Multi gene panel testing for hereditary breast cancer - is it ready to be used?

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Abstract
Breast cancer is one of the most common malignancies and the leading cause of death among women worldwide. About 20% of breast cancers are hereditary. Approximately 30% of the mutations have remained negative after testing BRCA1/2 even in families with a Mendelian inheritance pattern for breast cancer. Additional non-BRCA genes have been identified as predisposing for breast cancer. Multi gene panel testing tries to cover and explain the BRCA negative inherited breast cancer, improving efficiency, speed and costs of the breast cancer screening. We identified 23 studies reporting results from individuals who have undergone multi gene panel testing for hereditary breast cancer and noticed a prevalence of 1-12% of non-BRCA genes, but also a high level of variants of uncertain significance. A result with a high level of variants of uncertain significance is likely to be more costly than bring benefits, as well as increase the anxiety for patients. Regarding further development of multi gene panel testing, more research is required to establish both the optimal care of patients with cancer (specific treatments like PARP inhibitors) and the management of unaffected individuals (chemoprevention and/or prophylactic surgeries). Early detection in these patients as well as prophylactic measures will significantly increase the chance of survival. Therefore, multi gene panel testing is not yet ready to be used outside clear guidelines. In conclusion, studies on additional cohorts will be needed to better define the real prevalence, penetrance and the variants of these genes, as well as to describe clear evidence-based guidelines for these patients.

Keywords: multi gene panel, hereditary breast cancer, non-BRCA genes, prevalence, prophylactic measures

Introduction
Breast cancer (BC) is one of the most common malignancies and the leading cause of death among women worldwide [1]. About 20% of breast cancers are hereditary [2]. Hereditary BC is defined by an onset at a young age, bilateral breast cancer, multiple primaries and a history of first or second- degree family members with similar diagnoses [3].

Mutations in the BRCA1 and BRCA2 genes are responsible for two thirds of hereditary BC, being the most well-known cause of inherited cancer predisposition. The cumulative risk of developing BC by the age of 70 for a BRCA mutation carrier is 65% for BRCA1 and 45% for BRCA2 [4,5].

Although genetic predisposition testing for BRCA1 and BRCA2 has been available since 1996, about 30% of the patients have remained negative in BRCA1 and BRCA2 mutations even in families with a history of a Mendelian inheritance pattern (autosomal dominant or recessive) for BC [6,7]. Additional non-BRCA genes have been identified as predisposing for breast cancer: ATM, CHEK2, PALB2, PTEN, TP53, and others [8].

ATM is a protein coding gene which activates cellular responses to DNA double-strand breaks and plays a crucial role in DNA damage-pathways. The ataxia-teleangiectasia mutated (ATM) gene has been supposed to predispose to breast cancer when the findings from the epidemiological studies of ataxia teleangiectasia (AT) families showed an increased risk of breast cancer in AT heterozygote women [9].

The Checkpoint kinase 2 (CHEK2)
gene, located on chromosome 22, is involved in DNA repair and apoptosis, being a tumor suppressor gene. CHEK2 loss of function is implicated in different types of cancer, especially breast cancer [10].

PALB2 (Partner and Localizer of BRCA2) was firstly identified as a protein that interacts with BRCA2 and later, with BRCA1. It might function as a tumor suppressor. PALB2 loss of activity is associated with Fanconi’s anemia as well as breast and pancreatic cancer [11].

PTEN (phosphatase and tensin homolog deleted from chromosome 10) acts as a tumor suppressor gene affecting cell survival, proliferation and apoptosis through the action of its phosphatase protein product. Loss of PTEN function has been correlated with many primary and metastatic malignancies, including breast cancer [12].

TP53 gene regulates cell proliferation, cell repair and apoptosis and it is located on the short arm of the chromosome 17. TP53 is found altered in 20-40% of BC and it seems to be an early event in breast carcinogenesis [13].

