Underestimation of Risk of a *BRCA1* or *BRCA2* Mutation in Women With High-Grade Serous Ovarian Cancer by BRCAPRO: A Multi-Institution Study

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ABSTRACT

Purpose

Identification of the 10% to 15% of patients with ovarian cancer who have germline *BRCA1* or *BRCA2* mutations is important for management of both patients and relatives. The BRCAPRO model, which estimates mutation likelihood based on personal and family cancer history, can inform genetic testing decisions. This study's purpose was to assess the accuracy of BRCAPRO in women with ovarian cancer.

Methods

BRCAPRO scores were calculated for 589 patients with ovarian cancer referred for genetic counseling at three institutions. Observed mutations were compared with those predicted by BRCAPRO. Analysis of variance was used to assess factors impacting BRCAPRO accuracy.

Results

One hundred eighty (31%) of 589 patients with ovarian cancer tested positive. At BRCAPRO scores less than 40%, more mutations were observed than expected (93 mutations observed v 34.1 mutations expected; $P < .001$). If patients with BRCAPRO scores less than 10% had not been tested, 51 (28%) of 180 mutations would have been missed. BRCAPRO underestimated the risk for high-grade serous ovarian cancers but overestimated the risk for other histologies ($P < .001$), underestimation increased as age at diagnosis decreased ($P = .02$), and model performance varied by institution ($P = .02$).

Conclusion

Patients with ovarian cancer classified as low risk by BRCAPRO are more likely to test positive than predicted. The risk of a mutation in patients with low BRCAPRO scores is high enough to warrant genetic testing. This study demonstrates that assessment of family history by a validated model cannot effectively target testing to a high-risk ovarian cancer patient population, which strongly supports the recommendation to offer *BRCA1/BRCA2* genetic testing to all patients with high-grade serous ovarian cancer regardless of family history.

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INTRODUCTION

Fifteen percent to 22% of high-grade serous ovarian cancers (including fallopian tube and primary peritoneal cancers) are attributable to a germline *BRCA1* or *BRCA2* mutation, and mutations occur at lower frequency in other ovarian cancer histologies.¹⁻⁶ For the patient with ovarian cancer, *BRCA* mutation status has prognostic and therapeutic implications.⁷⁻¹¹ In addition, *BRCA1/BRCA2* genetic testing of patients with ovarian cancer with suggestive personal and/or family histories, followed by predictive genetic testing of family members, is a cost-effective strategy to prevent future breast and ovarian cancers.¹²

The likelihood of identifying a *BRCA1/BRCA2* mutation is increased in patients with ovarian cancer who have a family history of breast and/or ovarian cancer and in patients who are of Ashkenazi Jewish ancestry. Historically, genetic testing strategies have focused on patients at high risk based on personal and family history.¹³ In light of reports of *BRCA1/BRCA2* mutations detected in patients with ovarian cancer who lack a strong family history,^{1-4,14} the National Comprehensive Cancer Network now recommends that comprehensive *BRCA1/BRCA2* genetic testing should be considered for all women with epithelial ovarian cancer.¹⁵ Although a more universal testing strategy would no doubt identify

more *BRCA1/BRCA2* mutations, it does also significantly increase costs.¹²

One way to further examine the targeted versus universal testing approaches is to examine how well a commonly used risk model such as BRCAPRO (which estimates the likelihood of a *BRCA1/BRCA2* mutation based on personal and family history) performs among women with ovarian cancer. If, given a complete pedigree, the model could effectively specify a high-risk population to which genetic testing could be targeted and could also effectively specify a population in which risk of a *BRCA1/BRCA2* mutation is low enough that testing could be deferred, then targeted genetic testing could be both a cost-effective and a sensitive strategy. However, if this type of risk assessment is unable to effectively delineate these populations, then this would argue in favor of universal testing. Therefore, the objective of this study was to determine the accuracy of BRCAPRO in predicting germline *BRCA1* or *BRCA2* mutations in a multi-institution study population of women with ovarian cancer.

