Management of Women With Breast Cancer and Pathogenic Variants in Genes Other Than *BRCA1* or *BRCA2*

Mark Robson, MD[1]

The Oncology Grand Rounds series is designed to place original reports published in the Journal *into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in the* Journal of Clinical Oncology, *to patients seen in their own clinical practice.*

CASE PRESENTATION

A 47-year-old premenopausal woman presented with a 1.2 cm palpable mass. Her family history was significant for a paternal aunt diagnosed with postmenopausal estrogen receptor–positive (ER$^+$) breast cancer and her paternal grandmother with ovarian cancer. An ultrasound-guided core needle biopsy identified moderately differentiated infiltrating ductal carcinoma, an ER expression by immunohistochemistry of 99%, a progesterone receptor expression of 55%, and a human epidermal growth factor receptor 2 expression of 1+ (negative). Germline susceptibility testing was performed and identified a pathogenic variant (PV) in *ATM*, c.538C>T (p.Gln180Ter). She was referred to discuss local management and the appropriateness of breast conservation versus bilateral mastectomy.

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

The year 2013 was a momentous one for clinical cancer genetics. In that year, the Supreme Court decision in *Association of Molecular Pathology v Myriad Genetics Inc* relaxed barriers to competition in germline testing for cancer susceptibility in the United States. The rapid development of massively parallel sequencing for clinical testing reduced the costs of testing while allowing the simultaneous analysis of multiple genes. Multigene panel testing quickly became the standard method of assessing inherited risk,[1,2] identifying a number of germline alterations beyond *BRCA1/2*. Two reports from commercial diagnostic testing laboratories described PVs in approximately 8% of women with breast cancer referred for testing (Table 1).[3,4] Although alterations in *BRCA1* and *BRCA2* were the most common, 2.7% of women were found to carry PV in *CHEK2*, *ATM*, and *PALB2*. Alterations were observed in many other genes. These discoveries raised significant clinical challenges. Women with breast cancer and non-*BRCA* alterations

clearly cannot be managed in the same way as women with *BRCA* PV because of the different level and spectrum of risk. It has also been challenging to provide recommendations to unaffected female family members who share these moderate penetrance alterations (PV that confers two- to five-fold increased risks, as opposed to high-penetrance alterations in *BRCA1*, *BRCA2*, *PTEN*, and *TP53*). For some genes (eg, *NBN*), there has been controversy as to whether there is any association with breast cancer at all. The exact magnitude of risk has been difficult to establish for many genes, and there is limited information about the effectiveness of surveillance interventions in women whose average absolute risk is in the range of that of a woman whose sister was affected by breast cancer (which confers a relative risk of 1.8-2.3).[5,6] Guideline groups such as the National Comprehensive Cancer Network in the United States have made empiric surveillance recommendations on the basis of a 20% cumulative lifetime risk threshold, extrapolating from guidance provided for management of high-risk women,[7] but the optimal risk threshold and timing of intervention have not been studied. For this reason, the most appropriate management of both affected and unaffected women with moderate penetrance variants is incompletely defined.

SUMMARY OF THE RELEVANT LITERATURE

Genes Associated With an Elevated Risk of Breast Cancer

As noted, pathogenic germline variants are quite prevalent in women with breast cancer (Table 1). Huang et al[8] analyzed germline data from 1,076 patients with breast cancer enrolled in the Cancer Genome Atlas and identified PV in 9.9%. The pathogenicity of a variant only describes impact on gene function, however, and identifying a functionally significant PV in a gene is not enough to conclude that the gene confers susceptibility. Studies suggest that humans carry

TABLE 1. Prevalence of Germline PVs in Women With Breast Cancer Referred for Genetic Testing[3,4]

Gene	No.	No. (PV)	%
BRCA2	94,207	1,783	1.89
BRCA1	94,207	1,733	1.84
CHEK2	94,207	1,021	1.08
ATM	94,207	775	0.82
PALB2	94,207	732	0.78
BRIP1	94,207	229	0.24
PMS2	94,207	168	0.18
BARD1	94,207	162	0.17
TP53	94,207	152	0.16
RAD50	58,798	94	0.16
MSH6	94,207	144	0.15
NBN	94,207	132	0.14
RAD51C	94,207	114	0.12
NF1	58,798	59	0.10
MRE11A	58,798	48	0.08
MSH2	94,207	66	0.07
PTEN	94,207	63	0.07
CDH1	94,207	53	0.06
RAD51D	94,207	51	0.05
CDKN2A	94,207	48	0.05
MLH1	94,207	45	0.05
APC	35,409	11	0.03

