Cascade testing in Italian Hereditary Breast Ovarian Cancer families: a missed opportunity for cancer prevention?

Lucia Trevisan
IRCCS Ospedale Policlinico San Martino
Lea Godino
IRCCS Azienda Ospedaliero-Universitaria di Bologna
Linda Battistuzzi
IRCCS Ospedale Policlinico San Martino
Giovanni Innella
Università di Bologna
Elena Luppi
Università di Bologna
Giulia Buzzatti
IRCCS Ospedale Policlinico San Martino
Viviana Gismondi
IRCCS Ospedale Policlinico San Martino
Eva Blondeaux (evablondeaux@gmail.com)
IRCCS Ospedale Policlinico San Martino
Luigina Ada Bonelli
IRCCS Ospedale Policlinico San Martino
Daniela Turchetti
Università di Bologna
Liliana Varesco
IRCCS Ospedale Policlinico San Martino

Research Article

Keywords: cascade testing, BRCA1/2, HBOC, pathogenic variant

Posted Date: July 13th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3153904/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Familial Cancer on November 16th, 2023. See the published version at https://doi.org/10.1007/s10689-023-00349-w.

Abstract

Healthy carriers of *BRCA1/2* pathogenic variants (PVs) may benefit from risk-reducing measures of proven efficacy. The main approach to identify these individuals is cascade testing, and strategies to support this complex process are under investigation. In Italy, cascade testing has received little attention; therefore, we analyzed the uptake and characteristics of *BRCA1/2* cascade testing in families diagnosed with HBOC at two Italian genetics centers between 2017 and 2019.

All consanguineous family members who were older than 18 years of age at data collection time and who could be involved in the first step of cascade testing (i.e., all the living relatives closest to the proband) were included. In addition to first-degree relatives, individuals who were second-, third- or fourth-degree relatives were included if the closest relative(s) was/were deceased.

Overall, 213 families were included (103, Genoa; 110, Bologna). Most probands were women affected by breast and/or ovarian cancer (86.4%, Genoa; 84.5%, Bologna), and the branch segregating the PV was known/suspected in most families (62.1%, Genoa; 60.9%, Bologna). Overall, the uptake of cascade testing was low (22%, Genoa; 16%, Bologna). It was associated with female gender (OR = 5.74, Genoa; OR = 3.33, Bologna), age < 30 years (OR = 10.31, Genoa; OR = 4.84, Bologna), first-degree relationship with the proband (OR = 20,94, Genoa; OR = 12.44, Bologna) and segregation of the PV in the paternal branch (OR = 2.90, Genoa; OR = 2.54, Bologna). These real-world data may be important to inform the design and implementation of strategies aimed at improving the uptake of HBOC cascade testing in Italy.

Introduction

The Hereditary Breast-Ovarian Cancer (HBOC) syndrome is the most common hereditary cancer syndrome and is generally associated with pathogenic variants (PV) in the *BRCA1* and *BRCA2* genes. Because PVs in these genes confer a substantial risk of developing breast and ovarian cancer, identifying healthy *BRCA1/2* carriers and offering them risk-reducing measures of proven efficacy is an important cancer preventive intervention [1]. This holds especially true for i) young women and ii) ovarian cancer. Indeed, female *BRCA1/2* PV carriers already have a risk of breast cancer (BC) that is several times that of their non-*BRCA1/2* peers when they are younger than 40 years, well before the youngest recommended age for BC screening in the general population [2]. Moreover, female *BRCA1/2* PV carriers have such a high risk of developing ovarian cancer (OC) (40% in the case of *BRCA1*, 20% for *BRCA2*) that, absent any proven secondary prevention options, salpingo-oophorectomy is recommended around 40 years of age, once the desired family size is reached [2]. Recently, *ad hoc* preventive options have also been suggested for *BRCA1/2* male carriers, given their higher risk of aggressive prostate cancer [3].

Currently, *BRCA1/2* testing is mainly performed in cancer patients to orient their treatment and because, for preventive purposes, testing a cancer patient is more informative than testing a healthy relative in the same family.

To identify healthy *BRCA1/2* PV carriers, some have advocated for population screening, which however raises several concerns [4]. The main strategy being implemented thus remains cascade testing, which is the process of sequentially testing the relatives of the first recognized carrier within a given family, i.e., the proband, starting from her/his closest relatives. This process is now increasingly viewed as an emerging opportunity for population-wide cancer prevention [5]. It has been estimated that assuming a 7% prevalence of PVs across cancer types, an average family size of 3 per generation, and 15% of incident patients with cancers in the United States undergoing germline testing, 10 years would be enough to identify all individuals with a PV in 18 cancer susceptibility genes if 70% of all first-, second- and third-degree at risk relatives were tested for familial pathogenic variants [4].

It is not surprising, therefore, that cascade testing of the *BRCA1/2* genes is unvaryingly recommended by clinical guidelines [6, 7]. Yet, this strategy remains vastly underutilized: a recent systematic review and meta-analysis showed that, when information about genetic risk was shared with relatives by the proband, only 30% (24–37, 95% CI) of those relatives underwent *BRCA1/2* cascade testing [8].

Considering these difficulties and the potential role that cascade testing could have in cancer prevention, several studies have proposed strategies to support it and improve the uptake of testing [9]. Guidelines have been developed in some countries aimed at improving procedures to inform family members [10], but no standard protocols have been established.

In Italy, the issue of cascade testing seems to have received little attention [11, 12] and no recommendations exist to guide clinical practice.

In order to inform future action, we analyzed the uptake of cascade testing of the *BRCA1/2* genes and its characteristics in 213 families diagnosed with HBOC at two Italian genetics centers between 2017 and 2019.

Materials and Methods

Study design and setting

This is an observational, retrospective, multicenter study that took place at two Italian genetic centers: the Unit of Hereditary Cancer (UHC) of the IRCCS Ospedale Policlinico San Martino (HSM), Genoa, and the Unit of Medical Genetics (UMG) of the IRCCS Azienda Ospedaliero-Universitaria of Bologna.

