MEDICAL POLICY

POLICY TITLE	USE OF COMMON GENETIC VARIANTS TO PREDICT RISK OF NONFAMILIAL BREAST CANCER
POLICY NUMBER	MP- 2.250

Original Issue Date (Created):	**April 24, 2012**
Most Recent Review Date (Revised):	**March 25, 2014**
Effective Date:	**June 1, 2014**

I. POLICY

Testing for one or more single nucleotide polymorphisms (SNPs) to predict an individual's risk of breast cancer is considered **investigational** as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-reference:
MP 1.036 Prophylactic Mastectomy and Prophylactic Bilateral Oophorectomy
MP-2.211 Genetic Testing for Inherited Breast and/or Ovarian Cancer
MP-2.212 Tumor Markers and Tumor Related Molecular Testing
MP-2.249 Non-BRCA Breast Cancer Risk Assessment (OncoVue)

II. PRODUCT VARIATIONS

TOP

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N]	Capital Cares 4 Kids	[N]	Indemnity
[N]	PPO	[N]	SpecialCare
[N]	HMO	[N]	POS
[N]	SeniorBlue HMO	[Y]	FEP PPO*
[N]	SeniorBlue PPO		

* FEP PPO- Benefits are not available for genetic screening related to family history of breast or ovarian cancer. This testing maybe covered for members who actually have cancer, (e.g., cancer-affected), but not for screening for unaffected individuals.

POLICY TITLE	USE OF COMMON GENETIC VARIANTS TO PREDICT RISK OF NONFAMILIAL BREAST CANCER
POLICY NUMBER	MP- 2.250

III. DESCRIPTION/BACKGROUND

TOP

Several single-nucleotide polymorphisms (SNPs), which are single base-pair variations in the DNA sequence of the genome, have been found to be associated with breast cancer and are common in the population, but confer only small increases in risk. Some commercially available assays test for several SNPs and combine results to predict an individual's risk of breast cancer relative to the general population in order to identify those at increased risk who might benefit from more intensive surveillance.

Background

Rare, single gene variants conferring a high risk of breast cancer have been linked to hereditary breast cancer syndromes. Examples are mutations in BRCA1 and BRCA2. These, and a few others, account for less than 25% of inherited breast cancer. Moderate risk alleles, such as variants in the CHEK2 gene, are also relatively rare and apparently explain very little more of the genetic risk.

In contrast, several common SNPs associated with breast cancer have been identified primarily through genome-wide association studies of very large case-control populations. The high-risk alleles occur with high frequency in the general population, although the increased breast cancer risk associated with each is very small relative to the general population risk. Some have suggested that these common-risk SNPs could be combined to achieve an individualized risk prediction either alone or in combination with traditional predictors in order to personalize screening programs in which starting age and intensity would vary by risk. In particular, the American Cancer Society has recommended that women at high risk (greater than a 20% lifetime risk) should undergo breast magnetic resonance imaging (MRI) and a mammogram every year, while those at moderately increased risk (15% to 20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram.

At least 9 companies (Table) currently offer Internet-based testing for breast cancer risk profiles using SNPs. Most of these companies offer testing direct-to-consumers (DTCs), although Navigenics (Forest City, CA) appears to now offer testing only through physicians. The company does provide interested consumers with access to a network of physicians who are reported to be familiar with the company's test profile and who utilize the test.

The algorithms or risk models used for all the tests identified, except for those offered by deCODE (Reykjavik, Iceland), are proprietary and not described on company websites. In the 3 tests providing some information on the SNPs used for testing, these range from panels as small as 6 SNPs (GenePlanet, Dublin, Ireland) to as large as 16 SNPs (deCODE).

deCODE appears to offer two separate tests for breast cancer risk: one is the deCODE BreastCancer™ test and the other is part of the deCODEme Complete Scan for risk assessment of a broad assortment of diseases. Although in the past, these two tests appeared to use different SNP combinations for testing, both are now described as 16 SNP panels. It is likely that the

tests are the same, with the second of the two simply part of a larger assessment panel. The deCODE BreastCancer™ test includes a list of SNPs used and an explanation for the simple multiplicative model applied to this list.