Next generation sequencing (NGS) and the recent discovery of the new genes now permit multi gene panel testing, which provides clinicians with more information in a single test. Multi gene testing becomes a routine diagnosis in hereditary cancer syndromes. However, there are several details to consider when recommending testing, such as the large number of variants of unknown significance (VUS), low or incomplete penetrant mutations, high costs, as well as the emotional impact on the person and the family [14]. Multi-gene panel testing should always be preceded and followed by appropriate genetic counseling. In this context, the objective of this review is to evaluate the latest and most important literature data on multi gene panel testing in hereditary breast cancer.

**NGS and hereditary breast cancer**

The risk of developing inherited BC for an individual depends on the gene penetrance which can be divided into three categories based on the relative risk (RR): high penetrance (RR>4), moderate penetrance (RR=2-4) and low penetrance (RR<1.3) [15]. Multi gene panels testing doubles the detection of pathogenic mutations related to cancer pathogenesis and allows the analysis of 6 to more than 100 genes simultaneously, including more moderate risk genes [16,17].

Although, NGS has limitations compared with established technologies, such as Sanger sequencing, quantitative PCR, multiplex ligation-dependent probe amplification and copy number microarrays, multi gene panel testing for hereditary BC risk assessment is gaining acceptance and has proven to be useful as a diagnostic tool for disorders associated with specific phenotypes that can be influenced by multiple genes [18,19]. Nowadays, there is an increasing trend toward the use of multi gene panel testing among women with an apparent predisposition to BC, successfully replacing the single and two-gene tests [20]. Here, we identified 23 studies (on PubMed from 2006 to 2017) reporting results from individuals who have undergone multi gene panel testing for hereditary BC and tried to evaluate the prevalence of non-BRCA1 genes in the population with a family history of BC (Table I).

We noticed a prevalence of 1-12% of non-BRCA genes in individuals with inherited breast cancer, but also a high level of VUS—up to 88%. VUS are genetic alterations whose disease association is yet unknown. The majority of VUS seem to be benign, but more data are needed.

**The clinical application of NGS for hereditary breast cancer**

As NGS has made it possible to sequence multiple genes simultaneously at a cost that is often lower than testing BRCA1/2 alone, multi gene panels tend to be more applied in the clinic field [44]. Implementing multi gene panel testing for hereditary BC screening holds great promise to maximize health benefits for the patient, detect them early when they are easier and cheaper to treat as well as increase the survival rate. Given the low cost and the large availability, multi gene panel testing for hereditary BC will be adopted as a screening tool by the healthcare providers as soon as clear guidelines are available. Otherwise, poor implementation of genetic testing can lead to high health expenditures, waste of time and other resources, without benefits in health outcomes [45-47].

It is important to admit that benefits from genetic testing do not come from testing itself, but from placing the results in the right clinical context in order to make the proper recommendations and management [48]. Multiple studies have shown that multi gene panel testing identifies mutations that are both expected and unexpected and sometimes, the genotype does not match the phenotype [28,39,49]. Therefore, challenges are posed for both the patients together with their families and also for the healthcare providers who have to interpret the results and decide the medical management. Up to now, there is limited knowledge about cancer genetics and healthcare providers show less confidence when it comes to interpret multi gene panel tests, compared to single or double-genes tests [50].

One of the main considerations for the inclusion of multi gene panels in BC screening is the ability to interpret the results detected. A major challenge is VUS. VUS are genetic variants in genes that are not yet considered actionable and whose penetrance is still uncertain [51]. A result with a high VUS is likely to be more costly than bring benefits, as well as increase the anxiety for patients [52,53]. For example, in a small study regarding implications of the report of VUS after BRCA1/2 testing, 19 of 24 patients had a final perception that their variant is predisposing to cancer and 10 underwent preventive surgery [54]. Therefore, multi gene panel testing is not ready to be widely used unless clear boundaries are established.
Table I. The Prevalence of non-BRCA genes and the Rate of VUS in Individuals with Inherited Breast Cancer- Literature Results