Genetic counseling protocol

The process of genetic counseling included in-person pre-test and post-test counseling, according to standard procedures. Of notice, part of the genetic test disclosure session was dedicated to discussing the importance of the genetic test result for relatives and identifying at-risk family members eligible for the first step of cascade testing. If intrafamilial communication problems were reported, and if considered helpful by the proband, an information letter for the family members was also provided to support information sharing.

Study population

Probands

We enrolled cancer patients and cancer-free individuals who were found to carry a PV after undergoing a complete *BRCA1* and *BRCA2* genetic test between May 2017 and December 2019 at the UHC, Genoa or at the UMG, Bologna.

At the Genoa center, only probands who consented to participate in the Ligurian *BRCA* Registry (Ligurian Ethics Committee, approval n. 002REG2017), who spoke Italian, and who had *BRCA* test and post-test counseling at the UHC were included in the study. At the Bologna center, only probands who consented to participate in the REGIO Registry (the registry of individuals undergoing cancer risk assessment at the Bologna center, approved by the CE-AVEC Ethics Board n.272/2022/Oss/AOUBo on 14th April 2022) and who had *BRCA* test and post-test counseling at the UMG were included in the study.

From the clinical records of probands, we retrieved the following information: gender; date of birth; disease status; type of cancer(s); age at cancer diagnosis; genetic test result; date of genetic test result disclosure; pedigree; cancer family history; branch of the family suspected for HBOC.

Relatives

Relatives of probands included in the study were identified from the pedigrees that were built during counseling sessions.

All consanguineous family members who were older than 18 years of age at the time of data collection (September 2022) and who could be involved in the first step of cascade testing (i.e., the living relatives closest to the proband) were included. In addition to first-degree relatives (offspring, siblings), individuals who were second-, third- or fourth-degree relatives were included if the closest relative(s) was/were deceased. The proband's parents were evaluated separately as they were also tested to gain information about PV segregation in the family.

In a small number of cases, the individual involved in the first step of cascade testing was not the closest available relative but his/her offspring: all these individuals were included as a separate group. Also, in some families an additional individual underwent a complete *BRCA* test for a diagnostic reason: these relatives were considered separately as extra probands, and those among their close relatives who were eligible for cascade testing were also included as a separate group.

Individuals of both maternal and paternal branches of the family were included if no indication of PV segregation was available. When the family branch segregating the PV was known or suspected, only relatives from that side of the family were included.

For the families in which PV segregation was unknown, the probability of carrying the family PV was derived from the genetic distance. When the family branch segregating the variant was known/suspected, genetic distance and information about known (or presumed) carrier status of the parents were used to calculate the probability of carrying the family PV. Examples of individuals included in the study and their risk of carrying the family PV for pedigrees with unknown or known/suspected family segregation branch are reported in Supplementary Fig. 1.

For each relative, the following information was collected: gender; date of birth; disease status; degree of relationship with the proband; genetic test result, if any; date of genetic test result disclosure.

When only the year of birth was known, June 30th was used as the day of birth. When the year of birth was also unknown, it was estimated from other information reported in the pedigree (e.g., the age of closest relatives).

Data Analysis

Data were entered anonymously into a dedicated database and were analyzed using the SPSS software version 26. Frequencies, percentages (for categorical variables), means or medians, as appropriate, and interquartile ranges (for continuous variables) were used as descriptive statistics. The Chi-square test was used to compare differences among categorical variables. A binary multivariate logistic analysis was applied to estimate the probability of *BRCA* testing among relatives and the odds ratio (OR) and its 95% confidence intervals (95% CI) were calculated. When the 95% CI of the reported ORs did not include 1.0, the association with the outcome of each specific category, as compared to the reference stratum, was considered statistically significant. The OR estimates were adjusted (adjOR) for the following variables: gender, age of the relative (< 30 years, 30–70 years, > 70 years), age of the proband at testing (< 40, 40–49, 50–59, 60–69, ≥ 70 years), proband's reason for testing (prevention, medical treatment, prophylactic mastectomy), relative degree (first, second, third-fourth), family segregation branch (maternal, paternal, unknown).

To estimate the number of PV carriers who were undetected, individuals with a 50% and 25% risk of carrying the family PV were selected.

Results

Between May 2017 and December 2019, 129 probands who carried a *BRCA* PV (80 in *BRCA1* and 49 in *BRCA2*) were enrolled in the *BRCA* registry of the Liguria Region at the Genoa center. Among the 129 probands, 26 did not meet enrollment criteria: three had not had genetic counseling at HSM, one carried a *de novo BRCA* PV, one did not speak Italian, 21 had *BRCA* testing years before the *BRCA* registry was established. In the same time period, 110 probands carrying *BRCA* PV (54 in *BRCA1* and 56 in *BRCA2*) were included in the REGIO registry at Bologna center; all were eligible for the study.

Overall, 213 families were included in the study (103 from the Genoa center; 110 from Bologna). The main characteristics of the probands are reported in Table 1. At both centers, most probands were women affected by BC and/or OC (86.4% Genoa; 84.5% Bologna), and the branch segregating the family PV was known/suspected in the majority of families (62.1% Genoa; 60.9% Bologna). Twenty-four percent of female probands in Genoa and 27.2% of female probands in Bologna had *BRCA* testing to inform the decision about prophylactic mastectomy at primary surgery for BC.

The number of relatives according to their degree of relationship with the proband, and the total number of tests performed are reported in Supplementary Table 1. Including parents, 681 and 731 relatives were reported at the Genoa and Bologna center, respectively. Among the Genoa families, the 103 probands reported 67 living parents, 39 of whom (58.2%) had targeted *BRCA* testing after a PV was identified in the proband: they were 7/12 fathers (58.3%), 14/21 mothers (66.6%) and 9/17 (52.9%) couples of parents. Among the Bologna families, the 110 probands reported 78 living parents, 23 of whom (29.5%) had targeted *BRCA* test: they were 0/11 fathers (0.0%), 1/17 mothers (5.9%) and 11/25 (44.0%) couples of parents.

Overall, similar mean numbers of relatives per family were recorded at the two centers (6.61 Genoa; 6.65 Bologna) but a higher mean number of tests per family was reported for the Genoa families (1.71) compared with the Bologna families (1.27).

