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# Commentary: Why is genetic testing underutilized worldwide? The case for hereditary breast cancer

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It is thirty years since the *BRCA1* and *BRCA2* genes were discovered and genetic testing for *BRCA1* and *BRCA2* was introduced. Despite increasing awareness of the genetic basis of cancer and our evolving knowledge of effective means of prevention, screening, and treatment for hereditary breast and ovarian cancers, genetic testing is underutilized, and most mutation carriers remain unidentified. In this commentary, we explore possible reasons for why this might be so. Our focus is on factors that may influence or deter a patient from pursuing testing, rather than discussing the implications of receiving a positive test result. Issues of concern include an inadequate number of genetic counselors, restrictive (and conflicting) eligibility criteria for testing, the cost of the test, health insurance coverage, fear of future insurance discrimination, privacy issues, lack of familiarity with the testing process in primary care and gaps in both patient and provider knowledge about the impact and the value of testing. We discuss how these factors may lead to the underutilization of genetic testing in North America and throughout the world and discuss alternative models of genetic healthcare delivery. We have invited leaders in cancer genetic from around the world to tell us what they think are the barriers to testing in their host countries.

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## INTRODUCTION

Breast cancer is the most common solid tumor in women and there are few means of preventing it other than risk-reducing surgery [1–3]. Germline genetic testing identifies pathogenic or likely pathogenic variants (hereafter referred to as mutations) in over 12 genes that confer a moderate to high risk of breast cancer [4], which begins in early adulthood. The greatest burden is attributable to mutations in *BRCA1* and *BRCA2*, which confer high risks of breast and ovarian cancer. In the United States, between 5 and 10% of breast cancers are thought to be due to inherited genetic mutations [4], compared to 28% of ovarian [5], 7% of prostate [4], and 15% of colorectal cancers [6]. Support for universal germline testing after a breast cancer diagnosis is growing, however; targeted guidelines miss many patients [7–11]. About one-third of patients diagnosed with breast cancer meet guidelines for genetic testing [12–14] at the time of diagnosis, but many don't receive it. Katz et al. examined women aged 20–79 years of age diagnosed with early-stage breast cancer in 2014–2015 reported to the Georgia and Los Angeles County SEER registries, surveying them seven months and six years after diagnosis [15]. Patients were asked about genetic counseling, testing, and communication with relatives about results. Seventy-two percent of those that met criteria for testing at diagnosis (28% of the total group), underwent testing initially, with 53.3% of the additional 20% that met criteria at a later time point undergoing testing later. Only 3.4% had direct-to-consumer testing, suggesting that these tests don't currently substitute for clinical testing. There was no difference in the uptake of testing by race.

Identification of healthy individuals harboring these mutations allows for early detection and risk-reduction strategies, and in cancer patients, targeted treatment strategies. Our discussion focuses primarily on carriers of *BRCA1* and *BRCA2* mutations because these are the most studied. In general, testing will be conducted for a wide range of cancer predisposing genes (multigene panel testing) but all panels include both *BRCA1* and *BRCA2*.

Some have argued that all breast cancer patients be tested for *BRCA1* and *BRCA2* mutations [16], however, in most jurisdictions, testing is limited to those considered to be at high risk for carrying a mutation. Risk factors for carrying a mutation include a personal or family history of breast cancer (on either the maternal or paternal side; especially age at onset of 50 years or younger, triple-negative breast cancer, bilateral breast cancer, or male breast cancer) pancreatic cancer, ovarian cancer, or metastatic prostate cancer [10].

The frequency of *BRCA* mutations varies across populations. In the United States (US), approximately one in 300 adults carriers a *BRCA1* or *BRCA2* mutation [17]. In the Ashkenazi Jewish population approximately one in 40 individuals carries one of three founder mutations (two in *BRCA1* and one in *BRCA2*) [18]. Countries with a high prevalence of founder mutations include Iceland and the Bahamas [19, 20]. In Poland, the frequency of mutations in the population is not strikingly high, but approximately 90% of all mutations are one of four founder mutations in *BRCA1*, and genetic testing for these four mutations has a sensitivity in identifying carriers of approximately 90% [21]. In populations where founder mutations are over-represented, clinicians may opt

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for tests that include only these mutations, making the test much less expensive and possibly permitting expanded (or universal) testing. In Poland all adults are eligible for founder mutation screening but only those with a personal or family history of cancer are offered full gene sequencing [21]. One issue that arises throughout the world is lack of knowledge of one's family history.

> "Many women have limited information on extended family members – sometimes related to immigration, sometimes to taboos in discussing illness. This lack of information can lead to an erroneous assessment of the familial risk and a missed opportunity for genetic testing."
>
> Andrea Superti-Furga,
>
> MD - Professor emeritus of Pediatrics and Genetics, Switzerland

One barrier to genetic testing is that testing criteria and guidelines are inconsistent, creating confusion for both patients and providers. The National Comprehensive Cancer Network (NCCN) has detailed cancer testing and management guidelines [10], but these may not be practical for developing countries. The American Society of Breast Surgeons recommends testing all breast cancer patients [16]. The American Society of Clinical Oncology and the Society of Surgical Oncology recommend *BRCA1* and *BRCA2* testing to all newly diagnosed breast cancer patients aged 65 years or younger, and for those over 65, based on personal or family history, ethnicity, or eligibility for PARP inhibitor therapy [22]. Historically, testing began in the 1990s shortly after the *BRCA1* and *BRCA2* genes were discovered. Criteria for testing were created to restrict testing to those with a relatively high probability of testing positive, (e.g.10%) due to the lack of trained personnel and the high cost of testing. The implications of having a positive test had not yet been established and most testing was done in academic research centers. Over the past decade, the cost of testing has declined, results are returned rapidly as they may be actionable, and this argues for a reanalysis of testing criteria focusing on simplicity, improving access to testing, and increasing the number of carriers identified.

## WHY TEST?

The utility of testing for *BRCA1* and *BRCA2* is largely attributable to finding an *actionable* mutation; meaning that the discovery will prompt a change in management. Ideally, a woman with a mutation will be identified as a carrier *before* she develops cancer, but there are also therapeutic benefits of finding a mutation in those diagnosed with breast, ovarian, pancreatic, or prostate cancer. To maximize the opportunities for risk reduction, genetic testing should take place by age 30 [13, 23]. At present, there is little evidence to consider testing before age 25, the age when enhanced screening with magnetic resonance imaging (MRI) would begin [10].