A comprehensive list of companies offering DTC genetic testing for various diseases including breast cancer is maintained by the Genetics and Public Policy Center, available online at: http://www.dnapolicy.org/news.release.php?action=detail&pressrelease_id=137. This site was most recently updated in May 2010.

Table: Tests for Breast Cancer Susceptibility Using SNP Based Risk Panels

Company	Location	Test Offered Direct to Consumer	Number of SNPs Used in Risk Panel
23andme	Mt. View, CA	Yes	7
City of Hope	Duarte, CA	No	7
deCODE	Reykjavik, Iceland	Yes	deCode BreastCancer – 16; deCODE Complete Scan – 16
easyDNA	Elk Grove, CA	Yes	ND
GenePlanet	Dublin, Ireland	Yes	6
Matrix Genomics	Santa Fe, NM	Yes	6
MediChecks	Nottingham, UK	Yes	ND
Navigenics	Forest City, CA	No*	ND
Pathway Genomics	San Diego, CA	Yes	ND
The Genetic Testing Laboratories	Las Cruces, NM	Yes	ND

ND – not described
**Consumers are referred to a network of providers for testing*

Regulatory Status

No test combining the results of SNPs to predict breast cancer risk has been approved or cleared by the U.S. Food and Drug Administration (FDA). These are offered as laboratory-developed tests; that is, tests developed and used at a single testing site. Laboratory developed tests, as a matter of enforcement discretion, have not been traditionally regulated by FDA in the past. They do require oversight under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and the development, and use of laboratory developed tests is restricted to laboratories certified as high complexity under CLIA.

The FDA appears to be in the process of considering a change in its regulatory posture toward this group of DTC genetic tests (available online at: *http://www.genomicslawreport.com*).

The FDA has met with many of the companies listed in the Table and has sent out letters indicating the belief that premarket submissions are warranted.

On July 19-20, 2010, the FDA held an open public meeting to allow stakeholders to comment on this issue. The FDA has not announced its final decisions about regulatory policy in the area, and so future regulatory requirements remain unclear.

Under the current regulatory program, CLIA requires that laboratories demonstrate the analytical validity of the tests they offer. However, there is no requirement for a test to demonstrate either clinical validity or clinical utility. Some states (e.g., New York) have chosen to regulate DTC laboratories. Because these reviews are not public, it is not possible to determine what scientific standard is being applied to them.

IV. RATIONALE

TOP

Introduction

Genome-wide association studies (GWAS) examine the entire genome of each of thousands of individuals for single nucleotide polymorphisms (SNPs), single base-pair variations in the DNA sequence at semi-regular intervals, and attempt to associate variant SNP alleles with particular diseases. Several case-control GWASs have been carried out, primarily in white women, to investigate common risk markers of breast cancer. In recent years, a number of SNPs associated with breast cancer have been reported at a high level of statistical significance and have been validated in 2 or more large, independent studies. (1-9) Recently SNPs associated with breast cancer risk in Asian and African women have been the subject of more than a dozen articles, although these appear exploratory. (10-23) GWAS have also identified SNPs in specific genes associated with the onset or severity of chemotherapy-induced toxicity. (24, 25)

SNP-based Risk Assessment

As noted in the Background section, estimates of breast cancer risk, based on SNPs derived from large GWASs and/or from SNPs in other genes known to be associated with breast cancer are available as laboratory-developed test services from different companies. There is growing literature on these associations although public information on the actual models being offered commercially is sparse. Independent determination of clinical validity in an intended use population to demonstrate clinical validity has not been performed. There are also no studies to suggest that use of SNP-based risk assessment has any impact on health care outcomes.