Parents were excluded from the main analyses as their tests were required to establish PV segregation in the family. The number of tests performed by the other relatives and PV detection rates according to center, degree of relationship with the proband (first- to fourth- degree) and gender are reported in Table 2.

Overall, the uptake of cascade testing was low (22% Genoa; 16% Bologna). Among first- and second-degree relatives, 118/ 353 (33.4%) and 105/ 466 (22.5%) had cascade tests at the Genoa and Bologna centers, respectively. A higher number of cascade tests was performed in first-degree female relatives at the Genoa center (80 of 136, 58.9%) *vs.* the Bologna center (52 of 104, 50.0%). Among first-degree relatives, offspring had cascade tests more often than siblings (53 of 77, 68.8% vs 52 of 129, 40.3% in Genoa; 54 of 92, 58.7% vs 31 of 125, 24.8% in Bologna). Supplementary Table 2 reports the uptake of testing and test results among female relatives aged 30-70 years according to their degree of relationship with the proband: the majority of first-degree female relatives aged 30-70 years were tested [64 of 88 (72.7%) in Genoa and 41 of 76 (53.9%) in Bologna] but only a minority of second-degree female relatives of the same age range were [7 of 35 (20.0%) in Genoa and 9 of 69 (13.0%) in Bologna].

Table 3 shows the probability of having cascade testing among relatives: at both centers, it was associated with female gender (OR= 5.78, in Genoa; OR= 3.39 in Bologna), age below 30 years (OR=10.31 in Genoa and OR= 5.30 in Bologna), first-degree relationship with the proband (OR= 20.94 in Genoa; OR= 13.19 in Bologna) and segregation of the VP in the paternal branch of the family (OR= 2.90 in Genoa and OR= 2.55, Bologna). At the Genoa center, the uptake of testing decreased with increasing proband age while at the Bologna center, the opposite was observed. The relatives of the probands who had the test to decide about prophylactic mastectomy at primary surgery in the Genoa center had a two-fold increased probability of having cascade testing compared to the relatives of the probands who had the test for preventive reasons (OR= 2.17; 95% CI 0.96 – 4.89); the opposite was observed at the Bologna center (OR=0.44, 95% CI 0.22-0.86).

The distribution of the time elapsed between the disclosure of test results to the proband and cascade testing in relatives is shown in Figure 1. The median time elapsed was similar at the two centers (4 months, IQR 1.00-8.75 months, Genoa; 5 months, IQR 1.75 – 8.00, Bologna).

Among individuals with a 50% and 25% risk of carrying the family PV, an estimate of PV carriers who were undetected due to the low cascade testing uptake is shown in Table 4. Among the 50% risk individuals (i.e., first-degree and siblings of the parent carrying the family PV in the group of families where the PV segregation was known/suspected; first-degrees only in families where the PV segregation was unknown), most PV carriers were missed: 74/122 (60.6%) and 115/167 (68.8%) at the Genoa and Bologna centers, respectively. Given that enrichment of non-carrier women due to BC and OC deaths among carriers is expected, the observed detection rate was used to estimate the number of missed carriers among women who were not tested.

Discussion

The main finding of this study is that, overall, 78% of the relatives who were eligible for *BRCA* testing in Genoa and 84% of those who were eligible in Bologna did not have cascade testing. Uptake remained low among first- and second-degree relatives: 118/353 (33.4%) and 105/466 (22.5%) at the Genoa and Bologna centers, respectively.

Although these results are concerning, they are consistent with the literature [8]. In addition, our figure is probably an underestimation of the actual family uptake, as some members of the families included in the study may live outside the catchment areas of the Genoa and Bologna centers and may thus have been tested elsewhere. This may also explain in part the higher uptake that was observed in families seen at the Genoa center, which is the only HBOC referral genetics center in the region of Liguria, while the region of Emilia-Romagna has four HBOC referral genetics centers, including the one in Bologna [13], making it possible that relatives of probands tested in Bologna decided to contact one of the other referral centers for cascade testing. However, the geographic distribution of the families is unlikely to entirely explain why most relatives did not pursue *BRCA* testing.

The probability of having cascade testing among relatives was associated with female gender, first-degree relationship with the proband, paternal segregation of the VP, and age < 30 years. Female gender and first-degree relationship with the proband are known to influence HBOC cascade testing, as reported in the recent systematic review by Frey et al. [8]. In families affected by HBOC, the gender difference is explained to some extent by the fact that the benefits of being recognized as a *BRCA* carrier have long been known for women, while men were primarily involved in cascade testing for the benefit of their daughters (if they had

any). Also, the importance of the degree of relationship with the proband is somewhat explained by the fact that cascade testing is mediated by the proband, who may have less difficulty initiating conversations about genetic risk with closer relatives. In a survey of young adults, the majority (58.5%) reported having received the information about the family VP from one or both parents in an unplanned conversation [14]. Interestingly, both in this and in other studies [15, 16] offspring had testing significantly more often than siblings. Also, both in our analysis and in the study by Gauna Cristaldo and colleagues [17], the uptake of cascade testing was higher when the family PV segregated in the paternal branch. The explanation of this observation is unclear as parent of origin effect on intrafamilial communication is determined by several factors [18]. One hypothesis might be that, in some cultural contexts, masculinity is associated with notions of family protection, leading to male family members strongly encouraging relatives to seek out testing. Also, mothers of young women who may have inherited a PV from their father may support daughters' decision to have testing more actively than women who may have passed on the PV themselves, owing to feelings of guilt and/or by their disease status. In addition, when the carrier is a severely ill woman, daughters may be discouraged from pursuing testing by the fear of learning that they have inherited the cause of the disease.

Unlike previous studies [17, 19, 20], we found that relatives younger than 30 years old were more likely to have cascade testing. This finding may be explained at least in part by what was observed in a study on intrafamilial communication of genetic information in Italian women belonging to families affected by HBOC, to which the Genoa and Bologna centers both contributed: among participants, younger women were more likely than other probands to attend genetic counseling sessions with a family member and to talk about those sessions with their relatives [11]. Moreover, qualitative interviews previously conducted with young adults undergoing cascade testing in Bologna showed that the appointment for pre-test counseling was often made by their parents, suggesting a more active role of the family in promoting test uptake in the younger population [21]. However, proband age had a different impact on the uptake of cascade testing: at the Genoa center, the uptake of testing decreased with increasing proband age while at the Bologna center the opposite was observed. We found no information in the literature that could help us interpret this finding, which remains unexplained and may need specific assessment.