The benefits of finding a *BRCA1* or *BRCA2* mutation in a *healthy* woman largely accrue through intensified screening and through risk-reducing bilateral salpingo-oophorectomy (RRSO). Previously, a 76% reduction in all-cause mortality was demonstrated with RRSO in *BRCA*-positive women [24]. This was confirmed in a recent large prospective study [25]. It is important that the fallopian tubes be removed as these are likely the site of origin of ovarian cancers [26]. Studies are now underway to determine if salpingectomy with delayed oophorectomy (thus avoiding premature surgical menopause) offers the same benefit as pre-menopausal bilateral salpingo-oophorectomy.

There is evidence that birth control pills reduce the risk of ovarian (and endometrial; but not peritoneal) cancers, but oral contraceptives are not seen as an alternative to risk-reducing salpingo-oophorectomy, as the residual risk for ovarian cancer would be unacceptable, and screening for ovarian cancer is suboptimal [27]. Tamoxifen has been shown to be effective in reducing the risk of primary breast cancer in *BRCA2* carriers [28] and it has been shown to reduce contralateral breast cancer risk [29]. Very few women with a *BRCA*1 or *BRCA2* mutation choose to take preventive tamoxifen [28], however, largely due to timing issues and fear of side effects. Premenopausal carriers (with no personal history of breast cancer) are advised to undergo risk-reducing bilateral salpingo-oophorectomy (RRSO) between ages 35 and 45 (per NCCN guidelines) [10] and may take menopausal hormone therapy (HT) until the time of natural menopause, precluding the use of tamoxifen until that time.

There is also a benefit to intensified breast screening. Recently, Lubinski et al. reported a large reduction in breast cancer mortality in women with *BRCA1* mutations after entering an MRI program, compared to those women who were screened with mammography alone or who were not screened at all [30]. In this study, a similar reduction in mortality for *BRCA2* carriers was not seen. In a separate observational study, *BRCA1* carriers who underwent regular MRI surveillance presented with lower-stage disease and had higher five-year survival rates compared to those who did not have MRIs. (94% vs 78%; $p = 0.03$) [31].

There are also benefits to testing *affected* women (i.e., women with breast cancer). In breast cancer patients with a *BRCA1* or *BRCA2* mutation, poly-ADP-ribose polymerase (PARP) inhibitors have been shown to improve survival, both in patients with metastatic disease [32], and in those with high-risk HER2-negative disease [33]. Further, preventive salpingo-oophorectomy has been shown to reduce breast cancer fatality in women with *BRCA1*, *BRCA2*, and *CHEK2* mutations [34–36]. This is of particular benefit for those women who fail to achieve a pathological complete response after conventional neoadjuvant chemotherapy. Knowledge of germline status can also be important in surgical decision-making. Patients with *BRCA1*, *BRCA2, PALB2*, and *CHEK2* mutations have higher rates of subsequent contralateral disease [37] and may be candidates for bilateral mastectomy.

## MODELS OF GENETIC TESTING

### The traditional model

The traditional model of genetic testing involves patients being initially assessed by their healthcare provider and then being referred to a genetic counselor. The counselor collects information on family history and other risk factors and then determines whether the subject is eligible for genetic testing. Her risk of carrying a mutation is estimated based on her age, personal history, and family history. She discusses the pros and cons of genetic testing, including possible financial consequences and psychological sequelae. In some cases, confirmation of pathology in relatives is required before testing is offered. If the patient is willing, the counselor processes the genetic test request for the reference laboratory. If the patient does not qualify for testing but wishes to pursue it, one option in some countries (rarely utilized) is that she may be referred to an out-of-pocket next-generation direct-to-consumer testing service. In Canada, this is available through TheScreenProject.ca [38] and in the United States, there are several commercial laboratories that offer this service.

In the post-test counseling session, the test result is revealed, and follow-up recommendations are made. In many centers, the patient consents to receive results by phone. If the patient has an abnormal finding, an appointment should follow to further discuss the implications of the results. Given the current expansion in the number of women wishing genetic testing, limitations of the traditional model include a long period between referral and genetic counseling cappointment and many patients do not follow through.

## ALTERNATIVE MODELS

### Mainstream testing

Mainstream testing refers to testing initiated by the treating physician and not the genetic counselor. The mainstream approach developed because there is a scarcity of genetic counselors, long wait times between referral and appointment, and imminent therapeutic implications. In cases where universal testing is recommended (such as in patients with ovarian cancer, triple-negative breast cancer, or pancreatic cancer) [10], mainstream testing facilitates the process. In mainstream testing, genetic counseling referral is generally limited to those with a positive test, a variant of uncertain significance (VUS), findings that are inconclusive or that have conflicting interpretations. Mainstreaming requires non-genetics personnel to provide pre-test information and informed consent, and initiate follow-up recommendations for those both with a positive test result and those with a negative result.

In general, mainstreaming has resulted in much higher testing rates among eligible cancer patients. This approach reduces disparities in access, is cost-effective, and reduces clinic visits [39, 40]. In one surgical practice in the United States, 88% of eligible patients underwent testing [39]. However, mainstreaming is largely restricted to women who are already affected with breast or ovarian cancer. Testing is rarely offered to unaffected patients in the primary care setting.

> *"In Spain, access to germline testing for cancer susceptibility has been provided by the Spanish Public Health Service over the last 15 years and is implemented in cancer genetics units, mostly located within the medical oncology services of some tertiary care hospitals. In most cases, pre-test assessment and post-test risk management are carried out by trained medical oncologists and nurses; there are only a few genetic counselors. Priorities include training of more genetic counselors and medical consultants and the use of telemedicine in order to meet growing needs. New approaches and counseling dynamics are in demand to identify cancer susceptibility in a timely and more effective manner."*
>
> Teresa Ramon y Cajal MD PhD - Medical Oncology, Hospital Clinic of Barcelona

### Direct-to-consumer testing

Patients with sufficient resources will sometimes seek direct-to-consumer testing. The consumer pays the laboratory directly for the test and a blood or saliva sample is shipped directly to the laboratory. A physician referral is usually not necessary. The patient may be offered pre-test counseling by the laboratory, but this is optional and rarely utilized. The test result is reported to the patient. In the event of a positive test, many companies offer genetic counseling as a part of the process, or referral to a genetic counselor is advised. The advantages of direct-to-consumer testing are that there are no eligibility criteria for testing that must be met, no waiting time, and convenience. The disadvantages may include cost, variable adherence to laboratory standards, a lack of follow-up (in both patients who have a positive finding and those who test negative but have significant family history), and lack of subspecialty patient referral when indicated. In Canada, multigene panel testing is available to all adult men and women through the ScreenProject.ca [38].