METHODS

Data were collected through retrospective chart review at each study site, and institutional review board approval was granted by all three participating

institutions (The University of Texas MD Anderson Cancer Center, Duke University, and Washington University School of Medicine), each of which is an National Cancer Institute–designated comprehensive cancer center. All women who had been diagnosed with invasive epithelial ovarian cancer (including fallopian tube or primary peritoneal cancer), had been referred for genetic counseling (where complete pedigrees including all first- and second-degree relatives with and without cancer are collected as part of standard of care), and had undergone *BRCA1/BRCA2* genetic testing were included in the study. All such patients seen from 1996 to 2009 (MD Anderson), 2002 to 2011 (Duke), and 1998 to 2011 (Washington University) were included, for a total of 589 patients with ovarian cancer in the study population.

The study had 80% power to detect a difference between actual proportion of *BRCA* mutations and BRCAPRO-predicted mutations using a goodness-of-fit test with 5% type I error assuming BRCAPRO underestimated mutations on average by 15% among the women with the lowest risk (0% to 10% and 10% to 30% predicted probability of mutation) but was accurate for women of mid to high risk (> 30%), as was observed in a similar study by Ready et al.¹⁶ Power was estimated for a sample size of 180 women using 1,000 simulations. To improve generalizability of the findings, the study was then expanded to two additional sites.

BRCAPRO scores were calculated using CancerGene v5.1 (<http://www4.utsouthwestern.edu/breasthealth/cagene/>). BRCAPRO is a statistical model that uses Mendelian inheritance and Bayesian analysis to calculate an individual's chance to have a germline *BRCA1/BRCA2* mutation, based on age,

Table 1. Study Population Clinical Characteristics

Characteristic	All Sites		MDACC		Duke		Washington University		P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	
BRCAPRO score									< .001
Mean	0.21		0.25		0.22		0.16		
SD	0.31		0.33		0.30		0.27		
Median	0.05		0.07		0.06		0.04		
Age at diagnosis, years									.0087
Mean	55		55		53		57		
SD	11		11		13		11		
Median	55		55		53		57		
Range	20-86		21-85		20-86		27-87		
<i>BRCA</i> mutation positive									< .001
Total	180	31	107	39	33	25	40	22	
<i>BRCA1</i>	118	20	69	25	24	18	25	13	
<i>BRCA2</i>	62	11	38	14	9	7	15	8	
Categorization of BRCAPRO score									.026
0% to < 1%	122	21	42	16	30	23	50	27	
1% to < 3%	107	18	51	19	18	14	38	20	
3% to < 10%	126	21	55	20	28	21	43	23	
10% to < 40%	117	20	61	23	28	21	28	15	
≥ 40%	117	20	62	23	28	21	27	15	
Ashkenazi Jewish									.0276
No	529	90	236	87	126	95	167	90	
Yes	60	10	35	13	6	5	19	10	
High-grade serous component									.4759
No	143	26	62	24	28	26	53	29	
Yes	413	74	201	76	80	74	132	71	
Unknown	33		8		24		1		
Stage									.0021
I	70	13	29	12	18	16	23	13	
II	56	11	27	11	19	17	10	6	
III	336	64	145	61	63	55	128	74	
IV	63	12	36	15	15	13	12	7	
Unknown	64		34		17		13		

Abbreviations: MDACC, MD Anderson Cancer Center; SD, standard deviation.

*P < .05 indicates significant variation between sites.

ethnicity (Ashkenazi Jewish *v* non-Ashkenazi Jewish), personal history of breast and/or ovarian cancer, current age/age at death, and age of diagnosis of breast and/or ovarian cancer in all first- and second-degree relatives.¹⁷

