

Expanding the search for germline pathogenic variants for breast cancer. How far should we go and how high should we jump? The missed opportunity!

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Abstract

Since the identification of *BRCA1* and *BRCA2* genes 3 decades ago, genetic testing and genetic counseling have become an integral part of routine clinical practice. The risk of breast cancer among carriers of germline pathogenic variants, like *BRCA1* and *BRCA2*, is well established. Risk-reducing interventions, including bilateral mastectomies and salpingo-oophorectomies are both effective and have become more acceptable. Many researchers and professional societies view current guidelines as restrictive and may miss many at-risk women, and are calling to expand testing to include all patients with breast cancer, regardless of their personal or family history of cancer, while others are calling for wider adoption to even include all healthy women at age 30 or older. This review will address expanding testing in two directions; horizontally to include more patients, and even healthy women, and vertically to include more genes using next-generation sequencing-based multi-gene panel testing.

Introduction

Breast cancer continues to be the most common cancer worldwide; over two million cases are estimated to be diagnosed worldwide annually which represent almost 25% of all new female cancers.¹ A combination of both environmental and genetic factors

contributes to this high rate. It is estimated that 10-15% of all breast cancers are hereditary (Figure 1).^{2,3} Testing for *BRCA1* and *BRCA2* has been available for almost 25 years,⁴ and multiple professional organizations had published guidelines for testing breast cancer patients based on their personal or family history.⁵⁻⁷

More recently, next-generation sequencing (NGS) allowed the identification of many other genes with variable penetrance rates.^{8,9} Commonly encountered genes include ATM, BARD1, CDH1, CHEK2, PALB2, PTEN, RAD51C, RAD51D and TP53. The risks of breast and ovarian cancers among individuals with pathogenic variants are well-known for some genes, like *BRCA1* and *BRCA2*,¹⁰ and risk-reducing interventions are effective and well-studied.¹¹⁻¹³ However, risk of breast and ovarian cancers, and risk-reducing interventions are not as clear for genes other than *BRCA1/2*, but may be recommended once the carrier's absolute risk exceeds that of the average-risk population.

Current guidelines, however, are viewed by many researchers, clinicians and professional organizations as restrictive and that a proportion of patients might be missed.^{5,6,14} The American Society of Breast Surgeons (ASBS), for example, recommends testing all patients with breast cancer regardless of their personal or family history of cancer,¹⁵ while others are calling for testing all women at age 30 for breast cancer-predisposing genes and consider the occurrence of 'hereditary' breast cancer as a missed opportunity.¹⁶

Beyond prevention; therapeutic decisions

In addition to its role in identifying patients and relatives at risk for various cancers, identifying patients with germline pathogenic variants might also aid in treatment decisions. Two PARP (poly ADP ribose polymerase) inhibitors, olaparib and talazoparib, gained the U.S. Food and Drug Administration (FDA) approval for patients with metastatic breast cancer and a germline *BRCA1* or *BRCA2* mutation. In the OlympiAD trial, 302 patients with germline mutation and human epidermal growth factor receptor type-2 (HER2)-negative metastatic disease, were randomized to receive single-agent olaparib (300 mg twice daily) or the physician's choice of chemotherapy. Median progression-free survival (PFS) was significantly longer in the olaparib group than in the standard-therapy group (7.0 months vs 4.2 months; hazard ratio [HR] for disease progression or death, 0.58; 95% confidence interval [CI], 0.43 to 0.80; P<0.001).^{17,18}

In another trial, the EMBRACA, 431 patients with advanced-stage breast cancer were randomized to receive talazoparib (1 mg daily) or the physician's choice of chemotherapy. A significant improvement in PFS was also seen in talazoparib group compared to the standard-therapy group (8.6 vs 5.6 months; HR for disease progression or death, 0.54; 95% CI, 0.41 to 0.71; P<0.001).¹⁹

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More recently, Olaparib was also tried in similar patients with germline mutations in non-*BRCA1* or *BRCA2*-related genes; 87% were in *PALB2*, *sBRCA1/2*, *ATM*, or *CHEK2*. Fifty-four patients were enrolled and responses were seen with germline *PALB2* (ORR, 82%) No responses were observed with *ATM* or *CHEK2* mutations alone.²⁰

How far should we go?

