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BRCA1/2 testing for genetic susceptibility to cancer after 25 years: A scoping review and a primer on ethical implications

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ABSTRACT

Background: Mutations in the genes called *BRCA1* and *BRCA2* are associated with significantly elevated lifetime risk of developing breast and ovarian cancer. This year marks 25 years since genetic tests for *BRCA*1/2 mutations became available to the public. Currently, comprehensive guidelines exist regarding *BRCA*1/2 testing and preventive measures in mutation carriers. As such, *BRCA1/2* testing represents a precedent not only in genetic testing and management of genetic cancer risk, but also in bioethics. The goal of the current research was to offer a review and an ethical primer of the main ethical challenges related to *BRCA* testing.

Method: A systematic scoping review was undertaken following the PRISMA Extension for Scoping Reviews (PRISMA-ScR). Four databases were searched and 18 articles that met the inclusion criteria were synthetized narratively into a conceptual map.

Results: Ethical discussions revolved around the *BRCA*1/2 gene discovery, how tests are distributed for clinical use, the choice to undergo testing, unresolved issues in receiving and disclosing test results, reproductive decision-making, and culture-specific ethics. Several unique properties of the latest developments in testing circumstances (e.g., incorporation of *BRCA*1/2 testing in multi-gene or whole genome sequence panels and tests sold directly to consumers) significantly raised the complexity of ethical debates.

Conclusions: Multidisciplinary ethical discussion is necessary to guide not only individual decision making but also societal practices and medical guidelines in light of the new technologies available and the latest results regarding psychological, social, and health outcomes in cancer previvors and survivors affected by *BRCA* mutations.

Contents

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Breast cancer is the most common cancer in European women and the first-ranking cause of death due to cancer in this population [1]. In 2020, it represented 28.7% of cancer cases and 16.5% of cancer deaths among women in the EU member states [1]. Another common cancer in women is ovarian cancer. In 2020, it represented 3.2% of cancer cases and 4.9% of cancer deaths in European women [1]. Although ovarian cancer is less frequent than breast cancer, its five-year survival rates are much lower, with about 28%–47% of ovarian cancer patients alive 5 years after diagnosis compared to 85%–89% of breast cancer patients [2].

Both breast and ovarian cancer have important genetic components. In particular, mutations in any of two genes called *BRCA1* and *BRCA2* have been found to increase the risk of breast and ovarian cancer [3,4]. To illustrate, whereas the lifetime risk of developing breast cancer in the general population is estimated to be about 12%, the risk for *BRCA1/2* mutation carriers could round 70% [3,4]. Similarly, the risk of ovarian cancer in the general population is estimated to be 1%–2%, whereas that of *BRCA1/2* mutation carriers could range between 20% and 40% [3,4]. Recent studies indicate that about 3%–6% of breast cancer patients and 8%–15% of ovarian cancer patients are *BRCA1/2* mutation carriers [5,6]. In contrast, the prevalence of *BRCA1/2* pathogenic variants in the general population is estimated to be very low at roughly 0.07%–0.22% [7,8]. Fig. 1 offers a glossary of relevant terms and Fig. 2 summarizes key facts about the *BRCA* gene mutations in relation to cancer risk.

The *BRCA*1/2 genes and their relationship to breast and ovarian cancer risk were discovered in 1994 after extensive research on families affected by young age of-onset breast and/or ovarian cancer [9–11]. The discovery of the *BRCA* genes had an immediate impact on clinical practice [12] and shortly after, in 1996, *BRCA*1/2 mutation screening became available for clinical use. Currently, 25 years after this key moment, comprehensive guidelines exist regarding who should be tested for *BRCA*1/2 and other cancer-related genetic mutations, and what preventive measures are recommended to reduce the risk of developing and dying from cancer (see Fig. 2). Besides *BRCA1/2*, we now know that mutations in other genes, such as *p53* (Li Fraumeni Syndrome), *PTEN* (Cowden Syndrome), *CDH1, STK11* (Peutz–Jeghers Syndrome), *MLH1, MSH2, MSH6* and *PMS2* (Lynch Syndrome), can significantly elevate breast or ovarian cancer risk [13]. Also diverse preventive measures exist (see Fig. 2), some of which can reduce breast cancer risk by about 90% (risk-reducing mastectomy (RRM)) [14] and ovarian cancer risk by 80% (risk-reducing salpingo-oophorectomy (RRSO)) [15].

Because *BRCA* testing can have profound consequences for individuals and their families, and because the information about it is fairly complex, from the very early days after the *BRCA* test creation, experts have emphasized that genetic counseling should be an integral part of testing [16]. This is something that is now mandated by current EU guidelines for genetic tests, specifying that counseling should take place both before and after testing [13,17]. Among others, genetic counseling should help individuals understand the possible test results, their meaning, and implications for them and their family members, together with the possible advantages and disadvantages of the available risk reduction options.

BRCA testing, as a form of genetic testing, could also have a profound impact on us as a society because “the knowledge of the human genome and related genetic testing literally may open a Pandora's box” [18], making the ethical challenges that were only theoretical part of daily medical practice. The *BRCA* genetic discovery and the associated scientific developments in the past 25 years represent a precedent not only in genetic testing and management of genetic cancer risk, but also in bioethics. *BRCA* screening was one of the first tests to become commercially available to test for inherited susceptibility to a common (and also well-known and feared) disease such as breast cancer.

Ever since the beginning of *BRCA* testing, experts have dwelled on ethical issues related to privacy, autonomy, relatedness, and discrimination, among others [16,19–21]. The commercialization of the *BRCA* tests, the new genetic discoveries that followed, and the availability of new more comprehensive (and complex) genetic tests for cancer susceptibility then raised new issues related to the patenting of genetic tests [12], prenatal testing [22], variants of uncertain significance (VUS) [23], and the availability of direct-to-consumer testing [24].

In light of these advances 25 years since testing has become available, the goal of the current research was to offer a scoping review of the main ethical issues related to *BRCA* testing and to trace how these have evolved alongside the advances in practice, knowledge, and technology. In particular, we organize the ethical themes into a conceptual map that can introduce researchers, clinicians, and other interested stakeholders into the major ethical complexities of *BRCA* testing.

1. Methods

We used the scoping review methodology [34] and followed the PRISMA Extension for Scoping Reviews (PRISMA-ScR) when conducting and reporting the review [35]. We chose this methodology because it combines rigorous methodology standards regarding article search and inclusion typical of systematic reviews with the possibility to address broader research questions that pertain to mapping and summarizing the available information on a subject [34,35]. We conducted a systematic literature search of four databases: PubMed, Scopus, Web of Science, and Google Scholar, on July 9–13 2021. Google Scholar was specifically included because it locates student thesis and other unpublished materials such a preprints. There were no restrictions regarding the language or date of publication. Because we were interested in locating articles specifically focused on ethical issues related to *BRCA* testing, we used a very directed search strategy that aimed to locate articles the titles of which contained any word derivative of *BRCA** and *ethic**. The search strategies and results of each database are available as Supplementary material. We also searched articles in the reference lists of those included when there was a possibility that they report relevant content.