No peer-reviewed reports have been published in which these commercially available breast cancer risk estimators have been compared to each other to determine if they report similar

results on the same individuals specifically for breast cancer. In July 2008, deCODE, 23andme, and Navigenics agreed to work with the Personalized Medicine Coalition (PMC) on a set of standards regarding the scientific validity of their genotyping panels; in the process test individuals were genotyped for 3 disease associations, but the PMC provides actual information on only one (breast cancer) with very little detail. (Report available online at: http://cancercontrol.cancer.gov/od/phg/docs/pmcscivalid.pdf.)

Systematic reviews

Several meta-analyses of case-control studies have been performed to investigate the association between breast cancer and various SNPs. Meta-analyses have indicated that specific SNPs are associated with either an increased risk for breast cancer (XRCC3 [T241M], PON1 [L55M], 8q24 [G-allele of rs13281615]), (26-28) or a decreased risk of breast cancer (XRCC3 [A17893G], COMT [Va1158Met], COX11 [rs6504950]). (28-30) Some of these loci that are associated with breast cancer risk are included in the deCode™ SNP assay. Meta-analyses of GWAS have also been performed that have identified SNPs at new breast cancer susceptibility loci. (31-33)

Primary studies

Since there are no published studies of commercial SNP-based breast cancer risk predictors, other published studies of the clinical usefulness of other similar combinations of SNPs as risk predictors will be considered here. In 2008, Pharoah et al. (34) considered a combination of 7 well-validated SNPs associated with breast cancer, 5 of which are included in the deCODE BreastCancer™ test. A model that simply multiplies the individual risks of the 7 common SNPs was assumed, and would explain approximately 5% of the total genetic risk of non-familial breast cancer. Applying the model to the population of women in the U.K., the authors concluded that the risk profile provided by the 7 SNPs would not provide sufficient discrimination between those who would and would not experience future breast cancer to enable individualized preventive treatment such as tamoxifen. However, the authors did consider the effect on a population screening program that could be personalized with the results of SNP panel testing. They concluded that no women would be included in the high-risk category (currently defined as 20% risk within the next 10 years at age 40–49 years, according to the National Institute for Health and Care Excellence), and therefore none would warrant the addition of magnetic resonance imaging (MRI) screening or the consideration of more aggressive intervention on the basis of the SNP panel results.

Wacholder et al. (35) evaluated the performance of a panel of 10 SNPs with established associations with breast cancer that had, at the time of the study, been validated in at least 3

published GWAS. Cases (n=5,590) and controls (n=5,998) from the National Cancer Institute's Cancer Genetic Markers of Susceptibility GWAS of breast cancer were included in the study (women of primarily European ancestry). The panel contained 5 SNPs included in the deCODE BreastCancer™ test. The SNP panel was examined as a risk predictor alone and in addition to readily available components of the Gail model (minus mammographic density and diagnosis of atypical hyperplasia). The authors found that adding the SNP panel to the Gail model resulted in slightly better stratification of a women's risk than either the SNP panel or the Gail model alone but that this stratification was not adequate to inform clinical practice. For example, only 34% of the women who actually had breast cancer were actually assigned to the top 20% risk group. The area under the curve (AUC) for the combined SNP and Gail model was 61.8% (50% is random, 100% is perfect).

Reeves et al. (36) evaluated the performance of a panel of 7 SNPs with established associations with breast cancer in a study of 10,306 women with breast cancer and 10,383 without cancer in the U.K. The risk panel also contained 5 SNPs included in the deCODE BreastCancer™ test and used a similar multiplicative approach. Sensitivity studies were performed using only 4 SNPs and using 10 SNPs, both demonstrating no significant change in performance. While use of the risk score was able to show marked differences in risk between the upper quintile of patients (8.8% cumulative risk to age 70 years) and the lower quintile of patients (4.4%), these changes were not viewed as clinically useful when compared to patients with an estimated overall background risk of 6.3%. Of note, simple information on patient histories; for example, presence of one or two first-degree relatives with breast cancer provided equivalent or superior risk discrimination (9.1% and 15.4%, respectively).