Guideline-directed versus all patients with breast cancer

Referral of breast cancer patients for genetic testing and genetic counseling is suboptimal. Several factors may contribute to this lower than anticipated referral rate (Table 1).²¹ Even in Western societies and advanced health care systems, patients and physicians are not necessarily aware of such needs. Primary care clinics and media have been concentrating on issues related to early detection and down staging of breast cancer. Accuracy of family history and level of communication between family members might be an important issue as many patients and their close family members tend to keep such diagnosis confidential. Guidelines, like the one published by the National Comprehensive Cancer Network (NCCN), are viewed by many practicing oncologists as complex and not easy to follow. In one study that used pooled data from three Cancer Control Modules of the National Health Interview Survey (NHIS), 35.6% of the patients met one or more NCCN eligibility criteria for genetic testing and counseling for breast cancer; of those, 29.0% had a discussion, 20.2% were advised to undergo and only 15.3% underwent genetic testing.²² Another study that looked at the *BRCA*-carrier detection rate in Greater London area found that until 2014, only 2.6% of the general population and 10.9% of the high-risk Ashkenazi Jewish population *BRCA*-carriers have been identified.²³

It is estimated that 50% of patients with breast cancer who

carry a pathogenic variant of breast cancer predisposing gene may not have a family history; a mother may be among the lucky known proportion of variant carriers who may not develop the cancer, or at least not yet at the time of genetic counseling of her relative. To address these issues, a multicenter prospective study enrolled 959 patients at 20 community and academic sites to evaluate the capability of the NCCN guidelines to identify breast cancer patients with pathogenic or likely pathogenic variants. Patients aged between 18-90 years who had recently or formerly been diagnosed with breast cancer with no history of genetic testing, went through an 80-gene panel test; 50% of the enlisted patients did not meet NCCN criteria. Overall, 8.65% of the patients had a pathogenic or likely pathogenic variant. Positive mutation rates were 9.39%, and 7.9% among those who met and who did not meet the NCCN guidelines, respectively, $P=0.42$.²⁴

From the data presented, it seems that ‘restrictive testing’ following the NCCN guidelines would certainly miss a good portion of breast cancer patients. However, one can argue if such gains worth both the cost and the ‘noise’ caused by identifying genes with low penetrance rate or mutations classified as ‘variants of uncertain significance’ (VUS) as discussed below.

Table 1. Causes for underutilization of genetic testing.

- Physicians’ awareness
- Patients’ and family fears: stigmata, insurance
- Patients’ awareness
- Accuracy of family history
- Communication within or between families
- Timely referrals to clinical genetic departments
- Guideline complexity
- Expensive testing and lack of resources