To assess discriminatory power of BRCAPRO, a receiver operating characteristic (ROC) curve was constructed. To assess calibration of BRCAPRO, the study population was first divided into quintiles by BRCAPRO score, with cut points chosen such that each quintile represented 20% of the sample. χ^2 goodness-of-fit test was used to compare observed *BRCA1/BRCA2* mutations with the number predicted at each quintile. An analysis of variance model was used to assess the impact of study site, histology (high-grade serous component *v* other), ovarian cancer stage, and age at ovarian cancer diagnosis on BRCAPRO accuracy. Accuracy was calculated as mutation status (0 = no mutation and 1 = mutation) minus BRCAPRO-predicted probability of mutation. A negative value for accuracy indicated that the model was more likely to predict a mutation when one was not present; a positive value indicated that the model was less likely to predict a mutation when one was present. A statistically significant term indicated that model accuracy was impacted by that term. To assess BRCAPRO's ability to delineate high- versus low-risk testing populations, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using BRCAPRO cutoffs of $\geq 5\%$ and $\geq 10\%$ for recommending *BRCA1/BRCA2* genetic testing. These cutoffs were chosen because they are commonly discussed in the context of hereditary cancer. For example, Aetna covers *BRCA1/BRCA2* genetic testing for individuals with a 10% or greater risk of having a mutation.¹⁸ The American Congress of Obstetricians and Gynecologists practice bulletin on hereditary breast and ovarian cancer states that genetic risk assessment may be helpful for patients with a greater than 5% to 10% chance of having an inherited predisposition.¹⁹ In addition, previous BRCAPRO validation studies have also examined thresholds of 5% and 10%.^{20,21}

RESULTS

Study population clinical characteristics are listed in Table 1. Overall, 31% of the study population tested positive for a *BRCA1* or *BRCA2* mutation. Ten percent of the study population had Ashkenazi Jewish ancestry; all analyses were repeated excluding participants with Ashkenazi Jewish ancestry, and no significant changes in the results were noted. Seventy-four percent of the ovarian cancers included a high-grade serous component. Study population demographics did vary by site, including mean age at ovarian cancer diagnosis ($P = .0087$), ovarian cancer stage ($P = .0021$), mean BRCAPRO score ($P < .001$), and proportion testing *BRCA1/BRCA2* positive ($P < .001$).

Table 2 compares observed *BRCA1/BRCA2* mutations with the number predicted by BRCAPRO, both by site and for the whole study population. For the study population as a whole, significantly more mutations were observed than expected at all BRCAPRO scores less than 40%. Eighty percent of patients had BRCAPRO scores less than 40%, and 93 (52%) of 180 *BRCA1/BRCA2* mutations occurred in patients with BRCAPRO scores less than 40%. At BRCAPRO scores greater than 40%, the model nearly perfectly predicted the number of mutations observed. At all three study sites, significantly more mutations were observed than expected at BRCAPRO scores in the lowest two quintiles. Significantly more mutations were observed than expected in the 3% to $\leq 10\%$ BRCAPRO quintile at two of three sites, and significantly more mutations were observed than expected in the 10% to $\leq 40\%$ BRCAPRO quintile at one of three sites. These data

Table 2. Comparison of Observed *BRCA1/BRCA2* Mutations With the Number Predicted by BRCAPRO

BRCAPRO Probability	Observed No. of Women With Mutation	Expected No. of Women With Mutation	<i>P</i>	Observed-to-Expected Ratio	95% CI for Ratio
MDACC					
0% to < 1%	2	0.21	< .001*	9.52	1.60 to 31.47
1% to < 3%	12	0.89	< .001*	13.48	7.31 to 22.92
3% to < 10%	16	3.06	< .001*	5.23	3.10 to 8.31
10% to < 40%	26	12.7	< .001*	2.05	1.37 to 2.96
$\geq 40\%$	51	50.07	.8956	1.02	0.77 to 1.33
Duke					
0% to < 1%	3	0.15	< .001*	20.00	5.09 to 54.43
1% to < 3%	2	0.33	.0039*	6.06	1.02 to 20.02
3% to < 10%	2	1.63	.774	1.23	0.21 to 4.05
10% to < 40%	8	6.18	.4635	1.29	0.60 to 2.46
$\geq 40\%$	18	20.37	.5991	0.88	0.54 to 1.37
Washington University					
0% to < 1%	3	0.19	< .001*	15.79	4.02 to 42.97
1% to < 3%	3	0.67	.0046*	4.48	1.14 to 12.19
3% to < 10%	8	2.59	< .001*	3.09	1.44 to 5.87
10% to < 40%	8	5.53	.2933	1.45	0.67 to 2.75
$\geq 40\%$	18	20.28	.6127	0.89	0.54 to 1.38
All sites					
0% to < 1%	8	0.55	< .001*	14.55	6.76 to 27.62
1% to < 3%	17	1.9	< .001*	8.95	5.39 to 14.03
3% to < 10%	26	7.28	< .001*	3.57	2.38 to 5.16
10% to < 40%	42	24.4	< .001*	1.72	1.26 to 2.31
$\geq 40\%$	87	90.72	.6958	0.96	0.77 to 1.18

Abbreviation: MDACC, MD Anderson Cancer Center.