Abbreviation: PV, pathogenic variant.

between 250 and 300 loss-of-function variants in their genomes, most of which are not associated with disease in the individual.[9] It has been challenging to come to agreement on a definitive list of breast cancer predisposition genes. Clinical cancer geneticists came to consensus quickly on high-penetrance genes that confer a > 5-fold relative risk (BRCA1, BRCA2, TP53, PTEN, and CDH1) because PV in these genes causes autosomal dominant cancer syndromes with risks that can be estimated through pedigree analysis. PALB2 is a more recently identified gene for which PVs are associated with four- to eight-fold increases in risk (an average of 53% breast cancer risk by age 80 years).[10-12] PALB2 is often therefore considered a high penetrance gene, although it will be discussed here.

At the other end of the risk spectrum are common variants (single nucleotide polymorphisms [SNPs]) identified through large genome-wide association studies that individually confer a minimal increase in risk but that are incontrovertibly associated statistically with breast cancer.[13] Although it is not possible to use individual common variants to predict breast cancer risk, there is a strong association with polygenic risk scores (PRSs) derived from hundreds of individual variant genotypes.[14] These PRSs are now being incorporated into testing being offered by commercial diagnostic laboratories, although their clinical utility remains unclear.

Between rare high-penetrance genes and common SNPs lies a group of so-called moderate penetrance genes. These are genes in which PVs are found in < 1% of the general population, which confer between two- and five-fold increases in breast cancer risk. Because of the generally modest degrees of increased risk, PV in these genes cannot usually be identified through pedigree analysis as they often do not result in a recognizable Mendelian pattern of disease. They are best thought of as strong risk factors that interact with other factors such as family history, genetic background, mammographic density, and traditional risk factors to generate an individual woman's risk of breast cancer.[15] Establishing a definitive list of moderate penetrance breast cancer susceptibility genes has been a challenge. Recent publications from the Breast Cancer Association Consortium and the CARRIERS Consortium describe large population-based case control analyses of more than 80,000 women with breast cancer (Fig 1).[10,11] There is a canonical set of genes that are incontrovertibly associated with breast cancer, specifically BRCA1, BRCA2, PALB2, CHEK2, and ATM. Other previously reported associations were not validated, such as BRIP1, FANCC, FANCM, MRE11A, NBN (including the Slavic founder variant 657del5 [c.657_661del, p.Lys219fs]), RAD50, REQL, and RINT1. Risks described for known familial cancer syndrome genes such as CDH1, STK11, and TP53 were lower in these population-based studies than expected, possibly because recognition of these syndromes would remove subjects from both the case and control groups. Despite the size of these studies, the association of several genes with breast cancer remains unclear. This includes BARD1, MSH6, RAD51C, and RAD51D, for which the odds ratio point estimates of the associations are generally < 2.1 and statistically significant in one study but not the other. For BARD1, RAD51C, and RAD51D, associations with ER-negative (ER⁻) or triple-negative breast cancer are robust despite a lack of clear association with overall risk. The lack of impact on overall risk may result from the lack of association with the more prevalent ER-positive (ER⁺) breast cancer.