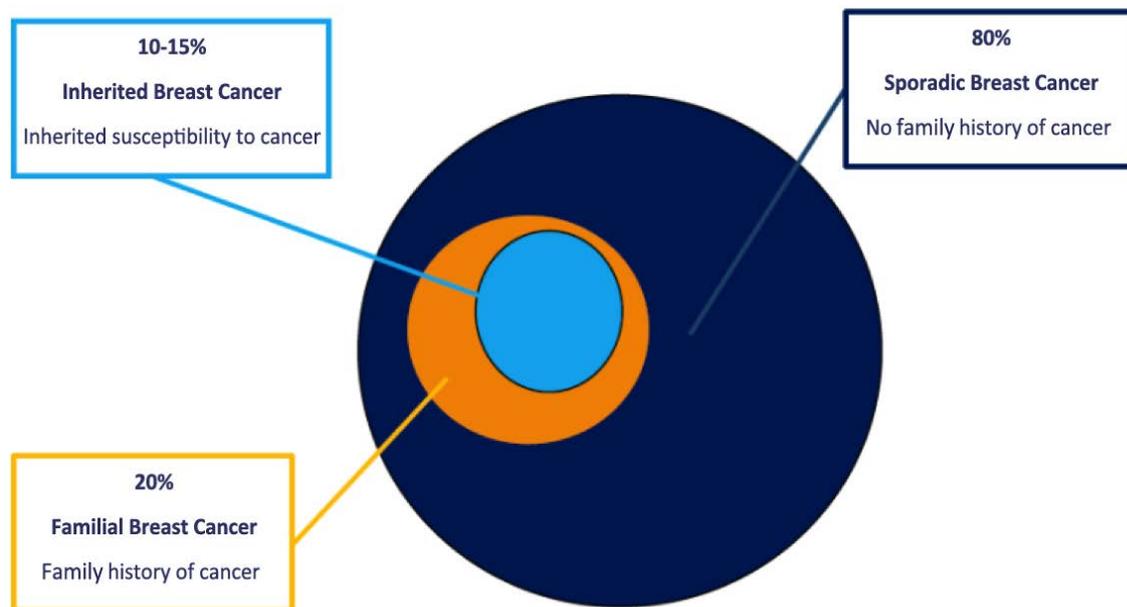


Figure 1. Inherited-Familial breast cancers. Expanding genomic testing for cancer-predisposing genes will likely increase the proportion of inherited breast cancers.

Population-based testing

The successful implementation of genetic testing for high-risk groups has led many researchers and clinicians to consider extending testing to the general population. Much of the experience was gained from studies conducted on Ashkenazi-Jewish population which assessed the feasibility, acceptability, impact, cost-effectiveness and long-term psychological outcomes among this high-risk ethnic group.²⁵⁻²⁷ Similar studies on 'population-based' genetic testing are beginning to emerge. Mary-Claire King, who was the first to describe *BRCA1*, suggested that genetic screening, of at least *BRCA1* and *BRCA2*, should be offered to every woman, at about age 30.¹⁶ However, large studies investigating the many dimensions of this approach in general population are needed. The UK national screening committee (NSC) had updated a bundle of criteria to better appraise the effectiveness, viability and appropriateness of a screening program (Table 2).²⁸ Such bundle, and similar others,²⁹ are comprehensive and can be a guide for researchers and policy makers prior to implementing a population-based genetic screening program.

A Canadian ongoing study, launched in March 2017, used an Internet-based system to offer genetic testing to all women and men who wish to be tested. Testing was done only for *BRCA1* and *BRCA2* through a guided 'direct-to-consumer' approach. Among the first 150 people tested, researchers identified 5 individuals with pathogenic mutations; 3 of them did not meet guideline-based criteria.³⁰ It is hoped that this study, when completed, will evaluate the feasibility and the yield of population-based genetic testing.

Identifying women with mutations that do not cause cancer,

may provoke unnecessary anxiety, and can lead to unnecessary diagnostic and preventive procedures, including surgeries, with potential major complications.³¹ Prophylactic oophorectomy, for example, may enhance osteoporosis and increase the risk of cardiovascular diseases.³² Potential harm may thus increase with decreasing penetrance rate for a mutation included in a panel.³³

How high should we jump?

Multiple studies had shown that restricting genetic testing to the traditional *BRCA1* and *BRCA2* alone misses potentially actionable genetic mutations in a substantial percentage of patients.³⁴⁻³⁶ The wide utilization of NGS-based testing provided clinicians with a variety of multi-gene test panel options for hereditary breast cancer risk assessment. Such panels include known genes for its association with hereditary breast and ovarian cancers (HBOC), while other broader panels include other genes better known for its association with other cancers.

The question would be if such broader panels would increase the identification rates of clinically relevant, meaningful and actionable mutations and if the cost of such testing and its related interventions, and its potential anxiety among patients and their family are justifiable.

Using a consecutive series of 20,592 women with breast cancer undergoing hereditary genetic testing in a commercial laboratory, researchers studied the pattern of ordering larger hereditary cancer panels, ranged from 2 to 79 genes. Testing was performed

Table 2. Criteria for appraising a genetic screening program.

