gene analysis

| Age | Nº LR | % LR | Nº IR | % IR | Nº HR | % HR | Nº BRCA1/2 | % BRCA1/2 | Total |
|-----|-------|------|-------|------|-------|------|------------|-----------|-------|
| <25 | 44    | 40   | 23    | 21   | 8     | 7    | 36         | 32        | 111   |
| 25-29| 23   | 23   | 19    | 19   | 24    | 24   | 35         | 35        | 101   |
| 30-34| 44   | 25   | 24    | 14   | 58    | 33   | 49         | 28        | 175   |
| 35-39| 68   | 24   | 38    | 13   | 115   | 41   | 62         | 22        | 283   |
| 40-44| 64   | 21   | 44    | 15   | 115   | 38   | 80         | 26        | 303   |
| 45-49| 83   | 26   | 45    | 14   | 123   | 39   | 66         | 21        | 317   |
| 50-54| 74   | 26   | 24    | 8    | 132   | 46   | 58         | 20        | 288   |
| 55-59| 57   | 26   | 15    | 7    | 107   | 49   | 38         | 18        | 217   |
| 60-64| 41   | 22   | 14    | 8    | 92    | 50   | 37         | 20        | 184   |
| 65-69| 40   | 25   | 3     | 2    | 82    | 51   | 35         | 22        | 160   |
| 70-74| 51   | 25   | 3     | 1    | 101   | 50   | 48         | 24        | 203   |
| Total| 589  | 25.1 | 252   | 10.8 | 957   | 40.9 | 544        | 23.2      | 2342  |
specialists were needed to identify young high-risk individuals, since the RBCSP begins at 45 years. In fact, 24.8% of women referred to the Spoke centers by GPs were younger than 35 years, such as women sent by specialists were mostly inclusive between 40 and 44 years (23.4%). As already seen in a recent paper that investigated the young women's perceptions regarding communication with healthcare providers about BC risk, people aged 18-29 years asked more than doctors about their risk, whereas women in the age group between 30 and 44 years were likely queried by GPs about their family history.31 Totally, only 34% of all women evaluated at the Spoke centers aged less than 45 years and this could represent a critical issue, in order to offer a very preventive strategy in young individuals at hereditary-HR for BC.

Another weakness was shown by the low rate of adherence to the Spoke evaluation among women eligible by the RBCSP (25.2%). The low rate of adherence to the second screening step could depend by the fact that the invitation was provided by the same letter in which the mammogram result was delivered. Probably by this way, women focused their attention on negative mammogram results rather than on the deepening of their BC risk. An attempt to recover women eligible for the second screening step has been performed at the subsequent round, where the grid was repeated with a little increased rate of acceptance (0.3%). In a Brazilian study performed on 20 000 women attending the mammogram screening program, a questionnaire regarding BC family history was proposed.
and 3121 (15.6%) were invited to the second phase of the study by a direct approach or by letter or by phone. The first two modalities of invitation provided a very low rate of adhesion (11.4% and 16%, respectively), lower than our rate of acceptance. The highest rate of adherence was reached by the phone call (72.6%), demonstrating the validity for this approach for identifying families at risk for BC.32 However, the telephone approach needs dedicated personnel, and expensive costs for a large regional screening program. Also, considering the recall carried out at the subsequent round, we concluded that women who did not attend the Spoke assessment did not want to know their BC risk, with respect to the nondirectiveness defined as procedures that promote and enhance the autonomy and self-control of patients.33

Nevertheless, among 11 337 women who received the Spoke evaluation, about 40% were HR, whereas 60% were considered as IR or LR. All LR (3600, 31.8%) and young IR women (aged 45 years or more, that is, 1868 equal to 16.6%), did not receive any personal prevention screening program but were invited to attend the RBCSP starting at 45 years. Only IR women aged less than 45 years (1294, 11.4%) and all HR individuals (4627, 40.8%) were offered a dedicated screening program for no hereditary risk of BC. Totally, the regional Spoke assessment identified about half of the women (5921, 52.2%) who needed an intensive screening program. A recent analysis performed on 2177 women at HR and IR followed at the Modena spoke center showed a BC detection rate of 8.5 and 16.1 × 1000 persons-years, respectively, which clearly increases in comparison with the BC detection rate provided by the RBCSP.34 This data confirms the usefulness of an intensive screening program for at-risk women and justifies a massive effort to identify the various parameters.

