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Title: Precision Tobacco Treatment: Genetic risk scores and biomarkers

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Introduction: This study aims to evaluate the potential of polygenetic markers to enhance current treatment by incorporating an individual's genetic and metabolic biomarkers.

Methods: We investigated two predictors: a) genome-wide polygenic risk scores (PRSs) for smoking phenotypes and b) nicotine metabolite ratio (NMR). We evaluated bio-verified end-of-treatment abstinence among smokers in two randomized control trials (N=1,898 including 807 in the Genetically Informed Smoking Cessation Trial (GISC) and 1,091 in the University of Wisconsin Trial).

Results: Both PRS for failed smoking cessation and PRS for delayed age of smoking initiation predict smoking abstinence in the treatment trials (meta-analysis OR=0.89, 95%CI=0.80-0.99, p=0.037; meta-analysis OR=1.2, 95%CI=1.1-1.4, p=0.00038 respectively, N=1,592 smokers of European Ancestry). Addition of genetic predictors to clinical predictors significantly increase the AUC (0.70 to 0.71, p=0.034). In addition, NMR predicts treatment response in 807 GISC participants of both European and non-European Ancestry. Specifically, slow nicotine metabolizers respond better to nicotine replacement vs. placebo (OR=4.7, 95%CI=1.7, 14.9, p=0.0040), but not varenicline vs. placebo (OR=2.5, 95%CI=0.87-8.1, p=0.11). In contrast, normal nicotine metabolizers respond to both nicotine replacement and varenciline vs. placebo (OR=2.04, 95%CI=1.12-3.8, p=0.021; OR=4.15, 95% CI=2.38-7.49, p=9.8e-7 respectively), but varenicline produces significantly higher end-of-treatment abstinence than does nicotine replacement (OR=2.0, 95%CI=1.2-3.3, p=0.0050 for varenicline vs. nicotine replacement).

Conclusion: Polygenic risk scores predict overall treatment success and NMR predicts differential treatment response. These findings strengthen the case that polygenic risk scores and a metabolism biomarker may provide complementary information that could be useful for treatment assignment and prognostic prediction.