The condition
<ul style="list-style-type: none"> The condition should be an important health problem as judged by its frequency and/or severity. All cost-effective primary prevention interventions should have been implemented. The natural history of carriers of identified mutation are understood.
The test
<ul style="list-style-type: none"> The screening test should be simple, safe, precise and validated. The distribution of test values in the target population should be known. The test should be acceptable to the target population. Further diagnostic investigation of individuals with a positive test result are agreed upon. The testing method for a particular mutation or set of genetic variants is clearly set out.
The intervention
<ul style="list-style-type: none"> There should be an effective intervention for patients identified through screening with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Availability of evidence-based policies covering which individuals should be offered interventions.
The screening program
<ul style="list-style-type: none"> High quality evidence that the screening program is effective in reducing mortality or morbidity. There should be evidence that the complete screening program is clinically, socially and ethically acceptable to health professionals and the public. The benefit gained by individuals from the screening program should outweigh any harms The screening program should be cost-effective.
Implementation criteria
<ul style="list-style-type: none"> Clinical management of the condition and patient outcomes should be optimized prior to participation in a screening program. All other options for managing the condition should have been considered. There should be a plan for managing and monitoring the screening program and an agreed set of quality assurance standards. Adequate staffing and facilities for testing, diagnosis, treatment and program management should be available. Evidence-based information, explaining the purpose and potential consequences of screening, investigation and preventative intervention or treatment, should be made available to potential participants to assist them in making an informed choice.

with NGS and all panels were offered at the same price to eliminate cost as a limiting factor. During the study period (Feb 2015-Aug 2016), a total of 2105 individuals with pathogenic/likely pathogenic variants were identified; 1020 were in *BRCA1* or *BRCA2* while an additional 1085 individuals had pathogenic/likely pathogenic findings in other genes associated with increased risk of heritable cancer. The genetic testing ordered was divided according to the panel type into three groups: first group were with 15 genes associated primarily with breast cancer (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *FANCC*, *MRE11A*, *NBN*, *NF1*, *PALB2*, *PTEN*, *STK11*, *TP53*). The second group had additional genes to make the total 42 while the third group were for a panel of 79 genes including those in the first two panels. Among the 1085 cases with non-*BRCA1* or *BRCA2* gene variants, 91.5% were in genes with medical management guidelines, and the majority of cases (72.6%) were in the second ordering group (42 gene panel). Breast management guidelines were most (97.5%) among patients in the first group followed by those in the second and the third groups; 63.6% and 50%, respectively. In the second and third groups, a significant portion of the identified mutations were in genes associated with increased risk of cancers other than breast. The most frequent pathogenic/likely pathogenic findings in *BRCA1/2*-negative patients were in *CHEK2* (27.6%), *MUTYH* (15%), *ATM* (14.9%), and *PALB2* (12.2%). As expected, the number of patients with VUS were significantly higher in the third group (49.6%) compared to a rate of 31.6% and 12.7% in the second and first groups, respectively.³⁷

Cost effectiveness

Expanding genetic testing horizontally by broadening both eligible patients, and even healthy women, and vertically by expanding the number of genes tested (panels), is apparently associated with incremental cost. Several studies have addressed the cost issue and utilized different models to study the cost-effectiveness of expanded testing.

Utilizing the Markov model, one study compared the lifetime cost of *BRCA1/BRCA2* testing of all women 30 years or older (Population-based) with guidelines-based testing. Analyses were performed for high-income countries (HIC) (UK, USA and Netherlands), upper-middle income countries (UMIC) (Brazil and China) and low-middle income countries (LMIC) (India). The model factored in all appropriate screening and prevention interventions *BRCA*-carriers would undergo to reduce breast and ovarian cancer risks. From a payer perspective, population-based *BRCA* testing was found to be highly cost-effective in HIC and cost-effective in UMIC but not cost-effective in LMIC. Population-based *BRCA* testing can prevent an additional 2319 to 2666 breast cancer cases and 327 to 449 ovarian cancer cases per million women than the current clinical strategy.³⁸