| No | Study                      | Patients | No. of genes tested | Prevalence                        | VUS                  |
|----|---------------------------|----------|---------------------|-----------------------------------|----------------------|
| 1  | Walsh et al (2006) [21]   | 300      | 5                   | 6% mutations in CHEK2, TP53, PTEN | Not specified        |
| 2  | Kuusisto et al (2011) [22]| 466      | 7                   | 12.1% CHEK2, PALB2, BRIP1, RAD50, CDH1 | Not specified        |
| 3  | Walsh et al (2011) [23]   | 360      | 12                  | 6.1% BARD1, BRIP1, CHEK2, MRE11A, MSH6, NBN, PALB2, RAD50, RAD51C, TP53 | Not specified        |
| 4  | Mauer et al (2014) [24]   | 1233     | 22                  | 10% mutations in non-BRCA genes  | 30%                  |
| 5  | Kurian et al (2014) [25]  | 198      | 42                  | 11.4% mutations in non-BRCA genes | 88%                  |
| 6  | Castera et al (2014) [26] | 708      | 27                  | 3% CHEK2, RAD51C, RAD50, PALB2, MRE11A, ATM, NBS1, CDH1, MSH2, PMS2, BARD1, PMS1, MLH3 | Not specified        |
| 7  | LaDuca et al (2014) [27]  | 2079     | 14-22               | 7.2-9.6% mutations in non-BRCA genes | 15.1-25.6%          |
| 8  | Churpek et al (2014) [28] | 289      | 8                   | 4.4% mutations in non-BRCA genes: PALB2, CHEK2, BARD1, ATM, PTEN, TP53 | 0.6%                |
| 9  | Chong et al (2014) [29]   | 3000     | 6                   | 11% TP53, 2.3% PTEN, 1.2% CDH1, 0.6% STK11 | Not specified        |
| 10 | Cybulski et al (2015) [30]| 144      | 8                   | 2.8% PALB2, 1.3% ATM              | Not specified        |
| 11 | Doherty et al (2015) [31] | 134      | 6                   | 0%                                | 6.7%                |
| 12 | Maxwell et al (2015) [32] | 278      | 22                  | 11% mutations in non-BRCA genes  | 19%                  |
| 13 | Tung et al (2015) [33]    | 2158     | 25                  | 4.32% mutations in non-BRCA genes: CHEK2, PALB2, ATM, MSH6, PMS2 | 41.7%               |
| 14 | Couch et al (2015) [34]   | 1824     | 17                  | 3.7% mutations in non-BRCA genes: PALB2, BARD1, RAD51D, RAD51C, BRIP1 | Not specified        |
| 15 | Schroeder et al (2015) [35]| 620      | 10                  | 0.97% CHEK2, 0.65% ATM, 0.48% CDH1, 0.32% PALB2, 0.32% NBN, 0.16% TP53 | Not specified        |
| 16 | Yang et al (2015) [36]    | 99       | 152                 | 3% TP53, 1% PALB2, 1% RAD51C, 1% RAD50, 1% CDH1 | 41%                |
| 17 | Lincoln et al (2015) [37] | 1062     | 29                  | 3.9% mutations in non-BRCA genes: ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2 | Not specified        |
| 18 | Aloraifi et al (2015) [38] | 104     | 312                 | 5% ATM, 3% RAD50, 2% CHEK2, 1% TP53, 1% PALB2, 1% MRE11A | Not specified        |
| 19 | Kapoor et al (2015) [39]  | 966      | 15                  | 3.9% PALB2, CHEK2, ATM            | 16.9%               |
| 20 | Desmond et al (2015) [40] | 1046     | 29                  | 3.8% mutations in non-BRCA genes: CHEK2, ATM, PALB2 | Not specified        |
| 21 | Thompson et al (2016) [41]| 3997     | 18                  | 0.6% PALB2, 0.1% TP53, <0.1% CDH1, PTEN, ATM | Not specified        |
| 22 | Tung et al (2016) [42]    | 488      | 25                  | 4.1% CHEK2, ATM, PALB2, PTEN, NBN, RAD51C, RAD51D, MSH6, PMS2 | 33.2%               |
| 23 | Couch et al (2017) [43]   | 65 057   | 21                  | 1.73% CHEK2, 1.06% ATM, 0.87% PALB2 | Not specified        |
| TOTAL |                       | 87318   | 5-312               | 1-12%                             | 0.6-88%             |

