Increased Identification of Candidates for High-Risk Breast Cancer Screening Through Expanded Genetic Testing

Eric T. Rosenthal, PhD, ScM[a], Brent Evans, MS[a], John Kidd, MS[a], Krystal Brown, PhD[a], Heidi Gorringe, MS, CGC[a], Michael van Orman, BS[a], Susan Manley, MS, CGC, MBA[a]

Abstract

Purpose: Breast MRI screening is recommended for women with a >20% lifetime risk for breast cancer on the basis of estimates derived from risk models dependent largely on family history. Alternatively, a >20% lifetime risk can be established through genetic testing of *BRCA1* and *BRCA2*, as well as a growing selection of other genes associated with inherited breast cancer risk. The aim of this study was to quantify the impact of testing for genes other than *BRCA1/2* and the extent to which mutation carriers in these genes would have been identified as candidates for enhanced screening on the basis of family history alone.

Methods: Women were tested with a 25-gene hereditary cancer panel including *BRCA1/2* and 7 additional genes known to be associated with a >20% lifetime risk for breast cancer (*ATM*, *CHEK2*, *PALB2*, *TP53*, *PTEN*, *CDH1*, and *STK11*). Women found to carry pathogenic variants (PVs) were evaluated with the Claus model to assess whether they would have been found to be at >20% lifetime risk on the basis of family history.

Results: In total, 9,751 PVs in the selected breast cancer risk genes were identified in 9,641 women. *BRCA1/2* accounted for 59.1% of the PVs, and 38.8% were in *ATM*, *CHEK2*, or *PALB2*. Only 24.7% of all women with PVs found in any gene reached the >20% lifetime risk threshold using the Claus model.

Conclusions: Expanding genetic testing beyond *BRCA1/2* significantly increases the number of women who are candidates for breast MRI and other risk reduction measures, most of whom would not have been identified through family history assessment.

Key Words: Inherited breast cancer risk, genetic testing, breast MRI

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INTRODUCTION

The accurate identification of women at an increased risk for breast cancer is of particular importance to radiologists, as one of the most frequently used medical management interventions for these women is modification of mammography recommendations, addition of breast MRI, and consideration of tomosynthesis [1]. Currently, a threshold of an estimated lifetime breast cancer risk >20% has been set for consideration of initiating mammography at <40 years of age and the addition of annual breast MRI [2,3]. Many women meet the >20% threshold on the basis of risk estimates derived from breast cancer risk models that rely largely on family breast cancer history, or they qualify because of personal histories of atypical ductal or lobular hyperplasia or lobular carcinoma in situ. Estimates of the percentage of women determined to be eligible for breast MRI range from 1% to 6%, depending on the risk model used [4]. Alternatively, and of increasing importance, women may be categorized as having a >20% lifetime risk through genetic testing for inherited pathogenic variants (PVs) in breast cancer risk genes.

Over the past 20 years, clinical genetic testing for inherited breast cancer risk has focused primarily on

[a]Myriad Genetic Laboratories, Inc., Salt Lake City, Utah.

Corresponding author and reprints: Eric T. Rosenthal, PhD, ScM, Myriad Genetic Laboratories, 320 Wakara Way, Salt Lake City, UT 84108; e-mail: erosenth@myriad.com.

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BRCA1 and *BRCA2*, the high-penetrance genes responsible for Hereditary Breast and Ovarian Cancer syndrome. It is estimated that PVs in these two genes are present in 0.2% to 0.3% of the general population and in 5% to 10% of patients with breast cancer [5]. PVs in *BRCA1* and *BRCA2* are associated with a 43% to 87% risk for female breast cancer to age 70 years, as well as increased risks for ovarian, prostate, and pancreatic cancer [1,6-9]. Until recently, patients testing negative for PVs in *BRCA1* and *BRCA2* rarely underwent additional testing, with the exception of a small subset of individuals displaying distinctive personal and/or family histories suggestive of other high-penetrance hereditary cancer syndromes, all of which include risks for a wide array of cancers in addition to breast cancer, such as those associated with the genes *CDH1* (hereditary diffuse gastric cancer syndrome) [10,11], *PTEN* (*PTEN* hamartoma tumor syndrome) [12-14], *STK11* (Peutz-Jeghers syndrome) [15], and *TP53* (Li-Fraumeni syndrome) [16,17].

As the pace of genomic research has accelerated, evidence has accumulated supporting a role for additional genes in inherited breast cancer risk, most of which are associated with lower but still substantive breast cancer risks. Most notably, data from multiple studies have demonstrated that three genes, *ATM* [18-20], *CHEK2* [21-24], and *PALB2* [25-28], are associated with an increased lifetime breast cancer risk estimated to exceed 20% (Table 1). Recently, the National Comprehensive Cancer Network (NCCN) added these three genes to the list for which there is sufficient evidence to recommend breast MRI for women carrying PVs, and risk-reducing mastectomy was added as an option for *PALB2* [1]. These new recommendations coincide with clinical laboratories introducing expanded multigene panels based on next-generation sequencing technology, which allow the cost-effective and efficient analysis of multiple genes associated with the risk for breast and other cancers.

To determine the impact of expanding genetic testing for breast cancer risk beyond *BRCA1/2*, we analyzed outcomes of clinical genetic testing using a 25-gene hereditary cancer panel including all of the genes currently established as conferring a lifetime risk >20% and for which there are explicit guidelines for intervention, including breast MRI. We determined the proportion of female carriers of PVs in these genes who would have been identified as candidates for intervention on the basis of family history alone, focusing particularly on *ATM*, *CHEK2*, and *PALB2*. We also documented the extent to which the inclusion of these three genes increases the number of women who are candidates for more aggressive medical management, including breast MRI, compared with testing for only *BRCA1/2* and the other genes traditionally regarded as clinically significant contributors to inherited breast cancer risk.

METHODS

All data were derived from clinical testing ordered for 194,107 female patients using a 25-gene hereditary cancer panel between September 2013 and February 2016 (Myriad Genetic Laboratories, Salt Lake City, Utah).

Table 1. Summary information for the 25 genes included in panel test used for this study

Gene	Lifetime Breast Cancer Risk Estimate	Consider Breast MRI?	Consider RRM?	Citations
Breast cancer risk genes with established professional society management				
BRCA1	46%-87%	Yes	Yes	[1,6,7,9]
BRCA2	43%-84%	Yes	Yes	[1,6,8,9]
CDH1	39%-52%	Yes	Yes	[10,11,42]
PTEN	77%-85%	Yes	Yes	[1,12-14]
STK11	45%-50%	Yes	Yes	[1,15]
TP53	High risk	Yes	Yes	[1,16,17]
ATM	17%-52%	Yes	No	[1,18-20]
CHEK2	23%-48%	Yes	No	[1,21-24]
PALB2	17%-58%	Yes	Yes	[1,25-28]
Breast cancer risk genes with uncertain risk estimates and currently without professional society guidelines for management				
BARD1, *NBN*				
Genes for which there are currently no established breast cancer risks				
APC, *BMPR1A*, *BRIP1*, *CDK4*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PMS2*, *RAD51C*, *RAD51D*, *SMAD4*				

Note: RRM = risk-reducing mastectomy.