Another study used data from 11,836 patients in population-based breast cancer cohorts recruited to 4 large research studies. A cost-effectiveness simulation modeling compared lifetime costs associated with testing of all unselected patients with breast cancer for *BRCA1/2* and *PALB2* with guidelines-based testing of *BRCA1/2* in two high-income health care systems; UK and USA. Data collection and analysis were performed during 2018 and 2019. Universal *BRCA1/BRCA2/PALB2* testing approach was found to be cost effective in both health care systems.³⁹

Similarly, another study found population-based testing using a panel of *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1* and *PALB2* for women aged 30 years or older is more cost-effective than any guidelines-based testing strategy. Additionally, guidelines-based

testing using this multi-gene panel was found to be more cost-effective than limited *BRCA1* and *BRCA2* testing.⁴⁰

The noise; variants of uncertain significance

VUS represent genetic mutations which currently cannot be identified as pathogenic or benign. During the past years, guidelines-based genetic testing used few genes; mostly *BRCA1* and *BRCA2*, and rates of VUS were mostly below 10%.⁴¹ Nonetheless, expanding testing to include more patients, like population-based screening, or using multi-gene panels utilizing NGS-based platforms had significantly increased VUS rates to levels approaching 50%.^{42,43} As we gain more experience with such variants and as genomic technologies evolve, it's expected that a proportion of VUS might be reclassified to pathogenic. Patients or healthy people tested need to be informed about this possibility which would obviously add to their anxiety and may push them to undergo unnecessary interventions

Future directions

Expanded testing to include more patients, and even young healthy women, and more genes using multi-gene panel testing might find its way to our daily clinics. This expanded testing might also be applied to cancers other than breast and ovaries. One recently published prospective study enrolled 2984 newly diagnosed patients with any cancer at Mayo Clinic facilities regardless of their primary site, age, stage, personal or family history. All patients underwent genetic testing using a greater than 80-gene NGS-based platform. In total, pathogenic germline variants were found in 13.3%, including 6.4% with clinically actionable findings that would have been missed by guidelines-based testing criteria.⁴⁴

However, expanding testing needs a parallel expansion in psychosocial support. Individuals found to have a mutation in a high-penetrance inherited cancer predisposition gene, carry the ethical obligation to communicate and share such findings with at-risk relatives so that they too can be proactive with cancer risk management.⁴⁵ Many studies had clearly shown that genetic testing is generally underutilized by even first-degree relatives; less than a third of at-risk relatives underwent testing after a family member was identified with hereditary cancer.⁴⁶ Efforts should focus on factors that may enhance family sharing including recognition of who is at risk and providing psychosocial support to deal with potential relatives' reactions and emotions.⁴⁷⁻⁴⁹ Additionally, special attention should be made to the financial burden on the patients and their relatives related to the test itself and its subsequent interventions. Many commercial labs had extended free-of-charge family testing of index cases if done within certain pre-specified period. Even such financial offers failed to increase family uptake testing in a recently published study.⁴⁴

The detection of germline pathogenic variant has relevant implications for carriers' family planning. Pre-implantation genetic testing for monogenic disorders (PIGT-M) to avoid transmittance of pathogenic variants to the offspring are growing. Though it was found to be cost effective,⁵⁰ the issue remains controversial and many raised ethical concerns, too.^{51,52}

Conclusions

With the recent advances in molecular medicine and the wider

application, availability and affordability of next generation sequencing, testing for cancer-predisposing genes beyond *BRCA1* and *BRCA2*, is increasingly utilized in routine clinical practice. Additionally, the complexity of existing guidelines, which may lead to poor referral for genetic testing, and the relatively high percentage of pathogenic variants in patients not eligible for testing using published guidelines, may enhance the concept of universal genetic testing of all breast cancer patients, regardless of their personal or family history of cancer. This wider adoption should also be accompanied by expansion in psychosocial support to deal with testing results and its consequences.

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