Finally, the mean time elapsed between the disclosure of test results to the proband and cascade testing of relatives was 4–5 months. A similar finding was reported by others [19], suggesting that most of the probands' efforts at sharing genetic risk information with their relatives take place relatively soon after the disclosure of test results.

Because this is an observational, retrospective study, we were not able to explore what the actual barriers to HBOC cascade testing may have been in the families seen at our two centers. However, to the best of our knowledge, this is the first study to report on the uptake of *BRCA* cascade testing in Italy. In addition, as far as we are aware, most Italian genetics centers where clinical *BRCA* testing is performed adopt the same approach followed at our two centers, i.e., cascade testing is discussed with probands during post-test counseling and is mentioned in the letter to the family, but no further action to promote information sharing within families is taken afterward. Therefore, this analysis provides real-world data that may be important to inform the design and implementation of strategies aimed at improving the uptake of HBOC cascade testing in Italy.

Based on the 30% uptake among first- and second-degree relatives observed in this study, most healthy individuals belonging to the hundreds of HBOC families identified in Italy every year will not be able to access genetic counseling and testing, and, among those healthy individuals, the ones who carry *BRCA* PVs will miss the opportunity of potentially life-saving preventive measures. Therefore, it is crucial that research efforts and innovations in clinical practice be directed at improving cascade testing in our country (Fig. 2).

In terms of clinical practice, measures that have been introduced in other countries can be adapted to the Italian situation, possibly within the framework of shared processes involving the interested national scientific societies e.g., SIGU (the Italian Society of Human Genetics) and AIFET (the Italian Association of Familial and Hereditary Cancer) and Italian patient advocacy groups (e.g., aBRCAdabra, a national association of *BRCA* PV carriers and their families) to ensure consistency and equity. For example, in 2013 the Dutch Society for Clinical Genetics produced a guideline on cascade testing for clinical geneticists that considered patient perspectives and legal constraints [9]. In brief, the following recommendations were made: a) the involvement of family members must be comprehensively explored at an early stage of genetic counseling; b) the primary responsibility for the communication of information lies with the proband. To support the communication process written information for all cases is to be provided. A separate "family letter" is sent to the patient to be distributed among family members; c) if necessary, in cases in

which relatives will not be contacted by the proband, a pro-active role can and should be adopted by the clinical geneticist; d) the patient should be offered support for the process of informing relatives. This support can include follow-up counseling by phone. Recently, Menko et al. [22] assessed the impact of these recommendations in 40 HBOC families and found that the uptake of cascade testing in first- and second-degree relatives was nearly 50%. These authors suggested that tailored approaches considering specific family needs should be introduced to further improve cascade screening. From the proband perspective, narrative data suggest that geneticists should be more directive in encouraging probands to share genetic risk information with their relatives, as a more straightforward approach than is usually adopted may help patients understand the importance of their role [23]. In addition, a study on 30 years' experience at a genetics center in the UK [24] reporting three cascade tests per positive diagnostic test (vs 1.7 cascade tests per family in our study) suggests that family registries and recall systems are useful tools to facilitate cascade testing. Finally, HBOC cascade testing should be explicitly mentioned as one of the objectives of the National Prevention Plan of the Italian Public Health Care System, which presently includes the identification of *BRCA* carriers but does not mention cascade testing [25].

In terms of research efforts, studies on family information sharing and pilot interventions should be promoted to understand the forces at work that can be addressed in future Italian multicenter/national interventions, as several barriers at different levels of cascade screening exist that must be considered and removed, some of which have yet to be fully understood [9, 26]. For example, the Swiss multicenter CASCADE study is producing evidence on probands' intention to inform relatives, the preference for patient-mediated versus provider direct communication, and reasons for forgoing cascade testing in a cohort of HBOC and Lynch syndrome at-risk relatives [23, 27, 28]. These findings may be used to build interventions that consider attitudes and preferences of the Swiss population and health providers. Well-described feasibility studies on cascade screening that include proactive interventions like direct contact by health providers are ongoing in other countries [29, 30]. Finally, new models should be explored in the design of pilot implementation studies in Italy, considering i) the emerging role of mainstream HBOC testing in our country, in which pre-test and post-test information to cancer patients eligible for *BRCA* testing is mainly provided by healthcare professionals who do not have a background in genetics, and ii) insufficient staffing levels at Italian cancer genetics centers (partly due to the fact that the genetic counsellor profession is not recognized in Italy). To address these limitations, networking approaches in which geneticists share the responsibility of cascade testing programs with oncologists and other suitably trained professionals involved in HBOC high-risk prevention (e.g., breast screening/surgeon, gynecologists) could be usefully explored.

Declarations

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

ACKNOWLEDGMENTS

None.

AUTHOR CONTRIBUTION STATEMENT

LT, LG, GI, EL and VG were responsible for data acquisition, manuscript revision, approval of final version and agreed to be accountable for all aspects of the work.

LB, GB, and EB were responsible for result interpretation, manuscript revision, approval of final version and agreed to be accountable for all aspects of the work.

LAB, DT and LV were responsible for conception and design of the study, data acquisition, manuscript drafting, approval of final version and agreed to be accountable for all aspects of the work.

LAB, DT and LV had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All the authors gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

This work was supported by grants from Italian Ministry of Health (Ricerca Corrente) to the IRCCS Ospedale Policlinico San Martino, Genoa, Italy.

ETHICAL APPROVAL

At the Genoa center, no specific ethics approval was required for this study as, by providing their written consent to be included in the Ligurian *BRCA* registry, individuals gave permission to retrieve information from their clinical records for research purposes related to HBOC. The Ligurian *BRCA* registry was approved by the Ligurian Ethics Committee (approval n. 002REG2017).

At the Bologna center, theREGIO (Registro mono-istituzionale di individui sottoposti a valutazione del rischio genetico oncologico) Registry was approved by the CEAVEC Ethics Board (approval n.272/2022/Oss/AOUBo, 14th April 2022).