### Founder mutations – Early studies of population screening introduce technological options

Another approach to testing focuses on identifying patients with founder mutations, such as the three specific *BRCA* mutations in the Ashkenazi community, in whom population-based screening is feasible and cost-effective. One study examined targeted *BRCA1* and *BRCA2* population screening among Ashkenazi women using a web-enabled medical model. The study demonstrated the acceptance of a digital portal with risk-adapted medical follow-up and engagement of primary care providers in results-sharing and management [41]. In an early Ontario population-based study, a brochure was provided to Ashkenazi women with information about *BRCA*, the implications of testing, and risk-management strategies [42]. More than 92% of women were satisfied with the testing process, and the uptake of risk-reducing strategies was significant. In the Szczecin region of Poland, over 500,000 individuals have been tested for four founder mutations in the *BRCA1* gene [21]. A concern with population-based testing is false reassurance with a negative test when there is a strong family history.

### Panel testing

Clear clinical utility has been demonstrated for *BRCA1* and *BRCA2* (and possibly *PALB2*), but testing for moderate penetrance genes is increasingly being offered. Most patients will opt to have the most information possible, including the maximum number of genes [43]. Practically, the criteria most predictive of a positive test in a newly diagnosed breast cancer patient are age at diagnosis under 50 years, a positive family history and triple-negative breast cancer [44].

### Cascade testing

For patients with an identified mutation, the genetic counselor or healthcare provider helps with contacting relatives to offer "cascade testing" for the same mutation. In general, the counselor informs the patient orally and/or in writing about the importance of testing relatives. The letters provided to the patient (by the ordering provider) to share with family members can be technical and difficult to understand, and this likely contributes to poor uptake of testing. In a recent US survey of previously diagnosed patients, of those identified with a pathogenic variant, 62.7% talked to most or all of their first degree relatives about testing [15]. There is evidence, however, that families may prefer a more direct approach to informing relatives (i.e. by the ordering healthcare provider), which could improve the uptake of cascade testing. In a study from the Bahamas, for example, the uptake of genetic testing was much higher when the relative was contacted by the counselor than by the patient herself [20]. In the US and some other countries, however, the patient's right to confidentiality supersedes the duty to warn at-risk relatives of genetic predisposition [45]. In other parts of the world such as the United Kingdom, variant information may be disclosed without naming the tested individual or disclosing any clinical information [46]. Barriers to cascade testing are discussed below.

> *"What's really unfortunate is the lack of cascade testing in families with a known genetic issue. Laws prevent practitioners from contacting family, few patients are willing to talk about their gene positive status even when cascade testing is free. Why? Guilt, shame and worry about insurance discrimination."*
>
> Jerry Lanchbury, PhD –Former chief scientific officer, Myriad genetics

## GROUP COUNSELING

Informational group sessions about germline genetics, patterns of inheritance, red flags for carrier identification, founder mutations frequency, how testing is performed, and implications of a positive result for the patient and for their family may also be offered at the population level. For example, a hereditary cancer clinic in British Columbia offered large-scale group pre-test genetic counseling to unaffected patients meeting family history criteria set forth by the clinic. Eight percent of patients declined large group counseling in favor of one-on-one counseling. The group counseling process saved time and was acceptable to patients, representing another alternative to traditional pre-test counseling [47].

## BARRIERS TO TESTING

### Access to genetic counselors

Pre-test genetic counseling has classically been provided by licensed Genetic Counselors, who may not always be accessible. This particularly impacts patients in rural or low-income areas, however, at present, wait times at many major medical institutions are also prohibitive. In most European countries and Latin America, genetic counselors are rare and the information is provided by nurses and physicians. Task forces and networks are being established throughout Europe, North America, Australia, and the Republic of South Africa to attempt to meet the world's needs, however, the demand outweighs the supply.

### Eligibility

In the United States, the majority of mutation carriers remain unidentified. Childers et al. estimated that there were approximately one million eligible breast and ovarian cancer patients in the US who have yet to undergo testing, and most have never discussed testing with a healthcare provider [48]. A study by Beitsch et al. in 2019 reported that the chance of finding a genetic change among breast cancer patients who did not meet NCCN guidelines for testing was similar to those who met guidelines; i.e., the mutation rate was the same in both arms [7]. Yang et al. in 2018 reported on 4196 Medicare patients consecutively undergoing genetic testing [49]. The rate of pathogenic variants for patients who met Medicare testing criteria was 10.5% and for those who did not was 9%. In a racially and ethnically diverse population studied by Westbrook et al., among women who had a pathogenic variant in either a gene for hereditary breast or ovarian cancer or a Lynch Syndrome gene, only 38.5% met the criteria for genetic testing [50]. The study demonstrated a 2% yield for participants who did not meet any guidelines.

> *"In the Czech Republic, genetic testing is fully reimbursed by public health insurance for those who meet the testing criteria, based on NCCN guidelines. Genetic testing can only be initiated by a clinical geneticist, who also provides the follow-up recommendation based on the test results. Cascade testing is recommended to relatives at risk and is fully reimbursed, but only the probands can inform their relatives.*
>
> *Regarding the barriers to genetic testing access, the capacity of clinical geneticists is currently more or less adequate, and the waiting time for the genetic counseling is not a major obstacle. However, a major problem is the capacity of specialists to provide follow-up care to individuals at risk. The main issue is still the lack of awareness among other professionals and the general public. To some extent, this is due to the complexity of the testing. Simplification of the testing criteria could significantly improve the situation. In 2016 all ovarian cancer patient deemed were eligible for testing and we have now achieved a testing rate of over 70% of all ovarian cancer patients."*
>
> Jana Soukupova - Institute of Medical Biochemistry and Laboratory Diagnostics, Charles University, Prague

### Cost

At present genetic testing is offered online direct-to-consumer for all women in Canada and the United States (US) by several laboratories. The cost of online testing is approximately four hundred dollars (Canadian) or two hundred fifty dollars (US). Genetic testing is covered by many health insurance companies in the United States, but cost remains an issue for the uninsured. In Canada, high-risk women are offered genetic testing through the provincial health plan, but they must qualify according to provincial guidelines, and waiting times often exceed one year. In Ontario, those who do not qualify for provincial testing are offered online testing through TheScreenProject.ca [38]. Over the past decade, in the United States, genetic testing has increased among insured women but not among the uninsured [51]. Cost remains an important barrier in many parts of the world.

> *Access to genetic testing for BRCA1 and BRCA2 mutations is increasing in Costa Rica. Public health institutions, such as the Caja Costarricense del Seguro Social (Costa Rican Social Security), are beginning to include genetic testing as part of their services. However, testing remains costly and not widely available to the general population, although some private healthcare providers offer it. Availability is limited and there is a need for increased awareness, funding and trained professionals. Efforts are being made to improve access, but widespread, affordable access to genetic testing for hereditary breast and ovarian cancer risk remains an important goal.*
>
> Dr. Gustavo A. Gutierrez-Espeleta, Professor of Biology and Rector, University of Costa Rica
>
> San Jose, Costa Rica

### Genetic discrimination

Black race and older age have been associated with decreased testing rates [52]. Reasons for this likely include structural racism, lack of awareness amongst both patients and providers about the importance of genetic testing, health insurance coverage, mistrust of the medical system in general, and, more specifically, of the process of evaluating genetic information.