Once again, only 60% of women sent to the Hub centers accepted to be evaluated, but the rate of adherence was increased with respect to the previous step, underlying more interest toward the knowledge of hereditary conditions. Of notice, 49% of women evaluated at the Hub centers skipped the Spoke assessment according to specific criteria at the primary questionnaire. Among 5554 women evaluated at the Hub centers, 42.8% were eligible for gene testing and 49% of women evaluated at the Hub centers skipped the Spoke assessment according to specific criteria at the primary questionnaire. Among 5554 women evaluated at the Hub centers, 42.8% were eligible for gene testing and 23.2% resulted positive. This multistep approach provides a long patient journey, deriving a very high benefit in terms of BRCA mutation carrier identification. In fact, the step-by-step process is able to select a shrinking number of women to be investigated by gene test analysis: this approach looks to be really cost-effective, although a recent study comparing BRCA1, BRCA2, PALB2, RAD51C, RAD51D, and BRIP1 analysis performed in selected and unselected women, seems to prevent more BC and OC in the general population, without previous selection.35 However, our mutation rate is in line with other series based on different eligibility criteria for HBOC, as referred in a recent review where the BRCA1/2 mutation rate in early onset BC, triple negative BC, bilateral BC, and family history of BC is about 30%.36 It also means that direct criteria for the Hub evaluation represent a significant way to collect women who are potentially at risk for HBOC syndrome, avoiding a multistep process and saving time and important costs.

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CONFLICT OF INTEREST
The authors declare that they have no financial disclosure and conflict of interests.

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Data available on request due to privacy/ethical restrictions.

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REFERENCES
1. Samadder NJ, Giridhar KV, Baffy N, Riegert-Johnson D, Couch FJ. Hereditary cancer syndromes—a primer on diagnosis and management: part 1: breast-ovarian cancer syndromes. Mayo Clin Proc. 2019;94(6):1084-1098.
2. Gómez-Flores-Ramos L, Álvarez-Gómez RM, Villarreal-Garza C, Wegman-Ostrosky T, Mohar A. Breast cancer genetics in young women: What do we know? Mutat Res. 2017;774:33-45.
3. Cybulski C, Nazarali S, Narod SA. Multiple primary cancers as a guide to heritability. Int J Cancer. 2014;135(8):1756-1763.
4. Heisey R, Carroll JC. Identification and management of women with a family history of breast cancer: practical guide for clinicians. Can Fam Physician. 2016;62(10):799-803.
5. Eng C. Mendelian genetics of rare—and not so rare—cancers. Ann N Y Acad Sci. 2010;1214:70-82.
6. Frank TS. Hereditary cancer syndromes. Arch Pathol Lab Med. 2001;125(1):85-90.
7. Cox DM, Nelson KL, Clytone M, Collins DL. Hereditary cancer screening: case reports and review of literature on ten Ashkenazi Jewish founder mutations. Mol Genet Genomic Med. 2018;6(6):1236-1242.
8. Hampel H, Bennett RL, Buchanan A, Pearlman R, Wissner GL. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2015;17(1):70-87.
9. Hilgart JS, Coles B, Iredale R. Cancer genetic risk assessment for individuals at risk of familial breast cancer. Cochrane Database Syst Rev. 2012;2:CD003721.
10. Kyne G, Maxwell S, Brameld K, Harrison K, Goldblatt J, O’Leary P. Compliance with professional guidelines with reference to familial cancer services. Aust N Z J Public Health. 2011;35(3):226-230.
11. D’Andrea E, Marzuillo C, De Vito C, et al. Which BRCA genetic testing programs are ready for implementation in healthcare care? A systematic review of economic evaluations. Genet Med. 2016;18(12):1171-1180.
12. Annuario Statistico Italiano. 2019. ISBN 978-88-458-2003-8. http://www.istat.it/it/archivio
13. Jatoi I. Risk-reducing options for women with a hereditary breast cancer predisposition. Eur J Breast Health. 2018;14(4):189-193.
14. Ferretti S, Naldoni C, Baldessari B, et al. Protocollo assistenziale nelle donne a rischio ereditario di tumore della mammella e/o ovaio. Regione Emilia-Romagna II edizione Anno. 2016;91:1-56.
32. Campacci N, de Lima JO, Carvalho AL, et al. Identification of hereditary cancer in the general population: development and validation of a screening questionnaire for obtaining the family history of cancer. *Cancer Med.* 2017;6(12):3014-3024.

33. Kessler S. Psychological aspects of genetic counseling. XI. Nondirectiveness revisited. *Am J Med Genet.* 1997;72(2):164-171.

34. Cortesi L, Canossi B, Battista R, et al. Breast ultrasonography (BU) in the screening protocol for women at hereditary-familial risk of breast cancer: has the time come to rethink the role of BU according to different risk categories? *Int J Cancer.* 2019;144(5):1001-1009.

35. Manchanda R, Patel S, Gordeev VS, et al. Cost-effectiveness of population-based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutation testing in unselected general population women. *J Natl Cancer Inst.* 2018;110(7):714-725.

36. Valencia OM, Samuel SE, Viscusi RK, Riall TS, Neumayer LA, Aziz H. The role of genetic testing in patients with breast cancer: a review. *JAMA Surg.* 2017;152(6):589-594.

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