Inclusion criteria were: articles that discussed in depth ethical issues related to *BRCA* genetic testing. Exclusion criteria: (i) conference abstracts, (ii) articles the full text of which could not be retrieved even after contacting the authors, (iii) articles the content

What does it mean?	
Germline genetic mutation	A gene change in a body's reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. Germline mutations, also called germline variants, are passed on from parents to offspring.
Gene penetrance	Gene penetrance measures the proportion of individuals in a population who carry a specific gene and express the related trait.
Preventive risk-reducing mastectomy (RRM)	Surgical removal of the breasts in the absence of malignancy to reduce breast cancer risk in women, usually followed by immediate or delayed breast reconstruction.
Preventive risk-reducing salpingo-oophorectomy (RRSO)	Surgical removal of the fallopian tubes and the ovaries to reduce the risk of ovarian and fallopian tube cancer. Results in a loss of fertility.
Variant of uncertain significance	A DNA alteration is detected but there is currently not enough evidence to classify this alteration as deleterious or neutral. VUS can later be re-classified once enough evidence is available.
Multi-gene panel test	A genetic test that uses next-generation sequencing to test multiple genes simultaneously.
Whole-genome sequencing test	A test that determines the entire, or nearly entire, DNA sequence of an organism's genome at a single time.
Cancer previvor	An individual who has a high predisposition to cancer (e.g., due to an inherited genetic mutation or family history of cancer) but who has not yet developed the disease.
Cancer survivor	Anyone who has ever been diagnosed with cancer no matter where they are in the course of their disease.
Prenatal diagnosis in the context of *BRCA* testing	Fetal DNA is collected through chorionic villus sampling or amniocentesis and is tested for *BRCA* mutations, with the option of terminating the pregnancy should the result be positive.
Pre-implantation genetic diagnosis in the context of *BRCA* testing	Embryos are fertilized in vitro and are then tested for the relevant *BRCA* mutations at the eight-cell stage; consequently, only embryos without the mutations of interest are implanted.

Fig. 1. A brief glossary to help understand the context of *BRCA* genetic testing.

of which did not contain detailed discussion of ethical issues related to *BRCA* testing, and (iv) articles that were mainly focused on genetic testing in general, on other genes, and/or not specific to *BRCA*. The protocol for the review was not pre-registered.

After removing duplicates, the full text of each article was read to decide whether it fulfilled the criteria. For each article that met the inclusion criteria, the first author, year of publication, and general topic was extracted in an excel sheet.

Two authors read the articles independently. Most articles meeting the inclusion criteria were perspective or opinion pieces not reporting results of original research. Hence, to synthetize the findings, we adopted an approach from qualitative research called thematic analysis, used to identify, analyze, and report recurring themes in textual data [36]. Articles were read multiple times, initially in the order based on their year of publication starting with the earliest, with the purpose to highlight new ethical themes raised in each subsequent article (i.e., not already discussed in a similar way or context in a previously published article) and record the themes that co-occurred across articles. Each new theme encountered was added to the excel sheet and for each article all ethical topics that were discussed were marked.

The main issues collected in the excel sheet were summarized and organized into a conceptual map by one author. This conceptual map was created by organizing the ethical themes on a simplified time-continuum starting from the discovery of the *BRCA* genes to the significance of test results for future generations. The map was then revised and discussed with the rest of the authors. Finally, the narrative results were organized according to this map.

The *BRCA* genes
BRCA1 (*Breast cancer gene 1*) and *BRCA2* (*Breast cancer gene 2*) are two tumor suppressor genes that produce proteins that help repair damaged DNA. The *BRCA1* gene is located on the long arm of chromosome 17 (17q21) and the *BRCA2* gene on chromosome 13 (13q12)[25]. Both genes are high penetrance genes, meaning that persons who are carriers of mutations in these genes have a high risk of developing cancer during their lifetime.
How are *BRCA* mutations inherited?
BRCA genes are inherited in an autosomal dominant manner, meaning that a person who has a harmful variant has an increased risk of developing the disease and this person, regardless of their sex, has a 50% chance of passing this variant and its corresponding increased risk on to their offspring.
Cancer risk of mutation carriers
A germline mutation in *BRCA1* or *BRCA2* is associated with significantly elevated lifetime risk of suffering breast and ovarian cancer, estimated at up to 7 and 25 times, respectively, that of the average risk population [26-29]. In particular, *BRCA1* mutation carriers are estimated to have a 72% chance (95% confidence intervals, CI, 65%-79%) of developing breast and 44% (36%-53%) ovarian cancer by the time they are 80 years old [3]. In the case of *BRCA2* mutation carriers, this risk is 69% (61%-77%) for breast, and 17% (11%-25%) for ovarian cancer, respectively [3]. Mutations in the two *BRCA* genes have also been found to increase the risk for other cancers such as fallopian tubes, peritoneal, and pancreatic cancer, and also prostate and breast cancer in men [13,30].
Types of *BRCA* testing
BRCA predictive testing aims to detect the presence of a mutation in asymptomatic (i.e., disease-free) family members of known *BRCA* mutation carriers or in families strongly affected by cancer, and is used to estimate future cancer risk. *BRCA diagnostic* testing is done in individuals diagnosed with cancer and its results have implications for family members and/or can be used to improve treatment selection [31].
BRCA mutation prevalence
BRCA gene mutations have very low prevalence in the general population, which is one of the reasons why there are few population screening programs [32]. However, persons with certain characteristics are more likely to be mutation carriers, including those who have had several close blood relatives (e.g., mother, grandmother, sister, aunt) who developed breast or ovarian cancer before the age of 50, persons diagnosed with triple-negative breast cancer, and persons from Jewish Ashkenazi descent [30].
Guidelines and recommendations regarding BRCA testing
The US NCCN Guidelines for Genetic/Familial High-Risk Assessment focus on pathogenic or likely pathogenic variants associated with increased risk of breast, ovarian, and pancreatic cancer and recommend approaches to genetic testing, counseling, and management strategies in individuals with pathogenic variants [30]. For instance, *BRCA*1/2 testing is recommended for individuals with any blood relative with a known pathogenic variant in a cancer susceptibility gene or individuals who developed cancer at a young age (≤45 years), as well as individuals who meet a number of other conditions detailed in the guidelines.
Guidelines and recommendations regarding cancer risk reduction in mutation carriers
Multiple relevant international guidelines are available [33]. For example, the European Society for Medical Oncology (ESMO) has published Clinical Practice Guidelines for cancer prevention and screening in *BRCA* mutation carriers and other breast/ovarian hereditary cancer syndromes [13].
Breast cancer risk
To reduce their risk of breast cancer and, as a function of their particular characteristics, mutation carriers are recommended to consider several strategies including lifestyle modifications (e.g., regular exercise, limiting alcohol consumption, etc.), intensive screening (e.g., clinical breast examination, breast MRI), risk-reducing drugs (e.g., tamoxifen), and/or risk-reducing mastectomy (RRM). RRM is the most effective method for reduction of breast cancer risk in this population (estimated by about 90%) [13,14].
Ovarian cancer risk
Similarly, to reduce their ovarian cancer risk, *BRCA* mutation carriers should consider lifestyle factors (e.g., oral contraceptive pills), screening with trans-vaginal ultrasound (although its effectiveness appears to be limited), and/or risk-reducing salpingo-oophorectomy (RRSO) [13,15]. In this case, the surgery is again the most effective method reducing risk by 80% [13,15]. However, affected women who wish to bear children should either complete childbearing before surgery or explore other fertility preservation options [13].