COMPETING INTERESTS

Eva Blondeaux reports research grant (to the Institution) from Gilead Science. All the other authors declare no conflict of interest.

References

1. Yoshida R (2021) Hereditary breast and ovarian cancer (HBOC): review of its molecular characteristics, screening, treatment, and prognosis. Breast Cancer 28:1167–1180. https://doi.org/10.1007/s12282-020-01148-2
2. Kuchenbaecker KB, Hopper JL, Barnes DR et al (2017) Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers. JAMA 317:2402. https://doi.org/10.1001/jama.2017.7112
3. Giri VN, Knudsen KE, Kelly WK et al (2020) Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol 38:2798–2811. https://doi.org/10.1200/JCO.20.00046
4. Offit K, Tkachuk KA, Stadler ZK et al (2020) Cascading After Peridiagnostic Cancer Genetic Testing: An Alternative to Population-Based Screening. J Clin Oncol 38:1398–1408. https://doi.org/10.1200/JCO.19.02010
5. Kurian AW, Katz SJ (2020) Emerging Opportunity of Cascade Genetic Testing for Population-Wide Cancer Prevention and Control. J Clin Oncol 38:1371–1374. https://doi.org/10.1200/JCO.20.00140
6. Forbes C, Fayter D, de Kock S, Quek RG (2019) A systematic review of international guidelines and recommendations for the genetic screening, diagnosis, genetic counseling, and treatment of BRCA-mutated breast cancer. Cancer Manag Res 11:2321–2337. https://doi.org/10.2147/CMAR.S189627
7. Sessa C, Balmaña J, Bober SL et al (2023) Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. Ann Oncol 34:33–47. https://doi.org/10.1016/j.annonc.2022.10.004
8. Frey MK, Ahsan MD, Bergeron H et al (2022) Cascade Testing for Hereditary Cancer Syndromes: Should We Move Toward Direct Relative Contact? A Systematic Review and Meta-Analysis. J Clin Oncol 40:4129–4143. https://doi.org/10.1200/JCO.22.00303
9. Whitaker KD, Obeid E, Daly MB, Hall MJ (2021) Cascade Genetic Testing for Hereditary Cancer Risk: An Underutilized Tool for Cancer Prevention. JCO Precis Oncol 5:1387–1396. https://doi.org/10.1200/PO.21.00163
10. Menko FH, Aalfs CM, Henneman L et al (2013) Informing family members of individuals with Lynch syndrome: a guideline for clinical geneticists. Fam Cancer 12:319–324. https://doi.org/10.1007/s10689-013-9636-9
11. Di Pietro ML, Zaçe D, Orfino A et al (2021) Intrafamilial communication of hereditary breast and ovarian cancer genetic information in Italian women: towards a personalised approach. Eur J Hum Genet 29:250–261. https://doi.org/10.1038/s41431-020-00723-7
12. Ongaro G, Petrocchi S, Calvello M et al (2022) Psychological Determinants of Men's Adherence to Cascade Screening for BRCA1/2. Curr Oncol 29:2490–2503. https://doi.org/10.3390/curroncol29040203
13. Cortesi L, Baldassarri B, Ferretti S et al (2020) A regional population-based hereditary breast cancer screening tool in Italy: First 5-year results. Cancer Med 9:2579–2589. https://doi.org/10.1002/cam4.2824

14. Godino L, Turchetti D, Jackson L et al (2019) Presymptomatic genetic testing for hereditary cancer in young adults: a survey of young adults and parents. Eur J Hum Genet 27:291–299. https://doi.org/10.1038/s41431-018-0262-8
15. Cody N, Green A, McDevitt T, Lynch SA (2008) Cascade screening in BRCA1/2 mutation carriers. Ir Med J 101:140–142
16. Jeong GW, Shin W, Lee DO et al (2021) Uptake of Family-Specific Mutation Genetic Testing Among Relatives of Patients with Ovarian Cancer with BRCA1 or BRCA2 Mutation. Cancer Res Treat 53:207–211. https://doi.org/10.4143/crt.2020.364
17. Gauna Cristaldo FB, Touzani R, Apostolidis T et al (2019) Uptake of genetic counseling among adult children of BRCA1/2 mutation carriers in France. Psychooncology 28:1894–1900. https://doi.org/10.1002/pon.5169
18. Dwyer AA, Hesse-Biber S, Flynn B, Remick S (2020) Parent of Origin Effects on Family Communication of Risk in BRCA + Women: A Qualitative Investigation of Human Factors in Cascade Screening. Cancers (Basel) 12:2316. https://doi.org/10.3390/cancers12082316
19. Sanz J, Ramón y Cajal T, Torres A et al (2010) Uptake of predictive testing among relatives of BRCA1 and BRCA2 families: a multicenter study in northeastern Spain. Fam Cancer 9:297–304. https://doi.org/10.1007/s10689-009-9313-1
20. Finlay E, Stopfer JE, Burlingame E et al (2008) Factors determining dissemination of results and uptake of genetic testing in families with known BRCA1/2 mutations. Genet Test 12:81–91. https://doi.org/10.1089/gte.2007.0037
21. Godino L, Jackson L, Turchetti D et al (2018) Decision making and experiences of young adults undergoing presymptomatic genetic testing for familial cancer: a longitudinal grounded theory study. Eur J Hum Genet 26:44–53. https://doi.org/10.1038/s41431-017-0030-1
22. Menko FH, Jeanson KN, Bleiker EMA et al (2020) The uptake of predictive DNA testing in 40 families with a pathogenic BRCA1/BRCA2 variant. An evaluation of the proband-mediated procedure. Eur J Hum Genet 28:1020–1027. https://doi.org/10.1038/s41431-020-0618-8
23. Pedrazzani C, Aceti M, Schweighoffer R et al (2022) The Communication Chain of Genetic Risk: Analyses of Narrative Data Exploring Proband-Provider and Proband-Family Communication in Hereditary Breast and Ovarian Cancer. J Pers Med 12:1249. https://doi.org/10.3390/jpm12081249
24. Woodward ER, Green K, Burghel GJ et al (2022) 30 year experience of index case identification and outcomes of cascade testing in high-risk breast and colorectal cancer predisposition genes. Eur J Hum Genet 30:413–419. https://doi.org/10.1038/s41431-021-01011-8
25. Piano nazionale della Prevenzione. https://www.salute.gov.it/portale/prevenzione/homePrevenzione.jsp. Accessed 11 May 2023
26. Roberts MC, Dotson WD, DeVore CS et al (2018) Delivery Of Cascade Screening For Hereditary Conditions: A Scoping Review Of The Literature. Health Aff (Millwood) 37:801–808. https://doi.org/10.1377/hlthaff.2017.1630
27. Sarki M, Ming C, Aceti M et al (2022) Relatives from Hereditary Breast and Ovarian Cancer and Lynch Syndrome Families Forgoing Genetic Testing: Findings from the Swiss CASCADE Cohort. J Pers Med 12:1740. https://doi.org/10.3390/jpm12101740
28. Sarki M, Ming C, Aissaoui S et al (2022) Intention to Inform Relatives, Rates of Cascade Testing, and Preference for Patient-Mediated Communication in Families Concerned with Hereditary Breast and Ovarian Cancer and Lynch Syndrome: The Swiss CASCADE Cohort. Cancers (Basel) 14:1636. https://doi.org/10.3390/cancers14071636
29. Cragun D, Beckstead J, Farmer M et al (2021) IMProving care After inherited Cancer Testing (IMPACT) study: protocol of a randomized trial evaluating the efficacy of two interventions designed to improve cancer risk management and family communication of genetic test results. BMC Cancer 21:1099. https://doi.org/10.1186/s12885-021-08822-4
30. Blasi PR, Scrol A, Anderson ML et al (2022) Feasibility, acceptability, and limited efficacy of health system-led familial risk notification: protocol for a mixed-methods evaluation. Pilot Feasibility Stud 8:174. https://doi.org/10.1186/s40814-022-01142-9

