



**Figure S3.** Receiver–operating–characteristic (ROC) curves of the wGRS (dashed line) in discriminating CYP2A6 slow and normal metabolizer groups using an NMR cut–point of  $\geq 0.31$  in the (A) training set (PNAT2+KIS3;  $N=954$ ) and (B) replication set (Q2L;  $N=216$ ). The wGRS for an NMR cut–point of 0.31 (slow:  $NMR < 0.31$ , normal:  $NMR \geq 0.31$ ) yielded an Area Under the Curve (AUC) estimate of 0.73 ( $P < 0.001$ ) and 0.77 ( $P < 0.001$ ) in the training and replication sets, respectively