Fig. 2. Key facts about *BRCA* gene mutations in relation to cancer risk. [25–29]

2. Results

Fig. 3 displays the flow chart of the search process, which resulted in the inclusion of 18 articles described in detail in Table 1. The Supplement contains the list of all articles that entered the search process along with reasons for exclusion.

Fig. 4 displays the conceptual map after which the narrative results below are organized.

2.1. Gene discovery

In the early years after the discovery of the *BRCA* genes and their role in breast and ovarian cancer risk several ethicists argued that it could open the door to cancer *geneticization* and *genetic exculpation*. Geneticization refers to the reduction of complex phenomena to the simple expressions of genes (Abby Lippman in Ref. [19]), whereas genetic exculpation refers to the idea that "those with an interest in doing so are beginning to explain away their own part in the causation of a given disease by pointing to genetic susceptibility" (Robert Proctor in Ref. [16]). Geneticization and genetic exculpation could then lead to reduced perceived importance of the other causes of cancer and reduced responsibility. This could in turn influence how resources are distributed, especially in the context of a multifactorial disease such as cancer [19], which has multiple environmental, socioeconomic, and behavioral determinants that actually explain a larger proportion of cancer cases than genetics [47]. Vineis [20] provides a compelling example of how simple cost-benefit analysis may estimate that genetic screening is less expensive and more convenient than primary prevention through eliminating environmental exposures or behavioral modifications; however, according to the fundamental ethical principle of *beneficence* primary prevention is an ethical obligation that should take precedence over screening and/or treatment on such occasion.

Another ethical challenge arises from the fact that we may obtain genetic information with which to predict the probability of developing cancer but we may not possess 100% effective evidence-based strategies to reduce this risk [16,40,40]. This raises questions about the inherent *value of knowledge* obtained with genetic tests. Although our knowledge of the effectiveness of the different risk-reducing strategies has greatly improved in the past 20 years, even the most effective ones (i.e., RRM or RRSO) do not fully eliminate the risk of cancer (although note that the risk reduction is very large, by 90% [14] and 80% [15], respectively). So, this issue remains at least partially relevant and leaves us in a state that Parens called "enlightened impotence" [16]. The same argument could be made regarding the psychological and social consequences of testing that are not yet fully understood [40,41].

Finally, the availability of genetic data raises fundamental questions about *confidentiality and data protection* as individual rights [39] and safe and confidential *data sharing* to increase knowledge and societal benefits [44], both strictly regulated by specific laws in different jurisdictions. Whereas data sharing for research, diagnosis, or treatment purposes might be ethically desirable for many types of health data, in the case of genetic

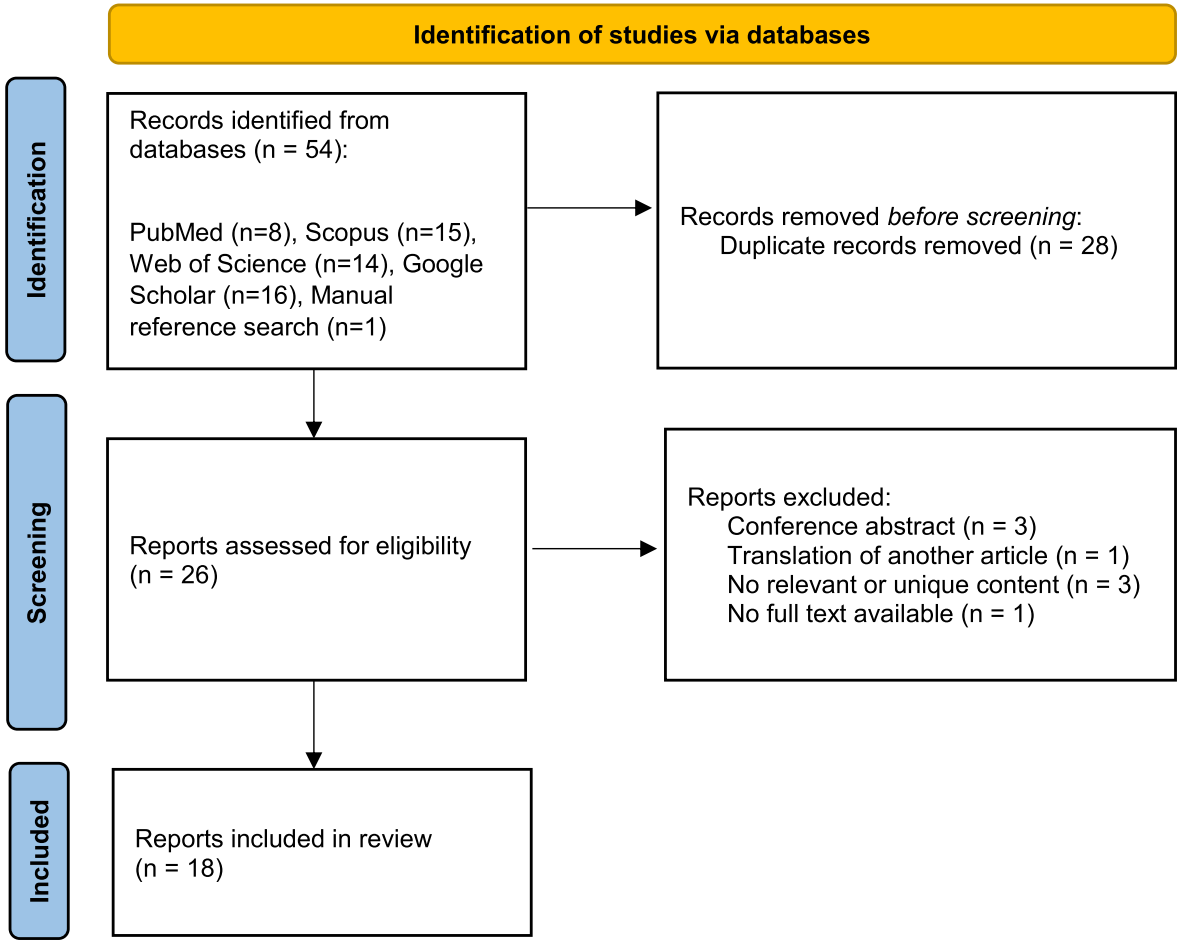

Fig. 3. PRISMA 2020 flowchart.

Table 1
Articles included in the review.