*Statistically significant.

Fig 1. Proportion of (A) all patients with ovarian cancer and (B) patients with ovarian cancer with a high-grade serous component testing *BRCA1/BRCA2* positive per quintile, plotted against mean BRCAPRO probability per quintile. The diagonal ideal line represents *BRCA1/BRCA2* positivity rate predicted by BRCAPRO. Vertical bars represent 95% CIs.

are graphically represented in Figures 1A (all ovarian cancers) and 1B (high-grade serous ovarian cancers only). Appendix Table A1 (online only) shows the ratio of observed to expected mutations broken down by high-grade serous versus not high-grade serous ovarian cancers. The ROC curve for the whole study population is plotted in Figure 2A. The area under the ROC curve is 0.81 (95% CI, 0.78 to 0.84). Figure 2B shows a similar ROC curve for high-grade serous ovarian cancers, with an area under the ROC curve of 0.83 (95% CI, 0.79 to 0.87).

Table 3 lists what the sensitivity, specificity, PPV, and NPV of BRCAPRO would be if cutoffs of $\geq 5\%$ or $\geq 10\%$ were used to determine whether to offer *BRCA1/BRCA2* genetic testing, analyzing the study sample as a whole. This showed a low sensitivity of BRCAPRO. Even using less than 5% as a cutoff, 20% of *BRCA1/BRCA2*-positive patients had BRCAPRO scores below the cutoff. The PPV of BRCAPRO scores above these cutoffs is quite high (47% to 55%). However, the NPV of a BRCAPRO score less than

5% is 88%; in other words, patients with BRCAPRO scores less than 5% still had a 12% chance to be *BRCA1/BRCA2* positive. Because PPV and NPV are impacted by mutation prevalence, which did vary by site, PPV and NPV also differed by site. At the 5% cutoff, PPV ranged from 38% at Duke and Washington Universities to 57% at MD Anderson, and NPV ranged from 83% (MD Anderson) to 91% (Duke and Washington Universities). Analysis of variance results are listed in Table 4. BRCAPRO accuracy did vary by site ($P = .0196$). BRCAPRO underestimated the likelihood of a *BRCA1/BRCA2* mutation in patients with high-grade serous ovarian cancer and overestimated the likelihood in ovarian cancers with no high-grade serous component ($P < .001$). BRCAPRO accuracy also varied by age at ovarian cancer diagnosis; for each decade decrease in age at diagnosis, mean BRCAPRO underestimation increased by 0.03 (95% CI, 0.005 to 0.10; $P = .0235$). Each of these three variables acted independently in multivariable analysis. Ovarian cancer stage did not impact BRCAPRO accuracy.

Fig 2. BRCAPRO receiver operating characteristic curves in (A) all patients with ovarian cancer and (B) patients with ovarian cancer with a high-grade serous component.

Table 3. BRCAPRO Model Performance Using Cutoffs of $\geq 5\%$ and $\geq 10\%$

BRCAPRO Score	Sensitivity (%)		Specificity (%)		Positive Predictive Value (%)		Negative Predictive Value (%)	
	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
$\geq 5\%$	80	74 to 86	61	56 to 65	47	41 to 53	88	83 to 91
$\geq 10\%$	72	65 to 78	74	70 to 78	55	48 to 61	86	82 to 89