MODIFIERS OF BREAST CANCER RISK IN WOMEN WITH MODERATE PENETRANCE PATHOGENIC VARIANTS

CHEK2 was the first moderate penetrance gene to be identified because of a common pathogenic founder variant (c.1100del, p.Thr367fs) found in Northern Europe. In 2004, a consortium calculated that this variant resulted in a 2.34-fold increase in risk (95% CI, 1.72 to 3.20).[16] Subsequent studies of this variant and other PVs in CHEK2 illustrated the challenges of incorporating knowledge of moderate penetrance variants into clinical care. For
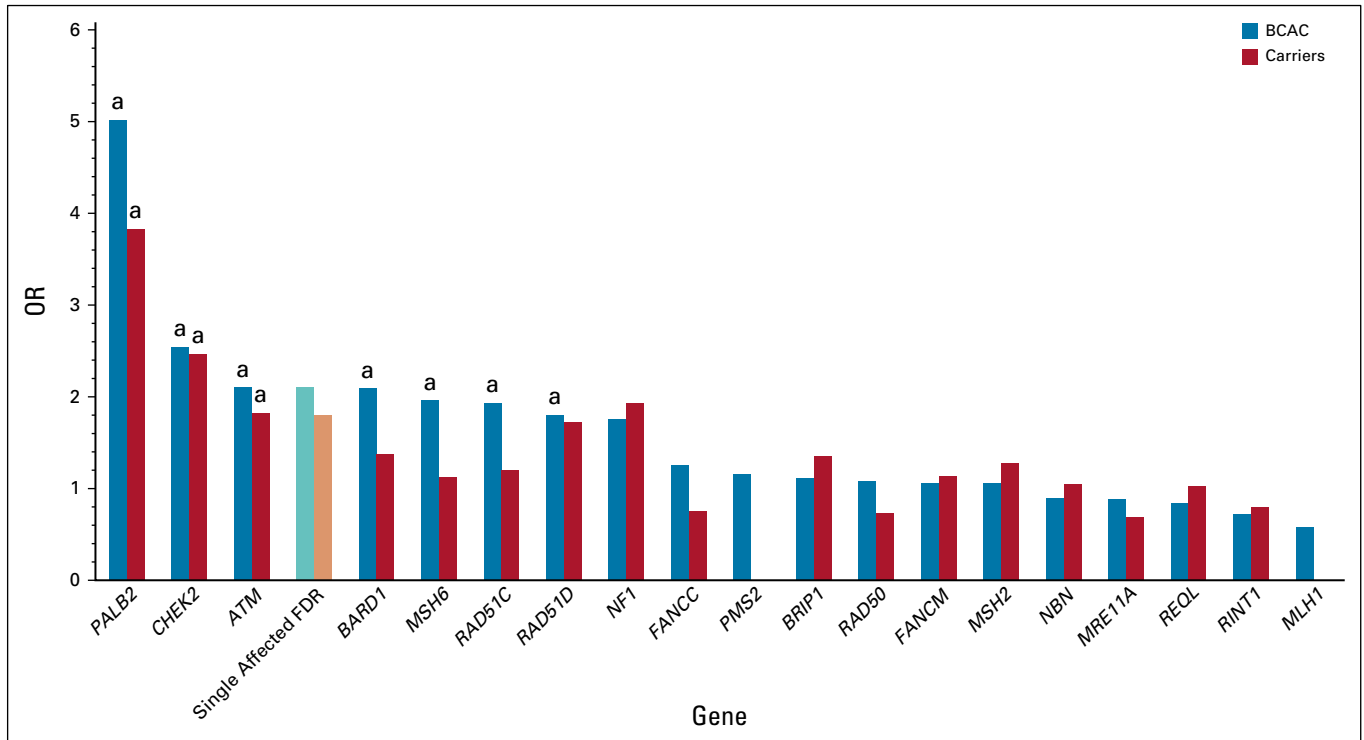
FIG 1. ORs for breast cancer for pathogenic variants in moderate penetrance genes (population-based studies[10,11]). Relative risks for unselected woman with an affected first-degree relative are indicated by "Single Affected FDR."[5,6] [a]Statistically significant associations within study. BCAC, Breast Cancer Association Consortium; OR, odds ratio.

example, the estimated risks associated with *CHEK2* varied from study to study not only because of expected statistical variation and differing methods for computing absolute risks but also because of variation in different studies in the distributions of other risk factors. *CHEK2* risk is modified by age,[17] family history,[18] and likely traditional reproductive risk factors and mammographic density.[15] There are also genotype-specific variations in risk as some variants, such as *CHEK2* c.470T>C (p.Ile157Thr), are associated with average risks that are in the range of a risk SNP rather than a rare variant.[19]

The degree to which moderate penetrance genes other than *CHEK2* are modified by traditional risk factors has not been explored. For several genes (such as *BRCA1*, *BRCA2*, *PALB2*, and *CHEK2*), the risk relative to the general population appears to decline with age,[10] but there is insufficient evidence that this applies for other moderate penetrance genes. It would be anticipated that genes that predispose to ER-positive breast cancer (*ATM*, *CHEK2*, and *PALB2*) would be more subject to modification by reproductive risk factors than genes that predispose to ER-negative cancers (*BARD1*, *RAD51C*, and *RAD51D*), but this hypothesis has not been tested.