Mealiffe et al. (37) evaluated a 7-SNP panel in a nested case-control cohort of 1,664 case patients and 1,636 controls. Again a multiplicative model was used and, as in the study by Wacholder et al., the genetic risk score was reviewed as a potential replacement for or add-on test to the Gail clinical risk model. These authors employed the net reclassification improvement, or NRI, to evaluate performance. While they concluded that statistically significant improvements could be observed by addition of the genomic risk assessment to the Gail clinical risk assessment, they were unable to posit or demonstrate that the observed changes would lead to improved clinical outcomes. They suggested further studies were needed and that benefit might be observed by careful selection of patients (e.g. those who on Gail score analysis exhibited intermediate risk) who might comprise a priori of candidates who would benefit from enhanced or improved risk assessment.

Darabi et al. (38) investigated the performance of 18 breast cancer risk SNPs), together with mammographic percentage density (PD), body mass index (BMI), and clinical risk factors in predicting absolute risk of breast cancer, empirically, in a well-characterized case-control study of postmenopausal Swedish women. The performance of a risk prediction model based on an initial set of 7 breast cancer risk SNPs was improved by additionally including 11 more recently established breast cancer risk SNPs (p=4.69 × 10-4). Adding mammographic PD, BMI and all 18 SNPs to a Swedish Gail model improved the discriminatory accuracy (the AUC statistic) from 55% to 62%. The net reclassification improvement was used to assess improvement in classification of women into low, intermediate, and high categories of 5-year risk (p=8.93 × 10-9). It was estimated that using an individualized screening strategy based on risk models incorporating clinical risk factors, mammographic density, and SNPs, would capture 10% more cases. The outcomes of such a change remain unknown.

It is assumed that many more genetic risk markers remain to be discovered as the majority of the genetic risk of breast cancer has not been explained by known gene variants and SNPs. One reason more genetic associations have not been found is that even large GWAS are underpowered to detect uncommon genetic variants. (39)

Two approaches have recently been described to help address this problem. Braun and Buetow (40) (2011) reported on a technique for multi-SNP analysis of GWAS data based on the study of patient cases selected using their association with known pathways related to disease risk. They coined the term Pathways of Distinction Analysis (PoDA) to describe this methodology and demonstrated that using this approach facilitated the identification of disease-related SNPs by creating clusters of similar variants within disease groups that stood out when compared to control groups.

Silva et al. (41) have recently reported on the use of DNA pooling methodology to aid in detection of genetic polymorphisms. They combined DNA from many individuals (up to 200 patients or controls) into a single sample in an effort to pre-select SNPs of interest in different populations. They concluded test accuracy was sufficiently robust to allow use of pooling to provide estimates on allelic distributions in different populations being studied.

Although there are no guidelines regarding the clinical use of SNP panels for estimating breast cancer risk, the published literature is in general agreement that their use in clinical or screening settings is premature due to a lack of a more complete set of explanatory gene variants and to insufficient discriminatory power at this time. (34-37, 39, 42, 43) Whether or not additional SNP studies are likely to be informative is under debate, as the study size to detect more and more rare variants becomes prohibitively large. As the cost of whole genome

sequencing continues to decrease, some predict that this will become the preferred avenue for researching risk variants. One challenge in sorting through the growing literature on this diagnostic approach is nonstandardization and nontransparency of studies. (44) Janssens et al. have recently published a methods paper providing a road map for optimal reporting and an accompanying detailed article describing good reporting practices. (45)

Recently, Bloss et al. (46) reported on the psychological, behavioral, and clinical effects of risk scanning in 3,639 subjects followed for a short-term period (mean of 5.6 months; standard deviation [SD] of 2.4 months). These investigators evaluated anxiety, intake of dietary fat, and exercise based on information from genomic testing. They concluded there were no significant changes before and after testing. They also noted no increase in the number of screening tests obtained in enrolled patients. While more than half of patients participating in the study indicated an intent to have screening tests performed in the future, during the course of the study itself, no actual increase was observed.