First author	Title	Pub. year	Type of article	Themes identified
Parens [16]	Glad and terrified: On the ethics of *BRCA*1 and 2 testing	1996	Perspective/opinion article	1, 3, 6, 7, 8, 9, 10, 14
Vineis [20]	Ethical issues in genetic screening for cancer	1997	Perspective/opinion article	2, 11, 14
Elger [37]	Prenatal diagnosis of hereditary tumors: Ethical controversy, for example the *BRCA*1-gene	1998	Perspective/opinion article	8
Cox [38]	Religious ethics of *BRCA* testing in the Orthodox Jewish community	2000	Masther tesis, qualitative study	21
Nebril [39]	Ethical implications of *BRCA*1/2 testing for breast cancer susceptibility	2003	Perspective/opinion article	4, 11, 14, 15
Sherwin [19]	*BRCA* testing: ethics lessons for the new genetics	2004	Perspective/opinion article	1, 2, 9
Kmet [40]	Systematic review of the social, ethical, and legal dimensions of genetic cancer risk assessment technologies	2004	Systematic review	3, 4, 8, 9, 7, 11, 12, 13, 14, 16
Winchester [41]	Psychosocial and ethical issues relating to genetic testing for *BRCA*1 and *BRCA*2 breast cancer susceptibility genes	2006	Perspective/opinion article	8, 10, 13, 14, 15
Mor [42]	Ethical issues related to *BRCA* gene testing in Orthodox Jewish women	2008	Perspective/opinion article	21
Quinn [43]	Decisions and ethical issues among *BRCA* carriers and the use of preimplantation genetic diagnosis	2009	Perspective/opinion article	13, 16
Surbone [21]	Social and ethical implications of *BRCA* testing	2011	Perspective/opinion article	1, 4, 11, 14, 15, 21
Cheon [44]	Variants of uncertain significance in *BRCA*: a harbinger of ethical and policy issues to come?	2014	Perspective/opinion article	4, 5, 12
Joly [12]	Social, ethical and legal considerations raised by the discovery and patenting of the *BRCA*1 and *BRCA*2 genes	2014	Perspective/opinion article	4, 5
Matloff [45]	Choosing a *BRCA* genetic testing laboratory: A patient-centric and ethical call to action for clinicians and payers.	2014	Perspective/opinion article	5, 6
Rubin [22]	Ethical analysis of PGD for *BRCA*: Attending to more than risks and benefits	2014	Book chapter, qualitative study	16, 17, 18, 19
Park [46]	The ethics of patenting the *BRCA* genes for breast cancer research	2017	Perspective/opinion article	5
Kilbride [24]	Ethical implications of direct-to-consumer hereditary cancer tests	2018	Perspective/opinion article	9
Gustavsson [23]	Genetic testing for breast cancer risk, from *BRCA*1/2 to a seven gene panel: an ethical analysis	2020	Perspective/opinion article	9, 12, 15

Note: (1) genetic exculpation, (2) distribution of resources, (3) the value of knowledge, (4) data confidentiality and sharing, (5) patenting of genetic tests, (6) testing to make money, (7) equitable access to testing, (8) testing of vulnerable populations, (9) achieving truly informed decision making, (10) need to non-directive counseling, (11) "the ties we have with each other", (12) VUS, (13) becoming a cancer previvor, (14) genetic discrimination, (15) disclosure of results, (16) "gentler eugenics" and "designer babies", (17) constraints on choice, (18) reductionist construct of health, (19) value assumptions about good parenting, (20) impact on the search for other solutions, (21) cross-cultural ethical norms.

testing data sharing is needed to make and verify clinical interpretations of genetic variants, and the more shared data there are, the better these predictions would be. However, currently there are diverse legal, policy, and ethical issues related to genetic data that come in the way of data sharing, although progress is being made [44].

2.2. Test distribution for clinical use

The distribution and clinical use of the *BRCA* tests created a legal and ethical precedent, specifically through *the patenting of the BRCA genes*. In particular, the company Myriad Genetics Inc. patented in the mid 1990s the *BRCA* genes that have been isolated or extracted from the person's body so that they could be studied in the laboratory [46]. This raised several controversial ethical and legal issues because the patents were being used in a way that restricted the ability of laboratories to provide in-house genetic tests or make improvements to the existing tests [12]. This in turn was perceived to have negative impact on both research on *BRCA* and the availability of tests to individuals at high risk [12].

Besides the effects on research and test availability, there were ethical concerns about whether isolated DNA sequences were at all an invention to be patented or a public good to be considered outside of the commercial realm [12]. Eventually, in the US the Supreme Court invalidated Myriad's patents, but they remained active in other jurisdictions such as the European Union [12,46], where Myriad continued to hold patents on isolated *BRCA* genes and the tests used to detect them [46]. Thus, isolated naturally occurring nucleotide sequences remain patentable in Europe, however, after a series of opposition proceedings, the scope of Myriad's BRCA patents was drastically reduced [48]. In addition, the company considers proprietary and hence holds access to databases, algorithms, and other processes through which gene variant classification occurs [44,45], something which allows it to maintain its monopoly on the market even in the absence of a patent in the US.

This conflict in the careful balance between making private profit (to stimulate innovation) and public good was foreseen by Parens [16,16] who called it simply "*testing to make money*". He put emphasis on the dangers inherent to what is nowadays known as Direct-to-Consumer (DTC) testing: the use of a genetic test that is marketed directly to consumers through the media [24], especially when using the public's anxiety and ignorance about cancer in the absence of proper medical supervision and counseling.

Finally, concerns about *equal and/or equitable access to testing* have also been raised [40], such as whether it should be available to all who request it or restricted to only those who appear to be high-risk; or if socioeconomic and other barriers could undermine access