There has been an increasing recognition that the risk of moderate penetrance PV is modified by genetic background, as represented by PRSs. This has been well-established for *CHEK2* PV,[20,21] and recent work has

extended the observation to *ATM* and *PALB2*.[22] The Original Report companion to this article by Gao et al[23] further evaluates the impact of PRS on risk in *ATM*, *CHEK2*, and *PALB2* carriers. In this report, all carriers of PV in *PALB2* were calculated to have a lifetime (by age 80 years) risk of > 20% (the US threshold for magnetic resonance imaging [MRI] surveillance), but risks ranged from 21.5% for a carrier with no family history and a PRS in the 10% percentile up to 59.5% for a carrier with a family history and a PRS in the 90% percentile. For *ATM* and *CHEK2* carriers, risks range from 12.8% (*ATM*) and 15.2% (*CHEK2*) for women with no family history and a PRS in the 10% percentile up to 40.9% (*ATM*) and 46.6% (*CHEK2*) for women with a family history and a PRS in the 90% percentile[23] and 31.3% of *CHEK2* PV carriers without a family history were calculated to have lifetime breast cancer risks under 20%. For women with a family history, the proportions were 21.2% for *ATM* and 10.1% for *CHEK2*.

SECOND CANCER RISKS IN WOMEN WITH MODERATE PENETRANCE PATHOGENIC VARIANTS

Breast Cancer

There are few data regarding second ipsilateral or contralateral breast cancer (CBC) risks associated with moderate penetrance PV. Not surprisingly, studies of *CHEK2* c.1100del are the most robust given the prevalence of this variant. The results of the studies are variable, with some

reports describing a three- to four-fold increased risk of CBC.[24,25] Other studies have not shown such an association.[26] PRS may modify CBC risk as it does primary cancer risk, but studies to examine this question have been underpowered.[20] *ATM* variants that are considered pathogenic by clinical diagnostic laboratories are not associated with an increased CBC risk, even after radiation therapy.[26] There are no data elucidating CBC risk in women with *PALB2* PV. There are no data indicating that women with moderate penetrance PV are at increased risk for ipsilateral tumor recurrence after breast-conserving treatment, although the question has not been studied.

Ovarian Cancer

The most common moderate penetrance breast cancer predisposition genes are *ATM*, *CHEK2*, and *PALB2*. *PALB2* has been linked to an increase in ovarian cancer risk in several studies.[12,27] This risk is generally similar to that experienced by a woman whose sister has been diagnosed with ovarian cancer.[28] In contrast, *CHEK2* has not been linked to increased risk. Although *ATM* has not been definitively associated with an increased risk of ovarian cancer, two studies comparing PV variants in patients with ovarian cancer with public database controls reported 2.25- to 2.85-fold increased risks.[29,30] *BARD1* is not robustly associated with an increased risk of ovarian cancer.[29-31]

BRIP1, *RAD51C*, and *RAD51D* are clearly moderate penetrance ovarian cancer predisposition genes,[29-34] but risk estimates have been labile as PVs are rare. A systematic analysis comparing the prevalence of PV in these genes with public databases generated point estimate odds ratios (ORs) of 4.94 for *BRIP1,* 5.59 for *RAD51C*, and 6.94 for *RAD51D*.[35] A large recent collaborative analysis assessing risk in families with *RAD51C* (relative risk 7.55) and *RAD51D* (relative risk 7.60) alterations produced estimated absolute ovarian cancer risks by age 80 years of 11% and 13%, respectively. Estimated absolute risks were substantially higher in women with a family history of ovarian cancer.[34]

Pancreas Cancer

ATM PVs were observed in familial pancreas cancer in 2012 and were present in 1.8% of a prospective ascertainment of patients with the disease.[36,37] A study comparing the prevalence of PV in 3,030 patients with pancreas cancer with public database controls calculated an point OR of 5.71, close to the OR for BRCA2 (6.20).[38] *PALB2* PVs were associated with an OR of 2.37 for pancreas cancer in one study,[12] but an elevated risk was not identified in another report.[38] Other genes have not been linked.

SUGGESTED APPROACH TO MANAGEMENT

Surgical Treatment

There is no current evidence that women are at increased risk for ipsilateral recurrence or ipsilateral second primary malignancies if they are found to carry a PV in *ATM*, *CHEK2*, *PALB2*, or other genes such as *BARD1*, *RAD51C*, or *RAD51D* (Table 2). Since *BRIP1*, *NBN*, and other genes do not play a clear role in breast cancer susceptibility, PV in these genes would also not be expected to affect risk of ipsilateral events. Therefore, women with PV in moderate penetrance genes should be considered candidates for breast-conserving treatment (BCT) if otherwise appropriate. Despite theoretical concerns, women with PV in *ATM* are not clearly at increased risk of CBC after radiation treatment. Women with *ATM* PV should not be precluded from considering BCT.