### Patient factors

Patients' knowledge, attitudes, emotions, and beliefs may influence genetic testing decisions. Anxiety, fear, and uncertainty are barriers to testing for many women, particularly in developing countries [3]. Furthermore, competing life concerns, transportation issues, and personal and cultural beliefs can influence testing. Some patients fear guilt in the context of a positive test result, and others feel that they may not do anything differently "if they knew," not realizing the high risk of ovarian cancer with *BRCA* mutations [53] and the opportunities for breast cancer risk-reduction or early detection.

> *"In addition, in many cultures, cancer, much less an inherited form, may be viewed as a stigma for the family"*
>
> Jerry Lanchbury, PhD – former chief scientific officer, Myriad Genetics

Historically, underserved populations have lower rates of genetic testing. A recent study at an Urban Safety-Net hospital examined genetic testing rates among those meeting NCCN criteria for testing [54]. Of the 637 patients included, 40% underwent genetic testing. Variables associated with uptake included female sex, Spanish language, family history of cancer, and referral for genetic testing. Black patients had a significantly lower uptake of genetic testing.

Another study in an urban academic medical center examined associations between sociodemographic factors, clinical factors, and genetic counseling and testing [55]. 510 women were referred for genetic counseling and most made appointments. More than half of these were White and employed. 268/425 patients kept their appointments. Being married and having insurance increased the likelihood of attending the counseling visit.

In a North London Ashkenazi population offered BRCA testing [56], 88% opted to take the test. Being married or cohabitating had four-fold higher odds for BRCA testing uptake ($P = 0.009$.) as did having children ($p = 0.005$). Reducing uncertainty and reassurance

were the most important factors contributing to decision-making, but concerns regarding risks, confidentiality, insurance, emotional impact, inability to prevent cancer, and stigma were also significantly associated with decreased uptake of testing.

**Provider factors**

The physician's recommendation is important in guiding a patient's decision to undergo genetic testing. However, providers often lack the time and confidence to discuss hereditary cancer predisposition (or options for risk management) or may focus on other acute health issues. Assessment of family history is not routine and referrals to genetic counseling are inconsistent. In one study conducted at a major academic institution, fewer than 25% of primary healthcare providers had ever referred a patient to genetics [9, 57]., Genetic testing needs to be simplified for the primary care provider. The complicated testing guidelines, long wait times, and competing health issues often preclude the opportunity for the busy primary care provider to initiate the process.

> *"KNOWLEDGE IS POWER. We need to help the busy primary care physicians by automating referrals for conditions where counseling would always be recommended, such as ovarian cancer and triple negative breast cancer. With alternative models of pre-test counseling, consistent messaging must be responsibly conveyed. AI will help with that and much more"*
>
> Charis Eng MD, PhD – Chairwoman, Genomic Medicine Institute Cleveland Clinic

> *"This is a first-world problem as well as a developing-world problem. We realize the clinical utility and have the resources, yet many even here in the US do not get tested. A provider's views on testing strongly influences patient choice, and providers are often focused on the problems at hand, not a possible problem"*
>
> Mark Robson MD – Breast oncologist and clinical geneticist, Memorial Sloan Kettering Cancer Center

Studies have demonstrated provider knowledge gaps in discussing hereditary cancer risks, choosing the appropriate genetic tests, interpreting results, and communicating this information. Further, many primary care physicians lack a multidisciplinary infrastructure to care for identified patients.

> *"Typically, primary care providers won't order a test that they don't understand or don't know how to act on or explain. Many PCPs think that they know about genetics, but really are quite naïve when it comes to low penetrance variants, VUS and level of actionable risk"*
>
> Jennifer Preiss, MD – Internist, Allegheny Health Network

**Insurance concerns**

Consumers considering participation in genetic research or seeking genetic tests for personal health concerns often harbor fears about privacy and insurer misuse of information. On May 21, 2008, The Genetic Information Nondiscrimination Act (GINA) was signed into law in the United States aiming to prevent discrimination in the workplace and with health insurance based on genetic information [58]. It has reassured many regarding legal safeguards, and individual states often offer additional protection.

**Cascade testing**

Cascade testing of at-risk relatives represents a critical unmet need and is often thwarted by suboptimal communication within a family. This is possibly our greatest opportunity for improvement in carrier identification as family members of affected carriers have the highest pretest probability of receiving an actionable result (either positive or negative) of any group.

In the UK, Dheensa et al. [59] discuss the implications of giving patients "family letters" to alert relatives of their risk. They conclude that dissemination of information through this channel represents an uncontrolled form of communication, and may not be sufficient. They suggest using alternative and supplementary methods of communication, for example through using digital tools, and they propose direct contact by the health care professional which might be more effective. In a study from the Bahamas [20], we compared the uptake of the two approaches. We offered genetic testing to 202 first-degree relatives of 58 mutation carriers. Of the 159 women who were contacted by the proband or other family members, only 14 made an appointment for genetic testing (9%). In contrast, among 32 relatives who were contacted directly by the genetic counselor, 27 came for an appointment (84%). In a small study from Sweden [60], at-risk relatives indicated that they would prefer if they were notified by a family member before receiving the letter but agreed that hat notifying at-risk relatives was appropriate. However, privacy regulations in this regard vary from country to country In the UK, the health professional's duty of confidentiality is not absolute and is balanced by a duty of disclosure under certain circumstances.

A US study examined the impact of the proband's indication for genetic testing on the uptake of cascade testing among relatives [61]. Cascade testing due to a positive result in a hereditary cancer syndrome gene was more commonly pursued when the proband was White, female, had a personal history of cancer, or when the gene predisposed to a CDC Tier 1 condition. The Centers for Disease Control and Prevention has designated several conditions as Tier 1 genomic applications because they have strong evidence of pathogenicity. Hereditary breast and ovarian cancer syndrome and Lynch syndrome are two examples of CDC Tier 1 conditions.

**Risk management following testing**

Another barrier to testing is the lack of a multidisciplinary infrastructure to manage identified carriers. Ideally, providers need access to high-quality contrast-enhanced full-sequence MRI, and the availability of experienced oncologic breast surgeons and reconstructive plastic surgeons. In some parts of the world, cost and/or access may preclude the uptake of advanced risk management strategies such as MRI screening, risk-reducing surgeries, and PARP inhibitors.