DISCUSSION

This study examined the accuracy of BRCAPRO in predicting germline *BRCA1/BRCA2* mutations in a large multi-institution sample of patients with ovarian cancer referred for genetic counseling, most of whom had high-grade serous ovarian cancer. As evaluated by the ROC curve, BRCAPRO exhibited good discrimination in this patient population (area under the ROC curve was 0.81 for all ovarian cancers and 0.83 for high-grade serous only), consistent with previous BRCAPRO validation studies of different patient populations.²⁰⁻²⁴ However, examination of calibration of BRCAPRO by comparing observed versus expected mutations revealed that BRCAPRO significantly underestimated *BRCA1/BRCA2* mutations at BRCAPRO scores less than 40%. This underestimation was observed for the whole study population and was even more evident when only high-grade serous ovarian cancers were analyzed. This reveals a significant limitation of BRCAPRO, given that half of the observed *BRCA1/BRCA2* mutations occurred in patients with BRCAPRO scores less than 40%. BRCAPRO did perform quite well at BRCAPRO scores greater than 40%, but these patients have such a strong family history that it is quite apparent that they should be offered *BRCA1/BRCA2* genetic testing without need to refer to a model. We also examined what the outcome would have been if BRCAPRO score thresholds of 5% or 10% had been used to determine whether to offer *BRCA1/BRCA2* genetic testing. Even using a cutoff BRCAPRO score of less than 5%, 20% of *BRCA1/BRCA2*-positive patients had BRCAPRO scores under the cutoff, and the residual risk to have a *BRCA1/BRCA2* mutation with a score under the cutoff was 12%. Therefore, low BRCAPRO scores are not suffi-

ciently predictive of the lack of a *BRCA1/BRCA2* mutation to justify not offering *BRCA1/BRCA2* genetic testing. In its current form, therefore, BRCAPRO would not have been helpful in determining which patients with ovarian cancer should be offered *BRCA1/BRCA2* genetic testing.

Clinical practice guidelines, such as those from the National Comprehensive Cancer Network,¹⁵ already endorse *BRCA1/BRCA2* genetic testing for all women with high-grade serous ovarian cancer. Such a universal testing strategy significantly increases the cost per *BRCA1/BRCA2* mutation identified compared with a strategy of targeting genetic testing to women with suggestive family histories.¹² In that context, it is appropriate to ensure that all other viable possibilities have been evaluated. Although other studies have also shown that *BRCA1/BRCA2* mutations are found in patients with ovarian cancer who lack a strong personal/family history,^{1-4,14} we know of no other studies that collected and assessed family history regarding all first- and second-degree relatives with and without cancer. BRCAPRO incorporates information regarding both affected and unaffected relatives into its analysis, and it could have been the case that this level of family history information would have allowed a low-risk population to be excluded from genetic testing. Our results show that this approach could not exclude a low-risk population from genetic testing, thus strongly supporting the idea of universal testing.

It is also important to note that the recommendation for universal *BRCA1/BRCA2* genetic testing for patients with ovarian cancer is often not followed. Norquist et al¹⁴ found that one third of the *BRCA1/BRCA2* mutations present in their ovarian cancer study population had not been identified via clinical genetic testing, and specifically those who were diagnosed at older ages and lacked a strong family history were less likely to have been identified clinically. Similarly, Damsky et al²⁵ found that only 23% of women with invasive ovarian cancer were seen for genetic counseling, and women diagnosed at older ages were less likely to be seen. Thus, it seems that a referral bias yet remains such that women who lack a strong family history or early age at diagnosis are still less likely to receive *BRCA1/BRCA2* genetic testing. Our results demonstrate that women who on comprehensive family history collection and assessment lack these traditional hereditary cancer risk factors remain at significant risk for a germline *BRCA1/BRCA2* mutation. Effective implementation of the universal testing recommendation should be a focus of attention for the clinical oncology community.

Our results demonstrated that BRCAPRO underestimated mutation probability in patients with high-grade serous ovarian cancer and overestimated mutation probability in other ovarian cancer histologies. Although it is well established that high-grade serous ovarian cancer histology increases the likelihood of a *BRCA1/BRCA2* mutation,^{4,5} BRCAPRO does not currently use ovarian cancer histology

Table 4. Mean Underestimation/Overestimation of Probability of *BRCA1/BRCA2* Mutation

Factor	Least Squares Mean*	95% CI	P
Site			.0196
MDACC	0.09	0.04 to 0.14	
Duke	-0.02	-0.09 to 0.05	
Washington University	0.02	-0.04 to 0.07	
Age at ovarian cancer diagnosis, per decade decrease in age, β	0.03	0.005 to 0.1	.0235
High-grade serous component†			< .001
No	-0.08	-0.14 to -0.01	
Yes	0.13	0.09 to 0.17	

Abbreviation: MDACC, MD Anderson Cancer Center.