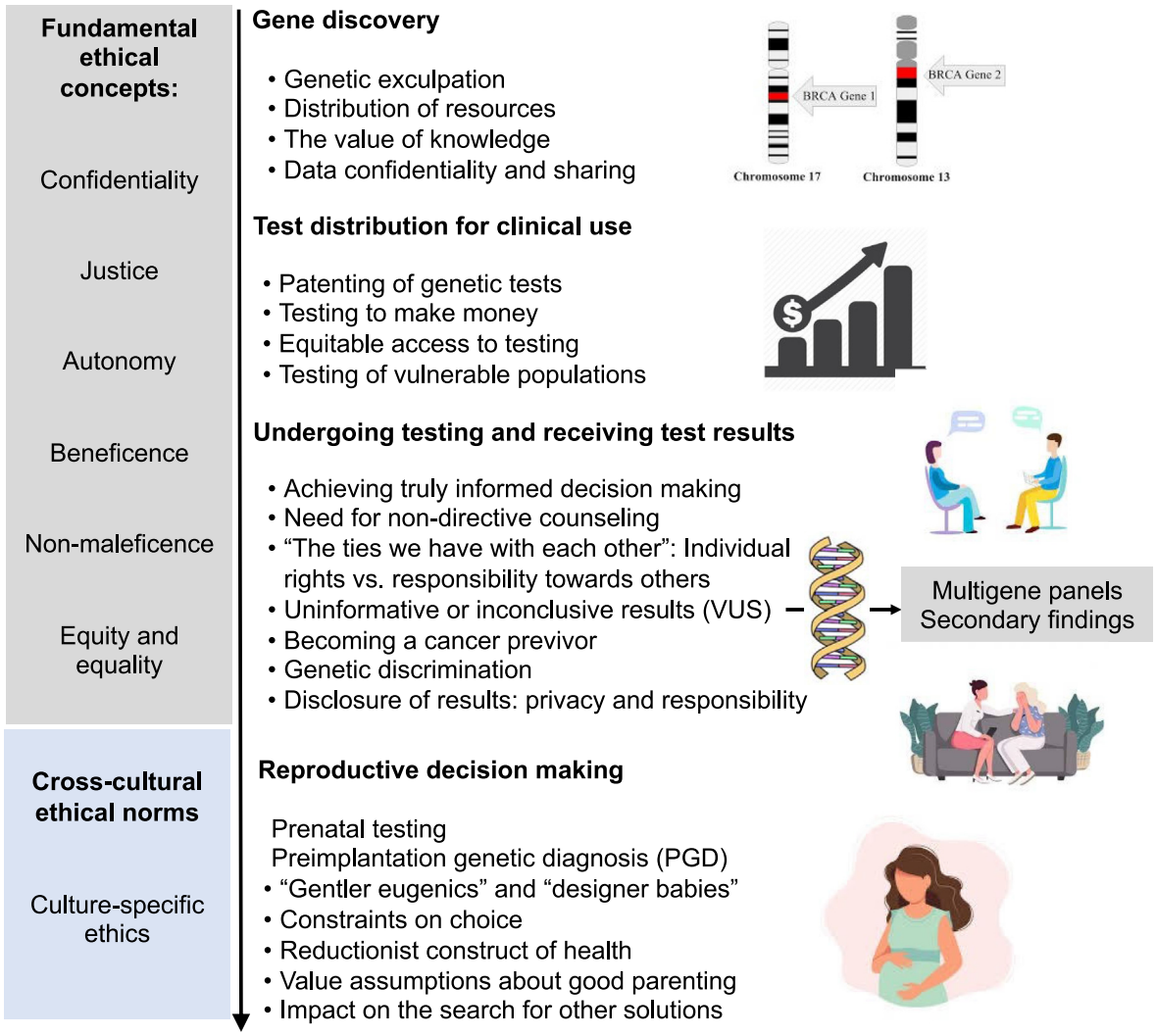

Fig. 4. Conceptual model of ethical challenges related to *BRCA*1/2 testing.

to testing and create a "genetic underclass" [40].

Testing of *vulnerable populations* such as minors has also been discussed [16,40,41], raising questions regarding when children become competent to make their own decisions regarding testing and when, if at all, it should be made available to them.

2.3. Undergoing testing and receiving test results

According to the ethical principle of autonomy, an individual must make an autonomous and *fully informed decision* regarding whether to undergo genetic testing, that is free from coercion and is consistent with the person's beliefs and values [41]. To make an informed decision, patients must understand not only the accuracy and meaning of test results but also the potential benefits and harms associated with each possible result [16], including the implications of the results for third parties (e.g., children, first-degree blood relatives, etc.) [39]. However, ensuring that decisions are truly informed can be difficult because of multiple reasons, including: the emotionally charged context of genetic testing, the fear of cancer that is often amplified in families strongly affected by the disease, the manipulative marketing, and the poor understanding of the statistical data used to describe the potential test results, benefits, and risks [19,40]. Because of such circumstances, *genetic counseling* is strongly recommended to take place both before testing and after getting the results and should be "nondirective", i.e., giving full information in "as nondirective manner as is possible" [16]. The difficulties of informed choice are likely to be exacerbates in the context of DTC, particularly when testing in not physician-mediated or no sufficient counseling is provided [24].

In difference to other types of medical information, genetic information is unique because it "reminds us of *the ties we have with each other*" [21]: it carries potential value and danger for individuals other than the person tested [21]. In light of this unique property, some authors have also portrayed the decision to undergo testing or not as a potential conflict between autonomy (e.g., the right not to know) and responsibility towards future generations (e.g., the duty to know for the sake of one's offspring) [20,39].

Positive and negative *BRCA* test results can have multiple benefits but also indirect harms that should be considered [16]. First, a positive result can generate perplexing issues, because it only speaks to the presence of the mutation and is not a guarantee that cancer will develop. A positive result is meant to be beneficial through the possibility to get ahead of the disease through various prevention and early detection actions or plan one's financial future, among others. However, a positive result could also lead to emotional difficulties (e.g., helplessness and depression) or

contribute to strained family dynamics.

In contrast, a negative result could help reduce anxieties about cancer, reproductive issues, or finances. However, it could also mistakenly make patients feel that they are not at risk of cancer at all and thus abandon prevention and early detection efforts, or could also strain family dynamics if other family members have tested positive.

An aspect that deserves special emphasis in the *BRCA* ethics discussion is the existence of results called *variants of uncertain significance* (VUS). A VUS result means that although the testing laboratory detected a DNA alteration, there was not enough evidence to classify this alteration as deleterious or neutral [44]. Hence, there is no clear indication regarding the risk for developing cancer and further studies are necessary in order to determine whether the variant identified has any bearing on cancer risk; as such VUS results are treated as clinically uninformative [44]. However, the existence of VUS results raises specific ethical issues about patient informed consent and patient-provider communication [44]. On one hand, it is not clear to what extent patients understand VUS results and how they deal with this information. On the other hand, it is not clear whether someone (and who in particular if anyone) has the duty to re-contact the patient if the VUS identified has been reclassified and now carries valuable clinical information.

These ethical challenges would only become more pertinent now that *BRCA* testing is part of *multi-gene panels*, whole-genome sequencing (WGS), and whole-exome sequencing (WES) [44]. Multi-gene panels test numerous variably penetrant genes or the entire genome and are hence much more likely to find VUS [23,44]. Multi-gene panels also generate the possibility for *secondary findings* (SF) defined as findings that go beyond the initial purpose of the genetic test (e.g., a test done with the purpose to find out about breast cancer risk finds a mutation associated with neurological disease). This generates a separate ethical discussion about how to discuss these possibilities in genetic counseling and under what conditions to inform (or not) the patient about SF, issues that go beyond the scope of the current article and are described in detail by Gustavsson et al. [23].

Should a person receive a positive *BRCA* result in the context of predictive testing, they become a "*cancer previvor*", a term used to refer to individuals who have not been diagnosed with cancer but have a known predisposition or higher risk of cancer due to a genetic mutation [43]. One consequence of being a cancer previvor, should this information become known to third parties, is that one can become subject to *genetic discrimination* [16,21,39]. In particular, cancer previvors may be susceptible to different forms of social discrimination due to their increased cancer risk such as increased health insurance premiums, access and cost of life insurance, work discrimination by current or future employers, and discrimination in child adoption proceedings [39]. Although various countries have specific legislation and regulations to protect against discrimination by insurance companies or employers (e.g., Genetic Information Nondiscrimination Act (GINA) in the US, the Charter of Fundamental Rights of the European Union), they may only provide an "illusion of protection" due to limited effectiveness in practice [21].

The *disclosure of results* to family members is another ethical issue that has not yet been resolved [41]. Once an index patient receives a positive *BRCA* test, their blood relatives at risk have the opportunity to undergo predictive genetic testing. However, Winchester et al. point out that communicating genetic information to extended family is ethically complex and that it is still a matter of debate with whom the responsibility lies: the index patient or the genetic counselor [41]. On one hand, the right to privacy of the index patient may be in conflict with the right to know of the affected family members. On the other hand, the direct disclosure of genetic information to the family members may also violate their right to privacy and not to know. In general, Winchester et al. report that the index patient is given the moral responsibility of disclosure and that the majority of patients disclose information to their first-degree relatives; however, disclosure to more distant relatives is less frequent and is influenced by diverse personal and family factors [41]. In such cases, the geneticist could take on the responsibility of disclosure, however, their involvement is still a matter of debate. In particular, "geneticists are faced with the ethical dilemma of respecting the confidentiality and privacy of their client and their duty to warn at-risk relatives of genetic information … while maintaining the relatives' right to privacy and autonomy" [41].