Tables

Table 1. Main characteristics of probands according to gender in the two study populations						
	Genoa			Bologna		
Characteristics	Females	Males	Total	Females	Males	Total
	96	7	103	103	7	110
Median age at testing (IQR)	52.0 (40.2-63.7)	69 (62.0-78.0)	53.0 (41.0-66.0)	52.0 (43.0-64.0)	64.0 (58.0-71.0)	54.0 (44.0-64.0)
Cancer [1]						
None	6	1	7	1	0	1
Breast	54[a]	0	54	56	4	60
Breast + ovary	8	0	8	11	0	11
Ovary	27[b]	NA	27	26	NA	26
Pancreas	1	2[c]	3	2	2	4
Prostate	NA	4[d]	4	NA	1	1
BRCA mutation						
BRCA1	58	2	60	54	0	54
BRCA2	38	5	43	49	7	56
Family segregation branch						
Maternal	37	1	37	30	2	32
Paternal	25	2	27	33	2	35
Unknown	34[e]	4	38	40	3	43
Reason for testing						
Secondary prevention	32	2	34	76	4	80
Prophylactic mastectomy	23	0	23	0	0	0
Medical treatment	41	5	43	27	3	30
N. relatives[f] (mean/family)	578 (6.02)	36 (5.14)	614 (5.99)	614 (5.96)	39 (5.71)	653 (5.94)
Females	302 (3.14)	22 (3.14)	324 (3.14)	310 (3.01)	20 (3.00)	330 (3.01)
Males	276 (2.87)	14 (2.00)	290 (2.81)	277 (2.69)	19 (2.71)	296 (2.69)
Gender not reported				27 (0.26)	0	27 (0.24)

[1] when two or more cancers had been diagnosed in one patient, the most recent was considered as the index cancer

[a] 10 cases of bilateral breast cancer and 1 case of breast cancer +condrosarcoma

[b] 1 case of ovarian cancer + colorectal cancer

[c] 1 case pancreatic cancer + prostate cancer and 1 case of pancreatic cancer +breast cancer

[d] 1 case of prostate cancer + breast cancer

[e] both family branches were suspected

[f] parents are excluded

Table 2. Number of tests performed by the relatives and pathogenic variants detected

Center	Age (yrs)	Females			Males			Total		
Family degree										
	(median,IQR)	N.	N. test (%)	N. pathogenic variants	N.	N. test (%)	N. pathogenic variants	N.	N. test (%)	N. pathogenic variants
Genoa **First**	**47.0 (36.0-60.0)**	**120**	**80 (66.7)**	**33**	**86**	**25 (29.1)**	**13**	**206**	**105 (51.0)**	**46**
Offspring	35.0 (36.0-43.0)	49	40 (81.6)	19	28	13 (46.4)	7	77	53 (68.8)	26
Siblings	55.0 (46.0-65.0)	71	40 (56.4)	14	58	12 (20.7)	6	129	52 (40.3)	20
Bologna **First**	**46.0 (32.5-59.0)**	**100**	**52 (52)**	**24**	**117**	**33 (28.2)**	**22**	**217**	**85 (39.2)**	**46**
Offspring	34.0 (24.0-44.0)	45	32 (71.1)	18	47	22 (46.8)	15	92	54 (58.7)	33
Siblings	54.0 (44.0-66.0)	55	20 (36.4)	6	70	11 (15.7)	7	125	31 (24.8)	13
Genoa **Second**	**71.0 (54-80.75)**	**78**	**10 (12.8)**	**3**	**69**	**3 (4.3)**	**1**	**147**	**13 (8.8)**	**4**
Grandparent	83, 87	-	-		2	0	-	2	0	-
Aunt/uncle	77.0 (68.0-82.2)	57	3 (5.3)	0	49	2 (4.1)	1	106	5 (4.7)	1
Niece/nephew	47.0 (41.0-52.0)	20	6 (30.0)	3	17	1 (5.9)	0	37	7 (18.9)	3
Half-sib	67F, 65M	1	1 (100.0)	0	1	0 (0.0)	-	2	1 (50.0)	0
Bologna **Second**	**60.0 (71.0-69.0)**	**145**	**14 (9.6)**	**4**	**104**	**6(5.8)**	**5**	**249**	**20 (8.0)**	**9**
Grand-parent	89.5 (86.7-93.0)	3	0	-	3	0	-	6	0	-
Aunt/uncle[1]	73.5 (65.0-80.0)	115	5 (4.3)	2	85	4 (4.7)	3	200	9 (4.5)	5
Niece/nephew	50.5 (41.7-59.0)	23	6 (26.1)	0	15	2 (13.3)	2	38	8 (21.0)	2
Half-sib	40.0 (37.5-47.5)	4	3	2	1	0	-	5	3 (60.0)	2
Genoa **Third-**	**59.0 (52-**	**114**	**9 (7.9)**	**1**	**126**	**4**	**3**	**240**	**13**	**4**