There is limited evidence that *CHEK2* PV may be associated with modest increased risks of CBC, but these risks are likely modified by genetic background (PRS) and may also be modified by endocrine therapy since a large proportion of *CHEK2*-associated cancers are ER-positive. There are no data to suggest that women with PV in *ATM*, *PALB2*, or other genes are at sufficient CBC risk to warrant a general recommendation for contralateral preventive mastectomy. It should be noted that the risks associated with *PALB2* are generally like those of *BRCA2* and that CBC risk has not been well-studied in women with *PALB2* PV. Consideration of contralateral preventive mastectomy may be reasonable in such women, particularly if they are young and with a significant family history of breast cancer.

Systemic Treatment

There have been studies suggesting that women with *CHEK2* PV experience worse breast cancer outcomes than women without PV.[25,39,40] These studies were performed before the widespread availability of prognostic genomic testing. Decisions about systemic adjuvant therapy should follow established decision pathways without regard to the presence of the *CHEK2* PV. There is no evidence that the presence of PV in other genes is associated with worse prognosis or should influence adjuvant therapy decisions.

The products of many of the moderate penetrance susceptibility genes operate in DNA damage repair pathways. PARP inhibitors are known to be effective in women with breast cancer and germline PV in *BRCA1* and *BRCA2*.[41,42] A small study, TBCRC048, has suggested that olaparib is highly active in patients with metastatic breast cancer and germline *PALB2* alterations but not in women with *CHEK2* or *ATM* PV.[43] The activity in women with alterations in other genes has not been studied, although there is reason to be optimistic that PARP inhibitors would be active in patients with PV in *RAD51C* and *RAD51D*.

MANAGEMENT OF RISK OF OTHER CANCERS

Although *PALB2* and perhaps *ATM* are associated with modestly increased risks of ovarian cancer, these risks resemble those of a woman with a first-degree relative with ovarian cancer and premenopausal risk-reducing salpingo-oophorectomy (RRSO) is unlikely to be of benefit. Even in

TABLE 2. Management Guidelines for Women With PV in Moderate Penetrance Genes Commonly Included on Multigene Panels

		Affected			Unaffected					
Gene	Subtype Predisposition	BCT If Feasible	CPM[a]	RRSO[b]	Overall BC Risk > 2×	MRI[c]	RRM[d]	RRSO[d]	SERM/AI Prevention	Others[e]
ATM	ER⁺	Y	NE	D	Y	Y	D if FH	D	NE	Pancreas[e]
BARD1	ER⁻	Y	N	N	N[f]	D if FH[f]	N	N	NE	
BRIP1	None	Y	N	Y (45-50 years)	N	N	N	Y (45-50 years)	NE	
CHEK2	ER⁺ > ER⁻	Y	NE	N	Y	Y	D if FH	N	NE	
NBN	None	Y	N	N	N	N	N	N	NE	
PALB2	ER⁻ > ER⁺	Y	D	D	Y	Y	D	D	NE	Pancreas[e]
RAD51C	ER⁻	Y	N	Y (45-50 years)	N[f]	D if FH[f]	N	Y (45-50 years)	NE	
RAD51D	ER⁻	Y	N	Y (45-50 years)	N[f]	D if FH[f]	N	Y (45-50 years)	NE	

Abbreviations: AI, aromatase inhibitor; BC, breast cancer; BCT, breast-conserving treatment (including adjuvant radiation); CPM, contralateral preventive mastectomy; D, discuss acknowledging limited evidence and uncertainty about risk; ER, estrogen receptor; FDR, first-degree relative; FH, familial hypercholesterolaemia; MRI, breast magnetic resonance imaging surveillance; N, no evidence to support (manage per family history); NE, insufficient evidence to support (manage per family history); PV, pathogenic variant; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy; SERM, selective estrogen receptor modulator; Y, recommended or supported.

[a]Contralateral risk is not defined for moderate penetrance genes. Younger age and stronger FH likely predict for higher risk. Presuming second cancer risk resembles primary cancer risk, and only PALB2 is likely to have sufficient risk to routinely discuss surgery on the basis of PV alone. Patients may elect CPM for personal utility regardless of underlying risk.