> *"In South Africa, as in the African continent at large, science has outrun the population. We need Africa-orientated innovative strategies to educate and test based on "Africa-time". People need time to listen and comprehend and do not want to be rushed into life-changing decisions. By conducting genetic testing and counseling in parallel in rural communities, we can make a fundamental change on ground level. However, there is a lack of multidisciplinary teams consisting of geneticists, surgeons, radiologists and psychologists. Operating time is limited for unaffected women, limiting risk-reducing surgeries. Novel treatments such as PARP inhibitors are not available and oncofertility services are lacking."*
>
> Nerina Van Der Merwe Ph.D- Senior Specialist Scientist: Human Genetics- Bloemfontein South Africa

## STRATEGIES FOR IMPROVED UPTAKE OF GERMLINE TESTING

Kurian et al. reported an increase in genetic testing between 2013 and 2019 in the US, however significant disparities remain by age, race, and insurance coverage [62]. Alternative models for pre-test counseling include digital portals and mailed brochures as have been used for population-based Ashkenazi counseling, testing,

and follow-up [41, 42]. Other alternate care models include "mainstreaming," telehealth, educational videos, computerized decision-support tools, and the use of genetic counseling extenders, embedded genetic counselors, and artificial intelligence. Social media can also influence a patient's awareness and acceptance of genetic testing.

In a meta-analysis exploring the uptake of genetic testing for the universal indication of ovarian cancer, different modes of pre-test counseling were studied [63]. Telehealth resulted in 75% of eligible patients undergoing testing. Embedding a genetic counselor results in improved testing rates but is impractical in most settings. Electronic Health Record-created reminders for referral to genetics or automatically generated referrals where a provider needs to merely approve the order for consultation can be produced in disease processes where universal testing is recommended such as serous ovarian cancer, male breast cancer, pancreatic cancer, or triple-negative breast cancer. This both guides and streamlines the process for referring providers.

Patients often prefer these technological innovations over an appointment with a genetic counselor. Pal et al. showed that a 12-minute web-based video could significantly increase genetic knowledge among a population of young Black breast cancer patients [64]. In the Genetic Education, Risk Assessment and Testing (GENERATE) study, two remote healthcare delivery models (telemedicine with online genetic information and online genetic information only) were studied in families with pancreatic cancer. Notably, the group receiving telehealth counseling in addition to the online information was less likely to test as compared to the information-only arm [65]. An educational video was compared to traditional in-person genetic counselor visits for patients with metastatic prostate cancer and yielded high genetic testing uptake without significant differences in measures of genetics knowledge and family communication [66]. Chatbots, artificial-intelligence-based computer programs that communicate with people by simulating human emotional and social dialog, offer broader access while maintaining a high level of standardization and quality. One study showed that the use of chatbots was effective in communicating information with excellent acceptance by the patients [67]. Computer-based clinical decision-support tools with standardized messaging and updated guideline incorporation will likely assist the primary care provider with pre-test counseling and clinical management. An obvious issue with the use of artificial intelligence is that it will not provide empathetic responses and cannot offer complex psychological support.

> *"Artificial intelligence is the answer to carrier identification – natural language mining of the EHR could identify patients appropriate for testing, and through training a dataset, could potentially enhance current models to improve identification of high-risk patients. It could automatically place pended orders on appropriate patients, gather Clinvar information on VUS annually, standardize templates and aid in professional education by providing updates on guidelines, etc…"*
>
> Rifaat Rawashdeh MS, LCGC – Genetic Counselor Abu Dhabi

We must educate more providers who are experienced in clinical cancer genetics and post-test management. There is also an urgent need to educate women's healthcare providers in genetics and genomics, beginning in medical schools and primary care residency programs. Professional societies such as the American Society of Clinical Oncology (ASCO) provide educational resources for providers. Podcasts have been produced. Meiser et al. reported that an online training course effectively increased genetic literacy and communication skills in oncology providers discussing genetic testing with cancer patients [68]. Another web-based intervention generating risk estimates using breast cancer risk models and providing high-risk screening recommendations showed improvement in the clinician knowledge base [69]. Efforts to improve public awareness to empower at-risk patients to inquire about genetic testing are also needed.

Finally, the choice of genes to be tested may be different in different settings. A recent meta-analysis was recently performed for three large population-based case-control studies (CARRIERS, BRIDGES and the UK Biobank) to quantify the frequency of pathogenic variants in unselected "population-type" breast cancer genes and their association with breast cancer risk and its subtypes. The frequency of *BRCA1, BRCA2* and *PALB2* were significant for ER− disease; for ER+ disease, CHEK*2* and *ATM* were strongly associated with breast cancer. This may help to inform the appropriate gene set as we continue to expand germline testing to more unselected population-based breast cancer cases [70].

All models of pre-test counseling must provide consistent messaging, and attention to patient knowledge and satisfaction. Understanding attitudes, perceptions, and beliefs among various racial and ethnic groups is also important for culturally appropriate cancer communication [71]. Remote forms of testing enable broad geographic coverage.

## INTERNATIONAL PERSPECTIVES

In many low- and middle-income countries, genetic testing for cancer susceptibility has not yet evolved. Limited resources will require careful priority planning (identification of individuals most likely to harbor mutations, screening for founder mutations, etc.), and focus on those interventions shown to improve survival including risk-reducing salpingo-oophorectomy and MRI screening.

> *"In Mexico, access to genetic cancer risk assessment is limited due to barriers including insufficient specialists in genetic counseling, suboptimal awareness among physicians regarding recommendations for referral to genetic cancer services, as well as restrictive out-of-pocket expenses resulting from lacking coverage of genetic testing, surveillance studies, and risk-reducing surgeries by public and private insurance policies. Financial reasons and communication challenges also hinder cascade testing which is a a crucial component of risk reduction and early diagnosis among carriers' at-risk relatives* [72].
>
> Cynthia Villarreal-Garza MD DSc- Breast oncologist and researcher, Hospital Zambrano Hellion Monterrey, Mexico
>
> *Let's talk simple economics, genetic testing in the third world is cost prohibitive. For profit next-generation direct-to-consumer genetic testing, via a middle provider, is the most common form of genetic testing in third world countries. The middle provider sends the sample via courier to a first world country for processing and this adds an additional cost. This higher cost for genetic testing in third world countries also precludes cascade testing. In Jamaica, genetic testing is not covered by the insurance companies and cost approximately seven to nine hundred dollars (US). In some cases, this reflects more than a several fold increase in cost compared to first world countries "*
>
> Patrick Roberts MD, Surgical oncologist, University of the West Indies, Mona, Jamaica

## CONCLUSION

Identification of patients with germline mutations in cancer susceptibility genes has substantial implications for cancer prevention, early detection, and treatment. Genetic testing is underutilized worldwide for a multitude of reasons ranging from patient and provider knowledge and attitudes, time constraints in primary care, cost, lack of access to subspecialty genetics consultations, and lack of Information Technology (IT) and post-

identification multidisciplinary management infrastructure. All are required to improve patient and provider awareness and to field the increasing demands as we broaden testing criteria.

