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Presentation Title: Individualized breast cancer risk prediction model utilizing functional single nucleotide polymorphisms and epidemiological factors

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Breast cancer is a complex disease with genetic and epidemiological determinants. In addition to germline mutations such as in *BRCA1/2*, *TP53* and *PTEN*, somatic mutations in many genes may modify the risk for breast cancer. On 7 December 2007, OMIM had 427 entries that mentioned breast cancer. In theory, a set of 13 genes, acting without interactions, would be sufficient to identify high risk individuals from the general population (Pharoah et al, *Nat Genet* 2002;31:33). We developed a predictive model by combining the Gail model with genetic information. In 6 US areas, breast cancer cases and cancer-free controls were genotyped for 117 polymorphic sites in 87 genes in an association study. The genes were picked for their biological and pathogenic relevance to breast cancer. A discovery (training) set of 5022 Caucasian women (1671 breast cancer cases and 3351 age-matched cancer-free controls) was used to develop the model, and an independent test set of 400 cases and 793 controls was used to validate the model. Multivariate logistic regression was utilized to systematically evaluate genotypes and epidemiological risk factors in both age-invariant and age-interactive analyses. The resulting model, dubbed OncoVue®, is composed of three integrated multivariate logistic regression components, employing 22 SNPs located in 19 distinct genes both individually and interacting with age. These genes are involved in steroid hormone synthesis, signaling or metabolism (n=7), DNA repair, cell cycle/apoptosis, growth factors and xenobiotic detoxification. In both discovery and validation sets, OncoVue improved individualized risk prediction by more effectively and uniquely identifying women who are truly at higher risk for breast cancer by correctly placing more cases and fewer controls at high risk. Thus, incorporating genetic information along with the Gail model risk factors resulted in improved performance in estimating individual breast cancer risk among women. An FDA Investigational Device Exemption Trial has recently ended and additional validation studies are being completed. When combined with individualized screening protocols based on individualized risk estimates, OncoVue could identify many women with moderate risk for breast cancer and eventually decrease mortality from breast cancer when offered in a proper medical and educational facility.