[b]RRSO should be discussed with all women with a family history of ovarian cancer regardless of genetic testing.

[c]MRI should always be discussed with US women whose cumulative lifetime risk exceeds 20% on the basis of family history–based models, regardless of PV.

[d]RRM and RRSO should be discussed with women if there is strong FH regardless of genetic testing.

[e]Referral for pancreas cancer screening of ATM/PALB2 PV and one or more FDR with pancreas cancer.

[f]BARD1, RAD51C, and RAD51D are associated with increased risks of ER-negative BC, but the overall BC risk is not reproducibly > 2. MRI is not clearly indicated on the basis of PV alone but should be discussed if there is an FH of BC in FDRs.

women with PV in BRCA2, which confers substantially higher risk, RRSO is often deferred until age 45 years, which supports deferring surgery until after menopause for PALB2 and ATM PV. Women with PV in BRIP1, RAD51C, and RAD51D are at higher risk and should strongly consider RRSO between 45 and 50 years.

The benefit of screening for pancreas cancer is not established. Gastroenterology professional societies recommend consideration of screening for women with PV in ATM or PALB2 who also have one or more first-degree relatives affected with pancreas cancer.[44,45]

MANAGEMENT OF UNAFFECTED RELATIVES

Unaffected relatives of women with moderate penetrance PV should be referred for genetic counseling and presymptomatic testing. Unaffected women with PV in ATM, CHEK2, or PALB2 have average lifetime risks exceeding 20% and are therefore candidates for enhanced surveillance with MRI in addition to mammography or contrast-enhanced mammography. The current recommendation is to begin such surveillance at age 40 years, although there may be benefits to starting younger, especially if there is a significant family history of breast cancer. PRS-modified absolute risk estimates may be provided by commercial

testing laboratories. In the absence of prospective validations, it would be unwise to forego enhanced surveillance on the basis of an adjusted absolute risk under 20%, particularly in the presence of a family history. Women with alterations in other genes, including BARD1, BRIP1, RAD51C, RAD51D, and NBN, should be followed as appropriate for their family history of breast cancer.

In general, the average breast cancer risks conferred by moderate penetrance PV are insufficient to support risk-reducing mastectomy (RRM). Furthermore, the studies of PRS modification indicate that a substantial proportion of women with PV in ATM and CHEK2 have lifetime risks below the 20% threshold used for MRI and it would be inappropriate to risk operating on such women. Conversely, however, caution should be used when employing a PRS-adjusted risk estimate to support RRM until robust validation studies have been published. For women with PV in PALB2, RRM may be considered, particularly if there is a significant family history of breast cancer. In women with PALB2 PV and no family history, the distribution of risk is such that some women may have lifetime risks in the range of 30% or even less. RRM would be an aggressive approach in such women.

Management of ovarian cancer and pancreas cancer risks in unaffected women should follow the earlier suggestions.

SUMMARY

Multigene panel testing identifies PVs in a substantial fraction of women with breast cancer. Cancer risks and management approaches are well-defined for women with PV in high penetrance cancer syndrome genes. For genes that confer more modest degrees of risk, best practices are less clear. In general, treatment of women with breast cancer and PV in moderate penetrance genes should proceed as treatment for women without such alterations. Some genes are associated with sufficient ovarian cancer or pancreas cancer risk to warrant intervention. Unaffected female family members should undergo cancer genetic counseling by a knowledgeable provider to be informed of the most up-to-date risk figures and recommendations for management. In most situations, the breast cancer risks for unaffected women will not warrant serious consideration of RRM although MRI surveillance will often be appropriate and RRSO will need to be considered for some PV.

The patient elected to undergo wide local excision and sentinel node biopsy. Her final stage was pT1cN0M0. Her 21-gene recurrence score was 16, and she elected adjuvant antiestrogen treatment alone. She was referred for adjuvant radiotherapy.

AFFILIATION

[1]Breast Cancer Medicine and Clinical Genetics Services, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

CORRESPONDING AUTHOR

Mark Robson, MD, Breast Cancer Medicine and Clinical Genetics Services, Department of Medicine, 1275 York Ave, Memorial Sloan Kettering Cancer Center, New York, NY 10065; Twitter: @MarkRobsonMD; e-mail: robsonm@mskcc.org.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Women With Breast Cancer and Pathogenic Variants in Genes Other Than *BRCA1* or *BRCA2*

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Mark Robson
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