2.4. Reproductive decision making

Being a female or male *BRCA* previvor can also raise difficult dilemmas about future childbearing or ongoing pregnancy [22,37,40,41,43]. Several options exist for previvors who wish to have biological descendance without the possibility of passing on the *BRCA* mutation including gamete donation, natural pregnancy with prenatal diagnosis (PND), and pre-implantation genetic diagnosis (PGD). In PND, fetal DNA collected through chorionic villus sampling or amniocentesis is tested for *BRCA* mutations, with the option of terminating the pregnancy should the result be positive. In PGD, embryos are fertilized in vitro and are then tested for the relevant mutations at the eight-cell stage; consequently, only embryos without the mutations of interest are implanted.

The ethical issues raised by the use of PND and PGD to avoid a cancer-related gene mutation range from concerns regarding the availability of treatment (e.g., a much better treatment may become available by the time of disease onset in the affected individual) to the dangers of making "*designer babies*" and engaging in "*gentler eugenics*" [16,40]. For instance, in difference to other conditions for which PGD is used, heritable breast and ovarian cancer has later disease onset, there are preventive measures and effective treatments available, and the associated gene mutations have lower penetrance [41]. In addition, the use of both technologies (PND and PGD) is not without any risk of complications for both mother and fetus (e.g., complications associated with in vitro fertilization).

Regarding the use of PGD, an in-depth analysis of Rubin and de Melo-Martin [22] highlights several issues that go beyond the traditional risk-and-benefit analysis framework. They illustrate how, ironically, the availability of an additional choice of PGD can put *constraints on previvors' choices* regarding reproduction, because once an option becomes available that eliminates the increased cancer risk, the other options (e.g., a natural pregnancy) seem less justifiable. Because the main goal of PGD is to produce healthy children, this technology indirectly prioritizes health over other concerns of human existence and provides a *reductionist definition of what it means to be healthy* (i.e., equal to *BRCA* mutation-free). It also comes with certain assumptions about *what it means to be a good parent* (e.g., choose favorable child characteristics vs. love whatever child comes along). Finally, similar to how the existence of genetic cancer risk knowledge may limit the resources allocated to identifying and eliminating other cancer causes, the existence of GPD can *limit the search for alternative solutions* to address *BRCA*-associated cancer risk in offspring [22].

2.5. Culture-specific ethics

Last but not least, there may be important differences in ethical norms across cultures, necessitating culturally sensitive counseling [38]. One example is the population of Ashkenazi Jews among

whom the prevalence of *BRCA* mutations is significantly higher [30]. Mor and Oberle [42] highlight how some fundamental differences between secular and Jewish ethics regarding health and healthcare that could have important implications for the process of informed decision making about testing, disclosure of results, or reproductive decision making.

3. Discussion

This scoping review identified multiple ethical challenges in *BRCA* testing, related to the *BRCA*1/2 gene discovery, the test distribution for clinical use, the choice to undergo testing, receiving and disclosing test results, reproductive decision making, and culture-specific ethics. Research has indicated that the common familial and risk-based approach to identifying *BRCA* mutation carriers misses a significant number of individuals with the mutations [33]. As a result, the scientific community is currently investigating and debating how best to expand *BRCA* testing to a broader range of individuals, if not even to the general population [32,33]. *BRCA*1/2 status is now also regarded as clinically relevant in the selection of therapy for patients already diagnosed with breast [31] and ovarian cancer [49]. As a result, genetic testing has started to be mainstreamed in the routine care of breast and ovarian cancer patients in several countries [50–52]. In such mainstream genetic testing, trained non-genetic experts (e.g., oncologists, surgeons, or gynecologists) arrange the testing, offer brief counseling, and deliver the results [53].

Hence, awareness of the ethical debates and doubts that surround *BRCA* testing is important part of the continued medical education of all health professionals who in one way or another may be involved in *BRCA* testing or the care of cancer previvors and *BRCA*-affected cancer patients. It is also important for the decision making of patients in the context of genetic cancer risk. Patients are meant to make informed decisions that are consistent with their values and beliefs, something that would be impossible without awareness of the ethical dilemmas and implications they may face as a consequence of their decision to get tested or not for a *BRCA* mutation.

The early ethical discussions (i.e., published right after the commercialization of the *BRCA* tests) anticipated many issues that remain central to *BRCA* testing 25 years after it became available and now extend to testing for other cancer-related genes and syndromes [16,20]. However, with the expansion of genetic technologies, the availability of further genetic tests for cancer susceptibility, and the way they are administered, many of these issues increase in scope and importance and deserve detailed consideration and multidisciplinary discussion.

Besides *BRCA1/2*, mutations in other genes such as *p53, PTEN, CDH1, STK11, MLH1, MSH2, MSH6,* and *PMS2* could increase the risk of breast and/or ovarian cancer [13,30]. For instance, the Li-Fraumeni syndrome is caused by a mutation in the *p53* gene that increases the risk of breast cancer and genetic counseling and testing for this syndrome is recommended in young breast cancer patients (under 30) [30,54,55]. As a result of the identification of multiple cancer-related genetic mutations, some guidelines now recommend multi-gene panel testing [30,33]. However, besides providing benefits, multi-gene panel and whole-genome testing also increase the possibility of reporting VUS and secondary findings, two essential aspects with important implications for genetic counseling, informed decision making about testing [23,44], and ultimately human health.

For instance, the American College of Medical Genetics and Genomics (ACMG) has published guidance for reporting secondary findings in the context of clinical exome and genome sequencing. They recommend that whenever possible, as part of testing for other purposes, the presence of variants of certain genes, among which *BRCA*1/2 mutations, should be investigated and reported to patients [56]. In contrast, the European Society for Human Genetics recommends a cautious approach in which genome analysis should be restricted to the original health problem of interest [57]. In practice this means that a European patient who has undergone cancer genetic testing would only receive information about secondary findings in relation to cancer risk. However, they would not be advised if *BRCA*1/2 mutations are found if they were tested for another (not cancer related) pathology. The divergent recommendations of these two leading scientific societies show us that there is a long road ahead and demonstrate just how difficult it is to ethically balance opportunity and risk in the context of genetic screening.

When it comes to individual cases, the presence of VUS and SF only adds to the already high complexity of the genetic and statistical information patients and counselors need to discuss. As a result, ensuring informed patient decision making only becomes more difficult, especially having in mind that a substantial proportion of the general population has low numeracy and health literacy skills, both essential for understanding cancer risk and risk reduction information [58,59]. We should not forget that deliberations would also be replete with emotions, especially among families in which multiple members have been affected by cancer, “and thus fear and terror of developing cancer are beyond what most people would experience” [43].

Another major challenge represents the current availability of direct-to-consumer testing (DCT) for *BRCA*1/2 and other cancer related mutations, the ethical implications of which are discussed in detail by Kilbride [24]. DCT for *BRCA*1/2 is now available in the US, UK, and Europe. The fact that it can be ordered on the internet for an acceptable price means that it can be obtained outside of existing clinical programs and even circumventing national restrictions on DCT [60]. This raises the question to what extent the information offered, and procedures followed by the private companies offering DCT guarantee informed decision making of consumers [61]. The simple answer appears to be that information is generally insufficient [61].

