Validation of the Manchester scoring system for predicting BRCA1/2 mutations in 9,390 families suspected of having hereditary breast and ovarian cancer.

The Manchester scoring system (MSS) allows the calculation of the probability for the presence of mutations in BRCA1 or BRCA2 genes in families suspected of having hereditary breast and ovarian cancer. In 9,390 families, we determined the predictive performance of the MSS without (MSS-2004) and with (MSS-2009) consideration of pathology parameters. Moreover, we validated a recalibrated version of the MSS-2009 (MSS-recal). Families were included in the registry of the German Consortium for Hereditary Breast and Ovarian Cancer, using defined clinical criteria. Receiver operating characteristics (ROC) analysis was used to determine the predictive performance. The recalibrated model was developed using logistic regression analysis and tested using an independent random validation sample. The area under the ROC curves regarding a mutation in any of the two BRCA genes was 0.77 (95%CI 0.75-0.79) for MSS-2004, 0.80 (95%CI 0.78-0.82) for MSS-2009, and 0.82 (95%CI 0.80-0.83) for MSS-recal. Sensitivity at the 10% mutation probability cutoff was similar for all three models (MSS-2004 92.2%,
MSS-2009 92.2%, and MSS-recal 90.3%), but specificity of MSS-recal (46.0%) was considerably higher than that of MSS-2004 (25.4%) and MSS-2009 (32.3%). In the MSS-recal model, almost all predictors of the original MSS were significantly predictive. However, the score values of some predictors, for example, high grade triple negative breast cancers, differed considerably from the originally proposed score values. The original MSS performed well in our sample of high risk families. The use of pathological parameters increased the predictive performance significantly. Recalibration improved the specificity considerably without losing much sensitivity.