## DATA AVAILABILITY

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

## REFERENCES


1. International WCRF. Worldwide cancer data. (2024) World Cancer Research Fund International. Published 2023. Accessed April 1. https://www.wcrf.org/cancer-trends/worldwide-cancer-data/
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49. https://doi.org/10.3322/caac.21660
3. American Cancer Society. American Cancer Society: Cancer Facts and Figures 2021. Atlanta: Ga Am Cancer Soc; 2021. Published online
4. Esplin ED, Nielsen SM, Bristow SL, Garber JE, Hampel H, Rana HQ, et al. Universal germline genetic testing for hereditary cancer syndromes in patients with solid tumor cancer. JCO Precis Oncol. 2022;6:e2100516. https://doi.org/10.1200/PO.21.00516
5. Weiss AS, Swisher E, Pennington KP, Radke M, Khasnavis N, Garcia RL, et al. Inherited mutations in fallopian tube, ovarian and primary peritoneal carcinoma: changes in diagnoses and mutational frequency over 20 years. Gynecol Oncol. 2020;159:214–20. https://doi.org/10.1016/j.ygyno.2020.06.509
6. Uson PLS Jr, Riegert-Johnson D, Boardman L, Kisiel J, Mountjoy L, Patel N, et al. Germline cancer susceptibility gene testing in unselected patients with colorectal adenocarcinoma: a multicenter prospective study. Clin Gastroenterol Hepatology Off Clin Pract J Am Gastroenterol Assoc. 2022;20:e508–e528. https://doi.org/10.1016/j.cgh.2021.04.013
7. Beitsch PD, Whitworth PW, Hughes K, Patel R, Rosen B, Compagnoni G, et al. Underdiagnosis of hereditary breast cancer: are genetic testing guidelines a tool or an obstacle? J Clin Oncol Off J Am Soc Clin Oncol. 2019;37:453–60. https://doi.org/10.1200/JCO.18.01631
8. Katz SJ, Ward KC, Hamilton AS, Mcleod MC, Wallner LP, Morrow M, et al. Gaps in receipt of clinically indicated genetic counseling after diagnosis of breast cancer. J Clin Oncol: Off J Am Soc Clin Oncol. 2018;36:1218–24. https://doi.org/10.1200/JCO.2017.76.2369
9. Kurian AW, Griffith KA, Hamilton AS, Ward KC, Morrow M, Katz SJ, et al. Genetic testing and counseling among patients with newly diagnosed breast cancer. JAMA. 2017;317:531–4. https://doi.org/10.1001/jama.2016.16918
10. Kurian AW, Li Y, Hamilton AS, Ward KC, Hawley ST, Morrow M, et al. Gaps in incorporating germline genetic testing into treatment decision-making for early-stage breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35:2232–9. https://doi.org/10.1200/JCO.2016.71.6480
11. Yadav S, Hu C, Hart SN, Boddicker N, Polley EC, Na J, et al. Evaluation of germline genetic testing criteria in a hospital-based series of women with breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2020;38:1409–18. https://doi.org/10.1200/JCO.19.02190
12. National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology (NCCN guidelines): guidelines. Genetic/familial high risk assessment: (2024) breast, ovarian and pancreatic version. V.3.2024. https://www.nccn.org
13. US Preventive Services Task Force, Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, et al. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: US preventive services task force recommendation statement. JAMA. 2019;322:652–65.
14. Center for Disease Control and Prevention: Genetic testing for hereditary breast and ovarian cancer. https://www.cdc.gov/genomics/disease/breast_ovarian_cancer/testing.html
15. Katz SJ, Abrahamse P, Furgal A, Hodan R, Tocco RS, Ward KC, et al. Genetic counseling, testing, and family communication into survivorship after diagnosis of breast cancer. J Clin Oncol Official J Am Soc Clin Oncol. 2024. JCO2400122. Advance online publication. https://doi.org/10.1200/JCO.24.00122
16. Manahan ER, Kuerer HM, Sebastian M, Hughes KS, Boughey JC, Euhus DM, et al. Consensus guidelines on genetic' testing for hereditary breast cancer from the American Society of Breast Surgeons. Ann Surg Oncol. 2019;26:3025–31. https://doi.org/10.1245/s10434-019-07549-8
17. Hu C, Hart SN, Gnanaolivu R, Huang H, Lee KY, Na J, et al. A population-based study of genes previously implicated in breast cancer. N. Engl J Med. 2021;384:440–51. https://doi.org/10.1056/NEJMoa2005936
18. Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N. Engl J Med 1997;336:1401–8. https://doi.org/10.1056/NEJM199705153362001
19. Johannesdottir G, Gudmundsson J, Bergthorsson JT, Arason A, Agnarsson BA, Eiriksdottir G, et al. High prevalence of the 999del5 mutation in icelandic breast and ovarian cancer patients. Cancer Res. 1996;56:3663–5.
20. Trottier M, Lunn J, Butler R, Curling D, Turnquest T, Royer R, et al. Strategies for recruitment of relatives of BRCA mutation carriers to a genetic testing program in the Bahamas. Clin Genet. 2015;88:182–6. https://doi.org/10.1111/cge.12468
21. Gronwald J, Cybulski C, Huzarski T, Jakubowska A, Debniak T, Lener M, et al. Genetic testing for hereditary breast cancer in Poland: 1998–2022. Hereditary Cancer Clin Pract. 2023;21:9 https://doi.org/10.1186/s13053-023-00252-6
22. Bedrosian I, Somerfield MR, Achatz MI, Boughey JC, Curigliano G, Friedman S, et al. Germline testing in patients with breast cancer: ASCO-society of surgical oncology guideline. J Clin Oncol Off J Am Soc Clin Oncol. 2024;42:584–604. https://doi.org/10.1200/JCO.23.02225
23. Monticciolo DL, Newell MS, Moy L, Lee CS, Destounis SV. Breast cancer screening for women at higher-than-average risk: updated recommendations from the ACR. J Am Coll Radiology JACR. 2023;20:902–14. https://doi.org/10.1016/j.jacr.2023.04.002
24. Finch AP, Lubinski J, Møller P, Singer CF, Karlan B, Senter L, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol Off J Am Soc Clin Oncol. 2014;32:1547–53. https://doi.org/10.1200/JCO.2013.53.2820
25. Gronwald J, Lubinski J, Huzarski T, Cybulski C, Menkiszak J, Siołek M, et al. A comparison of ovarian cancer mortality in women with BRCA1 mutations undergoing annual ultrasound screening or preventive oophorectomy. Gynecol Oncol. 2019;155:270–4. https://doi.org/10.1016/j.ygyno.2019.08.034