Increased awareness and availability of *BRCA* genetic tests without being properly informed may lead to unnecessary testing and treatment, as evidence by what is now called the Angelina Jolie effect [62]. In 2013 the popular actress and humanitarian disclosed in a public letter her decision to have double RRM after testing positively for a *BRCA*1 mutation; she later also had a salpingo-oophorectomy. Her story raised awareness about genetic testing for breast and ovarian cancer but its portrayal in the media did not help people comprehend their cancer risk better or understand how infrequent Ms. Jolie's case was [63,64]. The story was even followed up by an increase in RRM among *BRCA* carriers and other high-risk women in some jurisdictions [62].

Recently, there have also been concerns regarding the quality of results obtained in DCT laboratories, which are reported to find more false positive results and be more likely to classify benign variants as high risk [60]. Altogether, in relevance to the current ethical discussion, the current practices of DCT for *BRCA*1/2 and other cancer related genetic mutations seem to be insufficient to guarantee informed decision making of consumers. Indirectly they also create a conflict between consumers' right to have the option to choose a medical service and the obligation of public and medical authorities to ensure that only high-quality services are provided; services that have the potential to improve patients' lives and, first and foremost, do no harm. In fact, in the underlying hierarchy to the beneficence principle discussed by Vineis, “not to inflict harm” precedes “to prevent harm”, “to repair harm”, and “to do good” [20]. Accepting this hierarchy would lead us to find

stricter regulation and control on DTC testing for breast and ovarian cancer ethically acceptable.

BRCA mutation carriers may also face unique challenges and decisions that most people do not need to consider such as the possibility to use different reproductive technologies with the sole purpose of avoiding the very high cancer risk that comes with a *BRCA* or other cancer-related genetic mutation. Many factors, including ethical, religious, cultural, and socio-economic can influence a person's choice to utilize any of these technologies, which are also not available everywhere [13]. The increasing number of *BRCA* tests and as a consequence of cancer previvors and survivors who are mutation carriers may result in an increased use of these technologies. In order to offer adequate counseling and support, more research is needed about the reproductive decision-making processes of women who are *BRCA* positive [65].

This article was based on a systematic scoping review methodology. Limitations include the very directed systematic search strategy which was designed to streamline articles specifically focused on ethical issues in *BRCA* testing. This means that articles on broader topics related to genetic testing that could contain relevant ethical debates would have been missed. However, in accordance with the scoping review methodology, our goal was to provide an overview of and organize the main ethical issues discussed so far.

4. Conclusions

BRCA testing has been not only a medical but also an ethical precedent in genetic testing for breast and ovarian cancer risk. As pointed out by Sherwin [19], "individual deliberations, no matter how responsibly undertaken, cannot be counted on to produce the best practices". This is why, multidisciplinary ethical discussion is necessary to guide not only individual decision making but also societal practices and medical guidelines in light of the new technologies available and the latest results regarding psychological, social, and health outcomes in cancer previvors and survivors affected by *BRCA* mutations.

Ethical approval

This is a review article and no ethical approval was required.

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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.12.005.

References

[1] ECIS-European Cancer Information System. Data explorer. 2021. https://ecis.jrc.ec.europa.eu/explorer.php.
[2] EFPIA-European Federation of Pharmaceutical Industries and Associations. Cancer care in 2020 - an overview of cancer outcomes data across Europe. 2020. https://www.efpia.eu/publications/cancer-comparator-report/.
[3] Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips K, Mooij TM, Roos-Blom M, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317(23):2402–16.
[4] Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, et al., editors. GeneReviews((R)). Seattle (WA): University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved; 2016.
[5] Yoshida R. Hereditary breast and ovarian cancer (HBOC): review of its molecular characteristics, screening, treatment, and prognosis. Breast Cancer 2021;28(6):1167–80.
[6] Armstrong N, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of BRCA mutation in breast cancer. Clin Epidemiol 2019 Jul 11;11:543–61.
[7] Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br J Cancer 2000 Nov;83(10):1301–8.
[8] Whittemore AS, Gong G, John EM, McGuire V, Li FP, Ostrow KL, et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. Cancer Epidemiol Biomarkers Prev 2004 Dec;13(12):2078–83.
[9] Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994 Oct 7;266(5182):66–71.
[10] Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science 1994 Sep 30;265(5181):2088–90.
[11] Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature 1995;378(6559):789–92.
[12] Joly Y, Tonin PN. Social, ethical and legal considerations raised by the discovery and patenting of the BRCA1 and BRCA2 genes. New Genet Soc 2014;33(2):167–80.
[13] Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso M, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol 2016;27:v103–10.
[14] Li X, You R, Wang X, Liu C, Xu Z, Zhou J, et al. Effectiveness of prophylactic surgeries in BRCA1 or BRCA2 mutation carriers: a meta-analysis and systematic review. Clin Cancer Res 2016 Aug 1;22(15):3971–81.
[15] Marchetti C, De Felice F, Palaia I, Perniola G, Musella A, Musio D, et al. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. BMC Wom Health 2014;14(1):1–6.
[16] Parens E. Glad and terrified: on the ethics of BRCA1 and 2 testing. Cancer Invest 1996;14(4):405–11.
[17] Hastings R, Howell R, Bricarelli FD, Kristoffersson U, Cavani S. General guidelines and quality assurance for cytogenetics. European Cytogeneticists Association Newsletter 2012;29:7–25.
[18] Koenig BA, Greely HT, McCONNELL LM, Silverberg HL, Raffin TA. Members OF the breast cancer working group OF the Stanford program IN genomics, ethics, and society. Genetic testing for BRCA1 and BRCA2: recommendations of the stanford program in Genomics, ethics, and society. J Wom Health 1998;7(5):531–45.
[19] Sherwin S. BRCA testing: ethics lessons for the new genetics. Clin Invest Med 2004;27(1):19.
[20] Vineis P. Ethical issues in genetic screening for cancer. Ann Oncol 1997;8(10):945–9.
[21] Surbone A. Social and ethical implications of BRCA testing. Ann Oncol 2011;22:i60–6.
[22] Rubin LR, de Melo-Martín I. Ethical analysis of PGD for BRCA: attending to more than risks and benefits. Breast cancer gene research and medical practices. Routledge; 2014. p. 216–30.
[23] Gustavsson E, Galvis G, Juth N. Genetic testing for breast cancer risk, from BRCA1/2 to a seven gene panel: an ethical analysis. BMC Med Ethics 2020;21(1):1–8.
[24] Kilbride MK, Domchek SM, Bradbury AR. Ethical implications of direct-to-consumer hereditary cancer tests. JAMA Oncol 2018;4(10):1327–8.
[25] Ford D, Easton D, Stratton M, Narod S, Goldgar D, Devilee P, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 1998;62(3):676–89.
[26] King MC, Marks JH, Mandell JB. New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003 Oct 24;302(5645):643–6.
[27] Paul A, Paul S. The breast cancer susceptibility genes (BRCA) in breast and ovarian cancers. Front Biosci 2014 Jan 1;19:605–18.
[28] Walsh T, Casadei S, Lee MK, Pennil CC, Nord AS, Thornton AM, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma

identified by massively parallel sequencing. Proc Natl Acad Sci U S A 2011 Nov 1;108(44):18032–7.
[29] González-Santiago S, y Cajal TR, Aguirre E, Alés-Martínez J, Andrés R, Balmaña J, et al. SEOM clinical guidelines in hereditary breast and ovarian cancer (2019). Clin Transl Oncol 2020;22(2):193–200.
[30] Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 2021;19(1):77–102.
[31] Tung NM, Garber JE. BRCA 1/2 testing: therapeutic implications for breast cancer management. Br J Cancer 2018;119(2):141–52.
[32] Lippi G, Mattiuzzi C, Montagnana M. BRCA population screening for predicting breast cancer: for or against? Ann Transl Med 2017 Jul;5(13):275.
[33] Forbes C, Fayter D, de Kock S, Quek RG. 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 2019 Mar 22;11:2321–37.
[34] Ruiz-Perez I, Petrova D. Scoping reviews. Another way of literature review. Med Clin 2019 Aug 16;153(4):165–8.
[35] Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467–73.
[36] Braun V, Clarke V. Thematic analysis. 2012.
[37] Elger B. Pränatale Diagnostik hereditärer Tumoren: die ethische Kontroverse am Beispiel des BRCA1-Gens. Med Genet 1989;10(2):238–41.
[38] Cox EJ. Religious ethics of BRCA testing in the Orthodox Jewish community. Sarah Lawrence College; 2000.
[39] Nebril BA. Implicaciones éticas de los test BRCA1/2 en el estudio de la predisposición al cáncer de mama. Cirugía Española 2003;73(5):309–13.
[40] Kmet L, Lee RC, Cook LS, Lorenzetti D, Godlovitch G, Einsiedel E. Systematic review of the social, ethical, and legal dimensions of genetic cancer risk assessment technologies. Calgary: Alberta Heritage Foundation for Medical Research (AHFMR).[Google Scholar; 2004.
[41] Winchester E, Hodgson SV. Psychosocial and ethical issues relating to genetic testing for BRCA1 and BRCA2 breast cancer susceptibility genes. Wom Health 2006;2(3):357–73.
[42] Mor P, Oberle K. Ethical issues related to BRCA gene testing in orthodox Jewish women. Nurs Ethics 2008;15(4):512–22.
[43] Quinn GP, Vadaparampil ST, Bower B, Friedman S, Keefe DL. Decisions and ethical issues among BRCA carriers and the use of preimplantation genetic diagnosis. Minerva Med 2009 Oct;100(5):371–83.
[44] Cheon JY, Mozersky J, Cook-Deegan R. Variants of uncertain significance in BRCA: a harbinger of ethical and policy issues to come? Genome Med 2014;6(12):1–10.
[45] Matloff E, Barnett R, Nussbaum R. Choosing a BRCA genetic testing laboratory: a patient-centric and ethical call to action for clinicians and payers. Evidence-Based Oncology; 2014.
[46] Park JJ. The ethics of patenting the BRCA genes for breast cancer research. J Value Inq 2017;51(3):531–45.
[47] Anand P, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, et al. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res (N Y) 2008;25(9):2097–116.
[48] Nicol D, Dreyfuss RC, Gold ER, Li W, Liddicoat J, Van Overwalle G. International divergence in gene patenting. Annu Rev Genom Hum Genet 2019;20:519–41.
[49] George A, Kaye S, Banerjee S. Delivering widespread BRCA testing and PARP inhibition to patients with ovarian cancer. Nat Rev Clin Oncol 2017;14(5):284–96.
[50] Beard C, Monohan K, Cicciarelli L, James PA. Mainstream genetic testing for breast cancer patients: early experiences from the Parkville Familial Cancer Centre. Eur J Hum Genet 2021;29(5):872–80.
[51] Benusiglio PR, Korenbaum C, Vibert R, Ezenfis J, Geoffron S, Paul C, et al. Utility of a mainstreamed genetic testing pathway in breast and ovarian cancer patients during the COVID-19 pandemic. Eur J Med Genet 2020;63(12):104098.
[52] Flaum N, Morgan RD, Burghel GJ, Bulman M, Clamp AR, Hasan J, et al. Mainstreaming germline BRCA1/2 testing in non-mucinous epithelial ovarian cancer in the North West of England. Eur J Hum Genet 2020;28(11):1541–7.
[53] Hallowell N, Wright S, Stirling D, Gourley C, Young O, Porteous M. Moving into the mainstream: healthcare professionals' views of implementing treatment focussed genetic testing in breast cancer care. Fam Cancer 2019;18(3):293–301.
[54] Paluch-Shimon S, Pagani O, Partridge AH, Bar-Meir E, Fallowfield L, Fenlon D, et al. Second international consensus guidelines for breast cancer in young women (BCY2). Breast 2016;26:87–99.
[55] McCuaig JM, Armel SR, Novokmet A, Ginsburg OM, Demsky R, Narod SA, et al. Routine TP53 testing for breast cancer under age 30: ready for prime time? Fam Cancer 2012;11(4):607–13.
[56] Miller DT, Lee K, Chung WK, Gordon AS, Herman GE, Klein TE, et al. ACMG SF v3. 0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2021:1–10.
[57] de Wert G, Dondorp W, Clarke A, Dequeker EM, Cordier C, Deans Z, et al. Opportunistic genomic screening. Recommendations of the European society of human genetics. Eur J Hum Genet 2021;29(3):365–77.
[58] Garcia-Retamero R, Sobkow A, Petrova D, Garrido D, Traczyk J. Numeracy and risk literacy: what have we learned so far? Spanish J Psychol 2019;22.
[59] Portnoy DB, Roter D, Erby LH. The role of numeracy on client knowledge in BRCA genetic counseling. Patient Educ Counsel 2010;81(1):131–6.
[60] Rutgers E, Balmana J, Beishon M, Benn K, Evans DG, Mansel R, et al. European Breast Cancer Council manifesto 2018: genetic risk prediction testing in breast cancer. Eur J Cancer 2019;106:45–53.
[61] Kilbride MK, Bradbury AR. Evaluating web-based direct-to-consumer genetic tests for cancer susceptibility. JCO Precision Oncol 2020;4:161–9.
[62] Evans DGR, Barwell J, Eccles DM, Collins A, Izatt L, Jacobs C, et al. The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services. Breast Cancer Res 2014;16(5):442.
[63] Kamenova K, Reshef A, Caulfield T. Angelina Jolie's faulty gene: newspaper coverage of a celebrity's preventive bilateral mastectomy in Canada, the United States, and the United Kingdom. Genet Med 2014;16(7):522–8.
[64] Borzekowski DL, Guan Y, Smith KC, Erby LH, Roter DL. The Angelina effect: immediate reach, grasp, and impact of going public. Genet Med 2014;16(7):516–21.
[65] Skrovanek E, Dunbar-Jacob J, Dunwoody C, Wesmiller S. Integrative review of reproductive decision making of women who are BRCA positive. J Obstet Gynecol Neonatal Nurs 2020;49(6):525–36. https://doi.org/10.1016/j.jogn.2020.07.006.