*Negative values are indicative of overestimation, and positive values are indicative of underestimation.

†Analysis excluded patients for whom histology was not known.

information in predicting likelihood of a *BRCA1/BRCA2* mutation. Accuracy of BRCAPRO in the ovarian cancer patient population could likely be improved by incorporating histology information. BRCAPRO has previously been modified to incorporate estrogen receptor and progesterone receptor status of breast cancers,²⁶ and there is evidence that including tumor pathology information helps improve hereditary cancer risk assessment for patients with breast cancer.²⁷ Underestimation of mutation probability also increased as age at ovarian cancer diagnosis decreased, and this also could potentially be addressed by revising the BRCAPRO model. This is also consistent with a recent report showing a 24% frequency of *BRCA1/BRCA2* mutations in women diagnosed with ovarian cancer at ages 40 to 49.³

BRCAPRO performance also varied by study site, which has also been observed in other BRCAPRO validation studies.²¹ We performed this as a multi-institution study because we wanted to demonstrate that the results were generalizable, and we indeed found that the overall trend of underestimation of risk at low BRCAPRO scores was consistently demonstrated at each individual site as well as by the aggregate data, as shown in Table 2. Because full pedigrees including all unaffected first- and second-degree relatives were collected and inputted into BRCAPRO for all three sites, we do not believe the observed difference is a result of how the model was used at each site. The demographic differences between sites highlighted in Table 1 suggest that there could be other factors not captured by BRCAPRO (such as differing proportions of newly diagnosed v recurrent ovarian cancers) that could play a role in the observed difference in model performance. PPV and NPV in particular are also influenced by mutation prevalence in the population being studied, and these values did vary between sites and would also be different in a lower risk population.

Although these results support a universal testing strategy for all high-grade serous (or all high-grade nonmucinous epithelial) ovarian cancers, there is likely greater benefit to be gained from using family history as a tool to identify a higher risk population for genetic testing for other more common cancers with a lower background prevalence of *BRCA1/BRCA2* mutations (eg, breast cancer). In addition, a universal genetic testing strategy for patients with ovarian cancer must not lose sight of the importance of pretest genetic counseling and consideration of patient preferences. Although acceptance of *BRCA1/BRCA2* genetic testing among patients with ovarian cancer is high,^{28,29} some patients may choose to decline testing and/or have significant questions or concerns they would like addressed before testing.

This study has several strengths and limitations that should be considered. The multi-institution study population strengthens the generalizability of our findings. In addition, because all study patients had a complete pedigree taken by a cancer genetic counselor, the family history information available for the study was comprehensive,

reducing the concern that BRCAPRO's accuracy was reduced artificially by insufficient family history information. The study is limited by the fact that the study population had an a priori high risk to be *BRCA1/BRCA2* positive, given that all patients had been referred for genetic counseling, and this is reflected in the high rate of *BRCA1/BRCA2* mutations observed. However, the factors that commonly lead to genetic counseling referral, namely significant personal and family history, are exactly the factors that should be accounted for by BRCAPRO. In addition, the BRCAPRO model is designed for use in patients for whom a full pedigree is available, and such a pedigree is generally only available for patients who have been seen for genetic counseling, so we are studying the population of intended use for this model. Another limitation of the study is that it was a retrospective data collection, which could have introduced bias.

