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Polygenic Risk Scores Incorporating Functional Genomics Improve Prediction of Smoking Cessation

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Several genetic variants associated with smoking cessation have been identified. However, smoking cessation is polygenic, making clinical translation of genetic findings challenging. Polygenic risk scores (PRS) may help enhance clinical applications by aggregating the effects of multiple genetic variants. A state-of-the-art method, SBayesRC, integrates functional annotation and linkage data with genome-wide association study summary statistics to build PRS with improved prediction accuracy. We applied SBayesRC to build PRS for smoking cessation among participants in the Nurse's Health Study (NHS) and NHS II, two all-female, prospective cohorts that have collected smoking status (former, current, never) every two years beginning in 1976 and 1989, respectively. We then examined whether adding PRS for smoking cessation significantly improved the predictive performance of models of long-term smoking cessation that included age, year of follow-up, smoking intensity, menopausal status, hormone replacement therapy (HRT) use, early initiation of smoking, body mass index (kg/m2), and the first five genetic principal components. Adding PRS significantly improved discriminatory performance, raising the area under the curve (AUC) from 0.674 to 0.730 for NHS and from 0.670 to 0.734 for NHS II. This represents improved prediction accuracy of 5.7% (95% CI: 5.4% – 5.9%) for NHS and 6.4% (95% CI: 5.9% – 6.8%) for NHS II. Key strengths of this study are the longitudinal assessment of smoking cessation over decades of follow-up and replication in two independent cohorts. PRS significantly improved identification of individuals at high risk for long-term, persistent smoking and holds promise for guiding targeted cessation interventions.