26. Sowamber R, Nelson O, Dodds L, DeCastro V, Paudel I, Milea A, et al. Integrative transcriptome analyses of the human fallopian tube: fimbria and ampulla-site of origin of serous carcinoma of the ovary. Cancers. 2020;12:1090 https://doi.org/10.3390/cancers12051090
27. Xia YY, Gronwald J, Karlan B, Lubinski J, McCuaig JM, Brooks J, et al. Contraceptive use and the risk of ovarian cancer among women with a BRCA1 or BRCA2 mutation. Gynecologic Oncol. 2022;164:514–21. https://doi.org/10.1016/j.ygyno.2022.01.014
28. Kotsopoulos J, Gronwald J, Huzarski T, Aeilts A, Randall Armel S, Karlan B, et al. Tamoxifen and the risk of breast cancer in women with a BRCA1 or BRCA2 mutation. Breast Cancer Res Treat. 2023;201:257–64. https://doi.org/10.1007/s10549-023-06991-3
29. Gronwald J, Robidoux A, Kim-Sing C, Tung N, Lynch HT, Foulkes WD, et al. Duration of tamoxifen use and the risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. Breast cancer Res Treat. 2014;146:421–7. https://doi.org/10.1007/s10549-014-3026-3
30. Lubinski J, Kotsopoulos J, Moller P, Pal T, Eisen A, Peck L, et al. MRI surveillance and breast cancer mortality in women with BRCA1 and BRCA2 sequence variations. JAMA Oncol. 2024;10:493–9. https://doi.org/10.1001/jamaoncol.2023.6944
31. Hadar T, Mor P, Amit G, Lieberman S, Gekhtman D, Rabinovitch R, et al. Presymptomatic awareness of germline pathogenic BRCA variants and associated outcomes in women with breast cancer. JAMA Oncol. 2020;6:1460–3. https://doi.org/10.1001/jamaoncol.2020.2059
32. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N. Engl J Med. 2017;377:523–33. https://doi.org/10.1056/NEJMoa1706450
33. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant olaparib for patients with *BRCA1*- or *BRCA2*-mutated breast cancer. N. Engl J Med. 2021;384:2394–405. https://doi.org/10.1056/NEJMoa2105215
34. Narod SA, Huzarski T, Gronwald J, Byrski T, Marczyk E, Cybulski C, et al. Predictors of survival for breast cancer patients with a BRCA1 mutation. Breast Cancer Res Treat. 2018;168:513–21. https://doi.org/10.1007/s10549-017-4605-x35
35. Evans DG, Phillips KA, Milne RL, Fruscio R, Cybulski C, Gronwald J, et al. Survival from breast cancer in women with a BRCA2 mutation by treatment. Br J Cancer. 2021;124:1524–32. https://doi.org/10.1038/s41416-020-01164-1
36. Tomiczek-Szwiec J, Szwiec M, Falco M, Cybulski C, Wokolorczyk D, Jakubowska A.Polish Breast Cancer Consortium. et al. The impact of oophorectomy on survival from breast cancer in patients with CHEK2 mutations. Br J Cancer. 2022;127:84–91. https://doi.org/10.1038/s41416-022-01770-1. Epub 2022 Mar 7
37. Yadav S, Boddicker NJ, Na J, Polley EC, Hu C, Hart SN, et al. Contralateral breast cancer risk among carriers of germline pathogenic variants in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*. J Clin Oncol Off J Am Soc Clin Oncol. 2023;41:1703–13. https://doi.org/10.1200/JCO.22.01239
38. Narod SA, Gojska N, Sun P, Tryon A, Kotsopoulos J, Metcalfe K, et al. The screen project: guided direct-to-consumer genetic testing for breast cancer susceptibility in Canada. Cancers. 2021;13:1894 https://doi.org/10.3390/cancers13081894.
39. Chai TS, Yin K, Wooters M, Shannon KM, Hughes KS. Mainstreamed genetic testing of breast cancer patients: experience from a single surgeon's practice in a large US Academic Center. Fam Cancer. 2023;22:467–74. https://doi.org/10.1007/s10689-023-00342-3
40. 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;29:872–80. https://doi.org/10.1038/s41431-021-00848-3
41. Morgan KM, Hamilton JG, Symecko H, Kamara D, Jenkins C, Lester J, et al. Targeted BRCA1/2 population screening among Ashkenazi Jewish individuals using a web-enabled medical model: an observational cohort study. Genet Med Off J Am Coll Med Genet. 2022;24:564–75. https://doi.org/10.1016/j.gim.2021.10.016
42. Metcalfe KA, Poll A, Royer R, Llacuachaqui M, Tulman A, Sun P, et al. Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28:387–91. https://doi.org/10.1200/JCO.2009.25.0712
43. Kurian AW, Hare EE, Mills MA, Kingham KE, McPherson L, Whittemore AS, et al. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. J Clin Oncol Off J Am Soc Clin Oncol. 2014;32:2001–9. https://doi.org/10.1200/JCO.2013.53.6607
44. Metcalfe KA, Narod SA, Eisen A, Poll A, Zamani N, McCready D, et al. Genetic testing women with newly diagnosed breast cancer: what criteria are the most predictive of a positive test? Cancer Med. 2023;12:7580–7. https://doi.org/10.1002/cam4.5515
45. Lehmann LS, Sulmasy LS, Burke W. Ethical considerations in precision medicine and genetic testing in internal medicine practice: a position paper from the American College of Physicians. Ann Intern Med. 2022. https://doi.org/10.7326/M22-0743. Published online July 26
46. The British Society for Genetic Medicine. Confidentiality and genetic information. Accessed July 311, 2024 at https://bsgm.org.uk/healthcare-professionals/confidentiality-and-genetic-information/
47. Lohn Z, Fok A, Richardson M, Derocher H, Mung SW, Nuk J, et al. Large-scale group genetic counseling: evaluation of a novel service delivery model in a Canadian hereditary cancer clinic. J Genet Couns. 2022;31:459–69. https://doi.org/10.1002/jgc4.1512
48. Childers KK, Maggard-Gibbons M, Macinko J. National estimates of genetic testing in women with a history of breast or ovarian cancer. J Clin Oncol. 2017;35:3800–6.
49. Yang S, Axilbund JE, O'Leary E, Michalski ST, Evans R, Lincoln S, et al. Underdiagnosis of hereditary breast and ovarian cancer in medicare patients: genetic testing criteria miss the mark. Ann Surg Oncol. 2018;25:2925–31. https://doi.org/10.1245/s10434-018-6621-4
50. Westbrook L, Miltenburg D, Souter V, Maisenbacher MK, Howard KL, Sha Y, et al. Hereditary cancer testing in a diverse sample across three breast imaging centers. Breast Cancer Res Treat. 2024;203:365–72. https://doi.org/10.1007/s10549-023-07137-1