In a multi-institution sample of patients with ovarian cancer referred for genetic counseling, those classified as low risk by BRCAPRO were more likely to test positive for a germline *BRCA1* or *BRCA2* mutation than predicted. Even at BRCAPRO scores less than 5%, the residual risk for a patient with ovarian cancer to be *BRCA1/BRCA2* positive is high enough to warrant consideration of genetic testing. BRCAPRO performance could be improved by incorporating factors such as ovarian cancer histology. Given both the high prevalence of *BRCA1/BRCA2* mutations and the limitations demonstrated here of using family history to predict mutation probability in patients with high-grade serous ovarian cancer, these results emphasize the importance of implementing the recommendation to offer *BRCA1/BRCA2* genetic testing to all patients with high-grade serous ovarian cancer regardless of family history.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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REFERENCES

1. Pal T, Permuth-Wey J, Betts JA, et al: *BRCA1* and *BRCA2* mutations account for a large proportion of ovarian carcinoma cases. *Cancer* 104:2807-2816, 2005
2. Risch HA, McLaughlin JR, Cole DE, et al: Population *BRCA1* and *BRCA2* mutation frequencies and cancer penetrances: A kin-cohort study in Ontario, Canada. *J Natl Cancer Inst* 98:1694-1706, 2006
3. Zhang S, Royer R, Li S, et al: Frequencies of *BRCA1* and *BRCA2* mutations among 1,342 unselected patients with invasive ovarian cancer. *Gynecol Oncol* 121:353-357, 2011
4. Alsop K, Fereday S, Meldrum C, et al: *BRCA* mutation frequency and patterns of treatment response in *BRCA* mutation-positive women with ovarian cancer: A report from the Australian Ovarian Cancer Study Group. *J Clin Oncol* 30:2654-2663, 2012
5. Cancer Genome Atlas Research Network: Integrated genomic analyses of ovarian carcinoma. *Nature* 474:609-615, 2011
6. Vineyard MA, Daniels MS, Urbauer DL, et al: Is low-grade serous ovarian cancer part of the tumor spectrum of hereditary breast and ovarian cancer? *Gynecol Oncol* 120:229-232, 2011
7. Banerjee S, Kaye S: PARP inhibitors in *BRCA* gene-mutated ovarian cancer and beyond. *Curr Oncol Rep* 13:442-449, 2011
8. Bolton KL, Chenevix-Trench G, Goh C, et al: Association between *BRCA1* and *BRCA2* mutations and survival in women with invasive epithelial

ovarian cancer. *JAMA* 307:382-390, 2012

9. Kaye SB, Lubinski J, Matulonis U, et al: Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. *J Clin Oncol* 30:372-379, 2012

10. Konstantinopoulos PA, Cannistra SA: Comparing poly (ADP-ribose) polymerase inhibitors with standard chemotherapy in BRCA-mutated, recurrent ovarian cancer: Lessons learned from a negative trial. *J Clin Oncol* 30:347-350, 2012

11. Lacour RA, Westin SN, Meyer LA, et al: Improved survival in non-Ashkenazi Jewish ovarian cancer patients with BRCA1 and BRCA2 gene mutations. *Gynecol Oncol* 121:358-363, 2011

12. Kwon JS, Daniels MS, Sun CC, et al: Preventing future cancers by testing women with ovarian cancer for BRCA mutations. *J Clin Oncol* 28:675-682, 2010

13. Lancaster JM, Powell CB, Kauff ND, et al: Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol* 107:159-162, 2007

14. Norquist BM, Pennington KP, Agnew KJ, et al: Characteristics of women with ovarian carcinoma who have BRCA1 and BRCA2 mutations not identified by clinical testing. *Gynecol Oncol* 128:483-487, 2013

15. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Genetic/

Familial High Risk Assessment: Breast and Ovarian, V1.2012. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

16. Ready KJ, Vogel KJ, Atchley DP, et al: Accuracy of the BRCAPRO model among women with bilateral breast cancer. *Cancer* 115:725-730, 2009

17. Parmigiani G, Berry D, Aguilar O: Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. *Am J Hum Genet* 62:145-158, 1998

18. Aetna: Aetna clinical policy bulletin: BRCA testing, prophylactic mastectomy, and prophylactic oophorectomy. http://www.aetna.com/cpb/medical/data/200_299/0227.html

19. American College of Obstetricians and Gynecologists, ACOG Committee on Practice Bulletins—Gynecology, ACOG Committee on Genetics, et al: ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol* 113:957-966, 2009

20. Antoniou AC, Hardy R, Walker L, et al: Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: Validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. *J Med Genet* 45:425-431, 2008