Firstly, the best candidate genes for inclusion in the multi gene panels should have a low VUS to pathogenic ratio and a high prevalence of pathogenic mutations [14]. Otherwise, they are difficult to interpret and can cause anxiety for patients and their families.

Secondly, the lifetime risk for breast cancer is also important to be taken into account when establishing the clinical management. While in general population the risk is 10-12%, for patients found to be carrying a pathogenic mutations in BC susceptibility genes the risk is: 87% BRCA1, 84% BRCA2, 44-95% TP53, 85% PTEN, 33-58% PALB2, 39-52% CDH1, 15-52% ATM, 28-48% CHEK2. It is important to say that for many of these genes, there are limited data and no definitive guideline is available [13,55].

Given the fact that most hereditary BC are inherited in an autosomal dominant fashion, the risk of carrying a mutation among first and second- degree relatives is 50% and 25% respectively [56,57]. So, in order that the genetic testing reach its purpose, once an individual is found to carry a mutation for BC predisposition, it is essential to share this information with family members to undergo the same test. But, the question that rises is: are patients aware enough to take part in health policies and get involved in the cancer prevention system?

Screening and management of patients at risk for hereditary breast cancer should be based on family history [Personal history of early-onset breast cancer (<45 years of age); personal history of triple-negative breast cancer (<60 years of age); family history of first or second-degree relatives with breast or ovarian cancers, or other cancers associated with hereditary breast and ovarian cancer predisposition; personal history of male breast cancer] and other clinical risk factors (i.e., breast density and age of menstruation and menopause) instead of being genespecific. Also, patients should be periodically revaluated in the context of new clinical data being found [9,11].
The risk reduction strategies and treatment are similar to carriers of *BRCA1* and *BRCA2* mutations. Current options for breast cancer prevention are: screening mammography or MRI beginning at the age of 25, prophylactic oophorectomy between ages 35-40 and preventive mastectomy before the age of 40. Regarding further development of multi gene panel testing more research is required to better define both the optimal care of patients with cancer (specific treatments like PARP inhibitors) and the management of unaffected individuals (chemoprevention and/or prophylactic surgeries) [58-60].

Furthermore, it is important that all patients who undergo genetic testing have an appropriate pre- and posttest genetic counseling. Studies show that women who had undergone genetic counseling had a higher satisfaction with the genetic process. Oncologists, surgeons, medical geneticists, and other specialized health care professionals should form a multidisciplinary team involved in the clinical management of patients with mutations in the susceptibility genes and contribute to the better understanding of breast cancer pathogenesis [61-63].

**Conclusion**

Nowadays, genetic testing, cancer treatments and risk reduction strategies are fields in a continuous development. According to studies, the prevalence of non-*BRCA1/2* mutations is 4-16% [64]. Early detection in these patients as well as prophylactic measures will significantly increase the chance of survival.

Given the magnitude of this disease, multi gene panel testing is not yet ready for non-specialized clinical use outside clear guidelines [14]. The cancer genetic specialist plays a crucial role in understanding the pathogenesis of breast cancer as well as developing a clear guideline of clinical management and genetic counseling for patients with mutations in non-*BRCA1/2* genes.

In conclusion, studies on additional cohorts will be needed to find the real prevalence, penetrance and the variants of these genes, as well as to describe evidence-based guidelines for these patients. Further data might contribute to the developing of the era of personalized medicine, specific treatments and well-established prophylactic strategies for each pathogenic mutation in every breast cancer susceptibility gene.

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