Ongoing Trials

A search online of clinicaltrials.gov identified at least one prospective cohort U.S. study on SNP panels and risk assessment in women undergoing mammography (NCT01124019). The primary objective of this study is to compare the predicted lifetime risk values produced by SNP panel assessment to the risk values produced by the prediction models that are most commonly used. The estimated completion date of this trial is reported to be February 2013; however, this study is currently still listed as recruiting participants, with an estimated final enrollment of 1,600 women.

Summary

Common, single-nucleotide polymorphisms (SNPs) have been shown in primary studies and meta-analyses to be significantly associated with risk of breast cancer, some of which convey slightly elevated risk of breast cancer compared to the general population risk. Panels of well-documented and validated SNPs are commercially available, with results synthesized into breast cancer risk estimates. These have not been clinically validated and clinical utility has not been demonstrated. The majority of these tests are commercially available as DTC tests. The application of such risk panels to individual patient management or to population screening programs is premature due to the uncertain performance of these profiles in the intended use populations, and the expectation that the majority of the genetic risk of breast cancer has yet to be explained by undiscovered gene variants and SNPs. Long-term prospective studies with large sample sizes are needed to determine the clinical validity and utility of SNP-based models for use in predicting the risk of breast cancer risk. The

discrimination offered by the limited genetic factors currently known is insufficient to inform clinical practice. Therefore, the use of this testing is considered investigational.

Practice Guidelines and Position Statements

None found.

V. DEFINITIONS

TOP

NA

VI. BENEFIT VARIATIONS

TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

TOP

Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

POLICY TITLE	USE OF COMMON GENETIC VARIANTS TO PREDICT RISK OF NONFAMILIAL BREAST CANCER
POLICY NUMBER	MP- 2.250

The following codes are **investigational** when used to report common variants to predict risk of nonfamilial Breast Cancer:

CPT Codes®								
81599								

IX. REFERENCES

TOP

1. *Stacey SN, Manolescu A, Sulem P et al. Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 2007; 39(7):865-9.*
2. *Easton DF, Pooley KA, Dunning AM et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007; 447(7148):1087-93.*
3. *Hunter DJ, Kraft P, Jacobs KB et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 2007; 39(7):870-4.*
4. *Thomas G, Jacobs KB, Kraft P et al. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). Nat Genet 2009; 41(5):579-84.*
5. *Stacey SN, Manolescu A, Sulem P et al. Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 2008; 40(6):703-6.*
6. *Gold B, Kirchhoff T, Stefanov S et al. Genome-wide association study provides evidence for a breast cancer risk locus at 6q22.33. Proc Natl Acad Sci U S A 2008; 105(11):4340-5.*
7. *Ahmed S, Thomas G, Ghoussaini M et al. Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2. Nat Genet 2009; 41(5):585-90.*
8. *Zheng W, Long J, Gao YT et al. Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. Nat Genet 2009; 41(3):324-8.*
9. *Garcia-Closas M, Hall P, Nevanlinna H et al. Heterogeneity of breast cancer associations with five susceptibility loci by clinical and pathological characteristics. PLoS Genet 2008; 4(4):e1000054.*