Fourth	**67.7)**					**(3.2)**			**(5.4)**	
Great-aunt/uncle	82.0 (79.0-85.0)	3	1 (33.3)	1	2	0 (0.0)	0	5	1 (20.0)	1
First cousin	59.0 (52.0-67.0)	111	8 (7.2)	0	124	4 (3.3)	3	235	12 (5.1)	3
Second cousin	59.0 (53.2-68.0)	12	4 (33.3)	1	8	1 (12.5)	0	20	5 (25.0)	1
Bologna **Third - Fourth**	**56.0 (49.0-64.0)**	**85**	**11 (12.9)**	**5**	**75**	**1 (1.3)**	**0**	**260**	**11**	**5**
Great-aunt/uncle[2]	85.0 (81.7-88.2)	0	-	-	10	0	-	10	0	-
First cousin[3]	56.0 (49.0-64.0)	83	10 (12.0)	4	65	1 (1.5)	0	148	11 (7.4)	4
Second cousin	48, 61	2	1 (50.0)	1	0	-	-	2	1 (50.0)	1
Genoa **All degrees**	58.0 (47.0-69.0)	324	103 (31.9)	38	289	33 (11.5)	17	613	136 (22.2)	55
Bologna **All degrees**	60.0 (46.0-72.0)	330	77 (23.3)	33	296	40 (3.5)	27	626	104 (16.6)	60

Table 3. Relative and proband characteristics that affected the uptake of BRCA testing

	Genoa				Bologna			
Covariates	N.tested/total	OR	95% CI	P	N.tested/total	OR	95% CI	P
Gender (F vs M)								
Males	34/286 (11.9)	1 ref			40/296 (13.5)	1 ref		
Females	98/319 (31.0)	5.78	3.26 - 10.25	0.000	77/330 (23.3)	3.39	2.04 - 5.65	<0.0001
Age class of relatives				0.001§				0.002§
<30	21/39 (58.3)	10.31	2.63-40.41	0.001	18/44 (40.9)	5.30	1.86-15.13	0.002
30-70	106/424 (25.0)	8.56	2.84-25.79	0.000	90/420 (21.4)	4.03	1.82-8.96	0.001
70+	5/139 (3.6)	1 ref			9/162 (5.6)	1 ref		
Age class of probands				0.014§				0.026§
<40	25/71 (35.2)	1.17	0.39-3.55	0.777	6/82 (7.3)	0.21	0.07-0.68	0.009
40-49	14/96 (14.6)	0.28	0.09-0.81	0.020	17/141 (12.1)	0.45	0.20-1.02	0.057
50-59	41/180 (22.8)	0.51	0.20-1.30	0.161	41/192 (21.4)	0.96	0.47-1.97	0.915
60-69	35/174 (20.1)	0.40	0.16-1.00	0.05	26/122 (21.3)	0.57	0.27-1.23	0.156
70+	17/81 (21.0)	1 ref			27/89 (30.3)	1 ref		
Proband's reason for testing				0.051§				0.053
Prevention	47/220 (21.4)	1 ref			62/259 (23.9)	1 ref		
Medical treatment	50/275 (18.2)	0.80	0.43 - 1.475	0.471	36/174 (20.7)	0.95	0.55-1.64	0.850
Prophylactic mastectomy	35/108 (32.7)	2.17	0.96 – 4.89	0.062	19/174 (9.8)	0.44	0.22-0.86	0.017
Relative degree				0.000§				0.000§
First	104/205 (50.7)	20.94	10.52-41.68	0.000	85/217 (36.2)	13.19	6.20-28.09	0.000
Second	11/145 (7.6)	1.35	0.55-3.32	0.516	20/249 (8.0)	2.47	1.05-	0.038

							5.80		
Third - fourth	17/252 (6.7)	1 ref		0.000	12/160 (7.5)	1 ref			
Family segregation branch				0.008§					0.011§
Unknown	42/280 (15.0)	1 ref			47/277 (17.0)	1 ref			
Maternal	52/198 (26.3)	2.18	1.16-4.11	0.015	35/168 (20.8)	1.59	0.88-2.86	0.125	
Paternal	38/124 (30.6)	2.90	1.41-5.99	0.004	35/181 (19.3)	2.55	1.38-4.71	0.003	
§ chi-square test for heterogeneity over the covariate classes									

Table 4. Number of tests performed among relatives according to the risk of being a BRCA pathogenic variant carrier and estimate of the pathogenic variants potentially undetected among relatives who did not have the BRCA test

	Genoa						Bologna					
	Females*		Males		Total		Females*		Males		Total	
	50%	25%	50%	25%	50%	25%	50%	25%	50%	25%	50%	25%
n. individuals	162	92	114	95	276	187	165	140	167	104	332	244
n. tests	84	14	27	5	111	19	59	17	36	3	95	20
n. pathogenic variants	34	3	14	3	48	6	28	4	24	0	52	7
n. individuals not tested	78	78	87	90	165	168	106	123	131	101	237	224
n. pathogenic variants potentially lost	31	16	43	22	74	41	50	28	65	50	115	78

* For female relatives the observed percentage of positive tests was used to estimate the number of missed carriers (figures are rounded down)

