large independent association of the new marker is required for a meaningful improvement in AUC, and a substantial gain in performance may not yield a substantial increase in AUC. One suggested statistic for comparing nested models is the net reclassification index that is useful when risk categories are defined, and there is a consensus as to clinically meaningful cut points (3). The net reclassification index quantifies overall improvement in model sensitivity and specificity. A net improvement in risk classification implies upward reclassification of case patients and downward reclassification of control subjects.

We evaluated these metrics in our own internally validated risk prediction model for lung cancer that incorporated easily attainable epidemiological and clinical variables (4). In a genome-wide association analysis of 315,450 tagging SNPs in 115,400 patients with lung cancer who were current and former smokers and were of European ancestry and 113,700 frequency-matched control subjects (5), two SNPs, rs1051730 and rs8034191, that mapped to a region within 15q25.1 (which encompasses the nicotinic acetylcholine receptor subunit genes CHRNA3 and CHRNA5) were strongly associated with risk (odds ratio [OR] = 1.32, 95% confidence interval [CI] = 1.24 to 1.41, P = 3.15 × 10−18 for rs8034191; and OR = 1.32, 95% CI = 1.23 to 1.39, P = 7.00 × 10−16 for rs1051730). In a subsequent meta-analysis (6) involving the UK genome-wide association study, the International Agency for Research on Cancer genome-wide association study, and our Texas genome-wide association study, the strongest associations remained for SNPs mapping to 15q25.1 (ie, rs1051730, P = 2.83 × 10−18; and rs8034191, P = 4.03 × 10−16). There was also consistent evidence for a new disease locus at 5p15.33 (ie, rs401681, P = 4.40 × 10−16). This locus contains two known genes: TERT (human telomerase reverse transcriptase) gene and CLPTM1L (cleft lip and palate transmembrane 1-like) gene.

We therefore added one SNP from the 15q25.1 locus (ie, rs1051730, which was used because it was in strong linkage disequilibrium with rs8034191) and two SNPs from the 5p15.33 region (ie, rs2736100 and rs401681) to the baseline model and assessed discrimination improvement. Our AUC for the baseline epidemiological–clinical model including 1016 case patients and 1111 control subjects was 0.661 (95% CI = 0.64 to 0.68). With addition of the three SNPs, the AUC showed modest, yet statistically significant, improvement to 0.673 (95% CI = 0.65 to 0.70, P = .01). We defined risk categories on the basis of the lower and upper quartiles of predicted risk from our baseline model as proposed by Bach et al. (7): low (predicted risk <8%), intermediate (predicted risk = 8%–50%), and high (predicted risk >50%). The resulting net reclassification indices were 0.152 (95% CI = 0.112 to 0.193) overall, 0.089 (95% CI = 0.048 to 0.130) for case patients, and 0.064 (95% CI = 0.023 to 0.105) for control subjects (all statistically significant at the 0.2% level), indicating that the SNPs modestly improved both sensitivity (9%) and specificity (6%). Although it could be argued that models providing a continuous score are more appropriate in the clinical setting, it is likely that a variety of additional summary measures evaluating model performance will be needed to assess these multigenic models.

References
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Notes
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Affiliation of authors: Department of Epidemiology, University of Texas M. D. Anderson Cancer Center, Houston, TX (MRS, CIA, AD, QD, CE).

Correspondence to: Margaret R. Spitz, MD, Department of Epidemiology, University of Texas M. D. Anderson Cancer Center, 1155 Pressler Unit 1340, Houston, TX 77030 (e-mail: msptiz@mdanderson.org).

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