51. Lau-Min KS, McCarthy AM, Nathanson KL, Domchek SM. Nationwide trends and determinants of germline BRCA1/2 testing in patients with breast and ovarian cancer. JNCCN J Natl Compr Cancer Netw. 2023;21. https://doi.org/10.6004/jnccn.2022.7257
52. Drohan B, Roche CA, Cusack JC, Hughes KS. Hereditary breast and ovarian cancer and other hereditary syndromes: using technology to identify carriers. Ann Surg Oncol. 2012;19:1732–7.
53. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA. 2017;317:2402–16. https://doi.org/10.1001/jama.2017.7112
54. West KM, Blacksher E, Burke W. Genomics, health disparities, and missed opportunities for the nation's research agenda. JAMA. 2017;317:1831–2. https://doi.org/10.1001/jama.2017.3096
55. Sutton AL, Hurtado-de-Mendoza A, Quillin J, Rubinsak L, Temkin SM, Gal T, et al. Reducing disparities in receipt of genetic counseling for underserved women at risk of hereditary breast and ovarian cancer. J Women's Health. 2020;29:1131–5. https://doi.org/10.1089/jwh.2019.7984
56. Manchanda R, Burnell M, Gaba F, Sanderson S, Loggenberg K, Gessler S, et al. Attitude towards and factors affecting uptake of population-based BRCA testing in the Ashkenazi Jewish population: a cohort study. BJOG: Int J Obstet Gynaecol. 2019;126:784–94. https://doi.org/10.1111/1471-0528.15654
57. Linfield DT, Rothberg MB, Pfoh ER, Noss R, Cassard L, Powers JC, et al. Primary care physician referral practices regarding BRCA1/2 genetic counseling in a major health system. Breast Cancer Res Treat. 2022;195:153–60. https://doi.org/10.1007/s10549-022-06523-5
58. Payne PW Jr, Goldstein MM, Jarawan H, Rosenbaum S. Health insurance and the Genetic Information Nondiscrimination Act of 2008: implications for public health policy and practice. Public Health Rep. 2009;124:328–31. https://doi.org/10.1177/003335490912400222
59. Dheensa S, Lucassen A, Fenwick A. Limitations and pitfalls of using family letters to communicate genetic risk: a qualitative study with patients and healthcare professionals. J Genet Couns. 2018;27:689–701.
60. Öfverholm A, Karlsson P, Rosén A. The experience of receiving a letter from a cancer genetics clinic about risk for hereditary cancer. Eur J Hum Genet. 2024;32:539–44.
61. Schmidlen TJ, Bristow SL, Hatchell KE, Esplin ED, Nussbaum RL, Haverfield EV. The impact of proband indication for genetic testing on the uptake of cascade testing among relatives. Front Genet. 2022;13:867226. https://doi.org/10.3389/fgene.2022.867226.
62. Kurian AW, Abrahamse P, Furgal A, Ward KC, Hamilton AS, Hodan R, et al. Germline genetic testing after cancer diagnosis. JAMA. 2023;330:43–51. https://doi.org/10.1001/jama.2023.9526
63. Lin J, Sharaf RN, Saganty R, Ahsan D, Feit J, Khoury A, et al. Achieving universal genetic assessment for women with ovarian cancer: are we there yet? A systematic review and meta-analysis. Gynecol Oncol. 2021;162:506–16. https://doi.org/10.1016/j.ygyno.2021.05.011
64. Pal T, Shah P, Weidner A, Tezak A, Venton L, Zuniga B, et al. Inherited cancer knowledge among black females with breast cancer before and after viewing a web-based educational video. Genet Test Mol Biomark. 2023;27:1–4. https://doi.org/10.1089/gtmb.2022.0160
65. Rodriguez NJ, Furniss CS, Yurgelun MB, Ukaegbu C, Constantinou PE, Fortes I, et al. A randomized trial of two remote health care delivery models on the uptake of genetic testing and impact on patient-reported psychological outcomes in families with pancreatic cancer: the genetic education, risk assessment, and testing (GENERATE) study. Gastroenterology. 2024;166:872–85. https://doi.org/10.1053/j.gastro.2024.01.042.
66. Rana HQ, Stopfer JE, Weitz M, Kipnis L, Koeller DR, Culver S, et al. Pretest video education versus genetic counseling for patients with prostate cancer: ProGen, a multisite randomized controlled trial. JCO Oncol Pract. 2023;19:1069–79. https://doi.org/10.1200/OP.23.00007
67. Al-Hilli Z, Noss R, Dickard J, Wei W, Chichura A, Wu A, et al. A randomized trial comparing the effectiveness of pre-test genetic counseling using an artificial intelligence automated chatbot and traditional in-person genetic counseling in women newly diagnosed with breast cancer. Ann Surg Oncol. 2023;30:5990–6. https://doi.org/10.1245/s10434-023-13888-4
68. Meiser B, Woodward P, Gleeson M, Kentwell M, Fan HM, Antill Y, et al. Pilot study of an online training program to increase genetic literacy and communication skills in oncology healthcare professionals discussing BRCA1/2 genetic testing with breast and ovarian cancer patients. Fam Cancer. 2022;21:157–66. https://doi.org/10.1007/s10689-021-00261-1
69. Seitzman RL, Pushkin J, Berg WA. Effect of an educational intervention on women's health care provider knowledge gaps about breast cancer risk model use and high-risk screening recommendations. J Breast Imaging. 2023;5:30–39. https://doi.org/10.1093/jbi/wbac072
70. Rowlands CF, Allen S, Balmaña J, Domchek SM, Evans DG, Hanson H, et al. Population-based germline breast cancer gene association studies and meta-analysis to inform wider mainstream testing. Ann Oncol Off J Eur Soc Med Oncol. 2024:S0923-7534(24)01014-7. Advance online publication. https://doi.org/10.1016/j.annonc.2024.07.244
71. Sankar P, Wolpe PR, Jones NL, Cho M. How do women decide? Accepting or declining BRCA1/2testing in a nationwide clinical sample in the United States. Community Genet. 2006;9:78–86. https://doi.org/10.1159/000091484
72. Mesa-Chavez F, Chavarri-Guerra Y, Aguilar-Y-Mendez D, Becerril-Gaitan A, Vaca-Cartagena BF, Carrillo-Bedoya A, et al. Uptake of risk-reducing measures, cascade testing, and related challenges among carriers of breast cancer-associated germline pathogenic variants in Mexico. JCO Glob Oncol. 2024;10:e2300417. https://doi.org/10.1200/GO.23.00417

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## COMPETING INTERESTS

Dr. Pederson serves as a consultant for Myriad Genetics and for Vira Health. Dr. Narod has no disclosures.

## ADDITIONAL INFORMATION

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