Figures

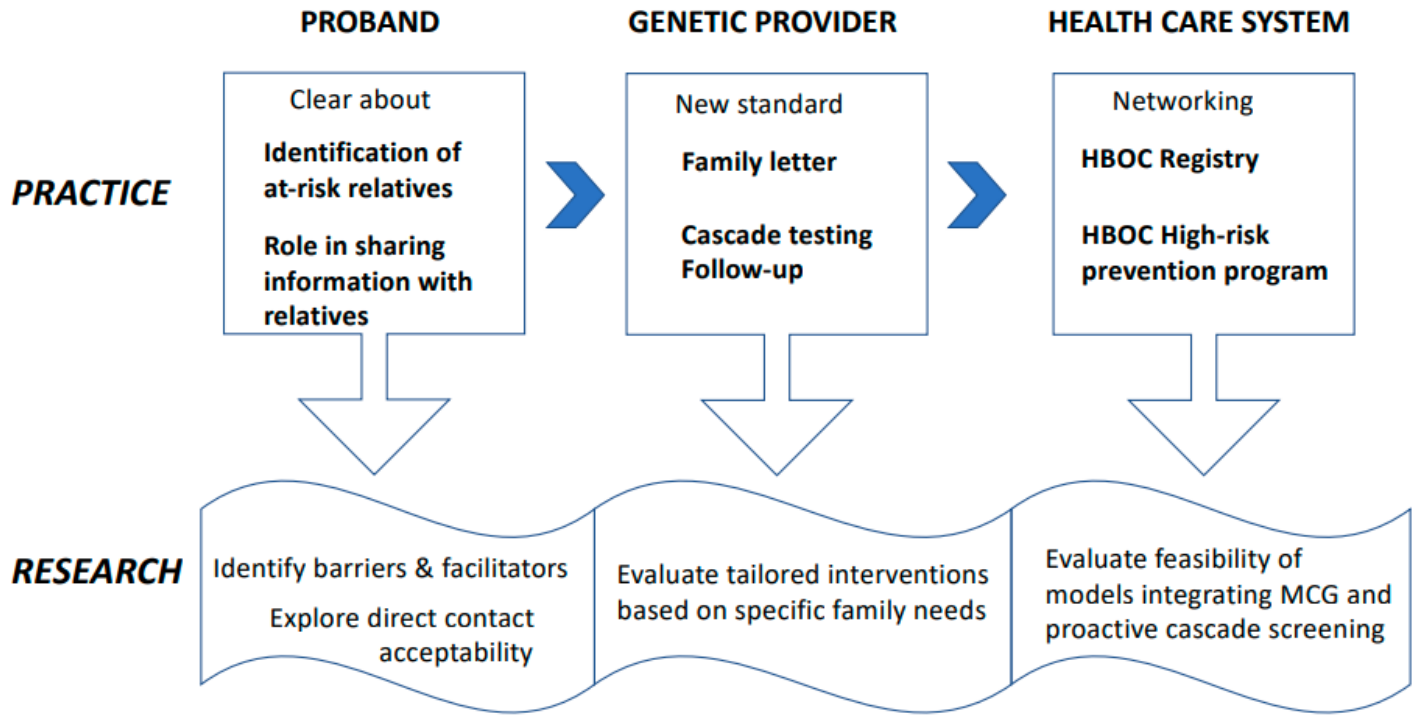

Figure 1

Priority actions in clinical practice and research to improve HBOC cascade testing

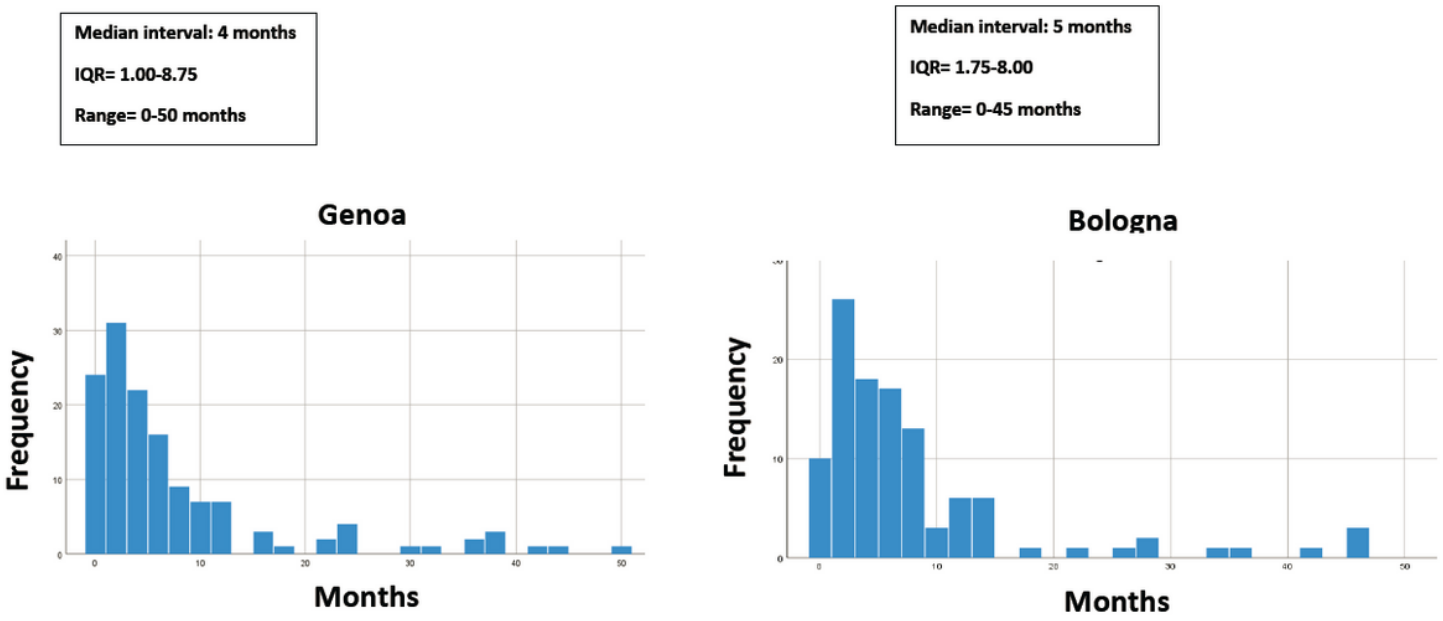

Figure 2

Priority actions in clinical practice and research to improve HBOC cascade testing

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfigure120230706.pdf
- Supplementarytables20230706.docx