10. *Beeghly-Fadiel A, Shu XO, Lu W et al. Genetic variation in VEGF family genes and breast cancer risk: a report from the Shanghai Breast Cancer Genetics Study. Cancer Epidemiol Biomarkers Prev 2011; 20(1):33-41.*
11. *Cai Q, Wen W, Qu S et al. Replication and functional genomic analyses of the breast cancer susceptibility locus at 6q25.1 generalize its importance in women of chinese, Japanese, and European ancestry. Cancer Res 2011; 71(4):1344-55.*
12. *Han W, Woo JH, Yu JH et al. Common genetic variants associated with breast cancer in Korean women and differential susceptibility according to intrinsic subtype. Cancer Epidemiol Biomarkers Prev 2011; 20(5):793-8.*
13. *Jiang Y, Han J, Liu J et al. Risk of genome-wide association study newly identified genetic variants for breast cancer in Chinese women of Heilongjiang Province. Breast Cancer Res Treat 2011; 128(1):251-7.*
14. *Mong FY, Kuo YL, Liu CW et al. Association of gene polymorphisms in prolactin and its receptor with breast cancer risk in Taiwanese women. Mol Biol Rep 2011; 38(7):4629-36.*
15. *Mukherjee N, Bhattacharya N, Sinha S et al. Association of APC and MCC polymorphisms with increased breast cancer risk in an Indian population. Int J Biol Markers 2011; 26(1):43-9.*
16. *Ota I, Sakurai A, Toyoda Y et al. Association between breast cancer risk and the wild-type allele of human ABC transporter ABCC11. Anticancer Res 2010; 30(12):5189-94.*
17. *Ren J, Wu X, He W et al. Lysyl oxidase 473 G>A polymorphism and breast cancer susceptibility in Chinese Han population. DNA Cell Biol 2011; 30(2):111-6.*
18. *Yu JC, Hsiung CN, Hsu HM et al. Genetic variation in the genome-wide predicted estrogen response element-related sequences is associated with breast cancer development. Breast Cancer Res 2011; 13(1):R13.*
19. *Pournaras DJ, Aasheim ET, Sovik TT et al. Effect of the definition of type II diabetes remission in the evaluation of bariatric surgery for metabolic disorders. Br J Surg 2012; 99(1):100-3 LID - 10 1002/bjs 7704 [doi].*
20. *Dai J, Hu Z, Jiang Y et al. Breast cancer risk assessment with five independent genetic variants and two risk factors in Chinese women. Breast Cancer Res 2012; 14(1):R17.*
21. *Long J, Cai Q, Sung H et al. Genome-wide association study in east Asians identifies novel susceptibility loci for breast cancer. PLoS Genet 2012; 8(2):e1002532.*
22. *Huo D, Zheng Y, Ogundiran TO et al. Evaluation of 19 susceptibility loci of breast cancer in women of African ancestry. Carcinogenesis 2012; 33(4):835-40.*

23. *McCarthy AM, Armstrong K, Handorf E et al. Incremental impact of breast cancer SNP panel on risk classification in a screening population of white and African American women. Breast Cancer Res Treat 2013; 138(3):889-98.*
24. *Baldwin RM, Owzar K, Zembutsu H et al. A genome-wide association study identifies novel loci for paclitaxel-induced sensory peripheral neuropathy in CALGB 40101. Clin Cancer Res 2012; 18(18):5099-109.*
25. *Romero A, Martin M, Oliva B et al. Glutathione S-transferase P1 c.313A > G polymorphism could be useful in the prediction of doxorubicin response in breast cancer patients. Ann Oncol 2012; 23(7):1750-6.*
26. *Saadat M. Paraoxonase 1 genetic polymorphisms and susceptibility to breast cancer: a meta-analysis. Cancer Epidemiol 2012; 36(2):e101-3.*
27. *Gong WF, Zhong JH, Xiang BD et al. Single Nucleotide Polymorphism 8q24 rs13281615 and Risk of Breast Cancer: Meta-Analysis of More than 100,000 Cases. PloS One 2013; 8(4):e60108.*
28. *He XF, Wei W, Su J et al. Association between the XRCC3 polymorphisms and breast cancer risk: meta-analysis based on case-control studies. Mol Biol Rep 2012; 39(5):5125-34.*
29. *Tang L, Xu J, Wei F et al. Association of STXBP4/COX11 rs6504950 (G>A) polymorphism with breast cancer risk: evidence from 17,960 cases and 22,713 controls. Arch Med Res 2012; 43(5):383-8.*
30. *He XF, Wei W, Li SX et al. Association between the COMT Val158Met polymorphism and breast cancer risk: a meta-analysis of 30,199 cases and 38,922 controls. Mol Biol Rep 2012; 39(6):6811-23.*
31. *Michailidou K, Hall P, Gonzalez-Neira A et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 2013; 45(4):353-61.*
32. *Siddiq A, Couch FJ, Chen GK et al. A meta-analysis of genome-wide association studies of breast cancer identifies two novel susceptibility loci at 6q14 and 20q11. Hum Mol Genet 2012; 21(24):5373-84.*
33. *Garcia-Closas M, Couch FJ, Lindstrom S et al. Genome-wide association studies identify four ER negative-specific breast cancer risk loci. Nat Genet 2013; 45(4):392-8.*
34. *Pharoah PD, Antoniou AC, Easton DF et al. Polygenes, risk prediction, and targeted prevention of breast cancer. N Engl J Med 2008; 358(26):2796-803.*
35. *Wacholder S, Hartge P, Prentice R et al. Performance of common genetic variants in breast-cancer risk models. N Engl J Med 2010; 362(11):986-93.*