21. Parmigiani G, Chen S, Iversen ES Jr, et al: Validity of models for predicting BRCA1 and BRCA2 mutations. *Ann Intern Med* 147:441-450, 2007

22. Vogel KJ, Atchley DP, Erlichman J, et al: BRCA1 and BRCA2 genetic testing in Hispanic patients: Mutation prevalence and evaluation of the

BRCAPRO risk assessment model. *J Clin Oncol* 25:4635-4641, 2007

23. Antoniou AC, Durocher F, Smith P, et al: BRCA1 and BRCA2 mutation predictions using the BOADICEA and BRCAPRO models and penetrance estimation in high-risk French-Canadian families. *Breast Cancer Res* 8:R3, 2006

24. Kurian AV, Gong GD, John EM, et al: Performance of prediction models for BRCA mutation carriage in three racial/ethnic groups: Findings from the Northern California Breast Cancer Family Registry. *Cancer Epidemiol Biomarkers Prev* 18:1084-1091, 2009

25. Demsky R, McCuaig J, Maganti M, et al: Keeping it simple: Genetics referrals for all invasive serous ovarian cancers. *Gynecol Oncol* 130:329-333, 2013

26. Tai YC, Chen S, Parmigiani G, et al: Incorporating tumor immunohistochemical markers in BRCA1 and BRCA2 carrier prediction. *Breast Cancer Res* 10:401, 2008

27. Mavaddat N, Rebbeck TR, Lakhani SR, et al: Incorporating tumour pathology information into breast cancer risk prediction algorithms. *Breast Cancer Res* 12:R28, 2010

28. Lacour RA, Daniels MS, Westin SN, et al: What women with ovarian cancer think and know about genetic testing. *Gynecol Oncol* 111:132-136, 2008

29. Meiser B, Gleeson M, Kasparian N, et al: There is no decision to make: Experiences and attitudes toward treatment-focused genetic testing among women diagnosed with ovarian cancer. *Gynecol Oncol* 124:153-157, 2012

Appendix**Table A1.** Ratio of Observed *BRCA1/BRCA2* Mutations to the Number Predicted by BRCAPRO by High-Grade Serous Versus Other Histologies

BRCAPRO Probability	High-Grade Serous		Not High-Grade Serous	
	Observed-to-Expected Ratio	95% CI	Observed-to-Expected Ratio	95% CI
MDACC				
0% to < 1%	6.33	0.32 to 31.21	0.00	NE
1% to < 3%	15.34	7.79 to 27.34	9.05	1.52 to 29.9
3% to < 10%	6.92	4.02 to 11.16	1.12	0.06 to 5.54
10% to < 40%	2.52	1.63 to 3.72	0.59	0.1 to 1.94
≥ 40%	1.09	0.79 to 1.46	0.70	0.28 to 1.45
Duke				
0% to < 1%	33.71	8.57 to 91.74	0.00	NE
1% to < 3%	9.85	1.65 to 32.55	0.00	NE
3% to < 10%	0.00	NE	1.61	0.05 to 4.93
10% to < 40%	1.61	0.65 to 3.35	0.00	NE
≥ 40%	1.01	0.6 to 1.6	0.00	NE
Washington University				
0% to < 1%	20.69	5.26 to 56.31	0.00	NE
1% to < 3%	4.72	0.79 to 15.58	4.02	0.2 to 19.81
3% to < 10%	4.17	1.83 to 8.26	0.00	NE
10% to < 40%	1.44	0.58 to 3	1.46	0.24 to 4.82
≥ 40%	1.03	0.6 to 1.67	0.52	0.13 to 1.41
All sites				
0% to < 1%	17.86	7.81 to 35.32	0.00	NE
1% to < 3%	10.95	6.23 to 17.93	4.99	1.27 to 13.59
3% to < 10%	4.97	3.19 to 7.39	0.84	0.14 to 2.77
10% to < 40%	2.06	1.45 to 2.83	0.71	0.22 to 1.71
≥ 40%	1.06	0.84 to 1.32	0.55	0.27 to 1.02

Abbreviations: MDACC, MD Anderson Cancer Center; NE, not estimable.