Breast cancer risks associated with mutations in cancer predisposition genes identified by clinical genetic testing of 50,000 breast cancer patients

F.J. Couch1,2, C. Hu1, J Lilyquist2, H. Shimelis1, M Akinhanmi1, J Na2, EC Polley1,2, SN Hart2, Robina Smith3, Melissa Pronold3, R Huether3, C Espenschied3, S Li3, T Pesaran3, R McFarland3, H LaDuca3, D.E. Goldgar4, J.S. Dolinsky3.

1) Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; 2) Department of Health Sciences Research, Mayo Clinic, Rochester, MN; 3) Ambry Genetics, Aliso Viejo, CA;4) University of Utah, Salt Lake City, UT.

Clinical genetic testing panels are broadly used to gather information about cancer predisposition in individuals with personal and/or family history of breast cancer. However, the involvement of several of the genes that are included on clinical testing panels in predisposition to breast cancer has recently come into question. In addition, accurate risk estimates for breast and other cancer are not well defined for the majority of genes on testing panels. We studied 50,000 women diagnosed with breast cancer who were tested for germline cancer predisposing mutations using hereditary cancer gene panels. Information on personal and family cancer history, age of diagnosis, and ethnicity of patients was obtained from test requisition forms. Greater than 90% met National Comprehensive Cancer Network HBOC testing criteria. To estimate gene-specific risks for breast cancer, case-control analyses were performed comparing the frequencies of pathogenic mutations from Caucasian cancer cases with frequencies from Caucasian, non-Finnish, non-TCGA controls from the Exome Aggregation Consortium (ExAC) database. Mutations were detected in 9% of breast cancer patients. Twelve genes displayed a significant association ($p<0.05$) with breast cancer including nine genes associated with moderate risk (RR>2.0) and three genes associated with high risk (RR>5.0) of breast cancer. This large clinical testing dataset of 50,000 women with breast cancer provides useful data for many predisposition genes previously lacking risk estimates, and should prove useful for clinical risk management of patients with inherited mutations in these
genes.