36. *Reeves GK, Travis RC, Green J et al. Incidence of breast cancer and its subtypes in relation to individual and multiple low-penetrance genetic susceptibility loci. JAMA 2010; 304(4):426-34.*
37. *Mealiffe ME, Stokowski RP, Rhees BK et al. Assessment of clinical validity of a breast cancer risk model combining genetic and clinical information. J Natl Cancer Inst 2010; 102(21):1618-27.*
38. *Darabi H, Czene K, Zhao W et al. Breast cancer risk prediction and individualised screening based on common genetic variation and breast density measurement. Breast Cancer Res 2012; 14(1):R25.*
39. *Hunter DJ, Altshuler D, Rader DJ. From Darwin's finches to canaries in the coal mine--mining the genome for new biology. N Engl J Med 2008; 358(26):2760-3.*
40. *Braun R, Buetow K. Pathways of distinction analysis: a new technique for multi-SNP analysis of GWAS data. PLoS Genet 2011; 7(6):e1002101.*
41. *Silva SN, Guerreiro D, Gomes M et al. SNPs/pools: a methodology for the identification of relevant SNPs in breast cancer epidemiology. Oncol Rep 2012; 27(2):511-6.*
42. *Devilee P, Rookus MA. A tiny step closer to personalized risk prediction for breast cancer. N Engl J Med 2010; 362(11):1043-5.*
43. *Offit K. Breast cancer single-nucleotide polymorphisms: statistical significance and clinical utility. J Natl Cancer Inst 2009; 101(14):973-5.*
44. *Janssens AC, Ioannidis JP, van Duijn CM et al. Strengthening the reporting of genetic risk prediction studies: the GRIPS statement. Eur J Clin Invest 2011; 41(9):1004-9.*
45. *Janssens AC, Ioannidis JP, Bedrosian S et al. Strengthening the reporting of genetic risk prediction studies (GRIPS): explanation and elaboration. Eur J Clin Invest 2011; 41(9):1010-35.*
46. *Bloss CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. N Engl J Med 2011; 364(6):524-34.*

POLICY TITLE	USE OF COMMON GENETIC VARIANTS TO PREDICT RISK OF NONFAMILIAL BREAST CANCER
POLICY NUMBER	MP- 2.250

X. POLICY HISTORY

TOP

MP 2.250	**CAC 4/24/12** Adopted BCBSA. Removed information regarding testing for one or more single nucleotide polymorphisms (SNPs) from MP-2.211, Genetic Testing for Inherited Breast and/or Ovarian Cancer, and created separate medical policy. Testing for one or more single nucleotide polymorphisms (SNPs) remains investigational per BCBSA medical policy.
	04/05/2013- Deleted codes removed from policy added 81599 -skb
	6/4/13 CAC- Consensus review.
	CAC 3/25/14 Consensus. No change to policy statements. References updated. Rationale section added.

Top