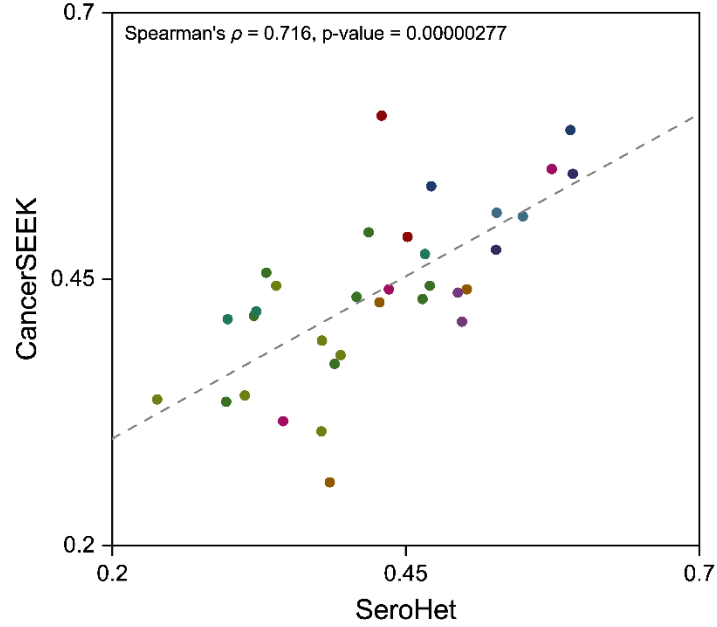
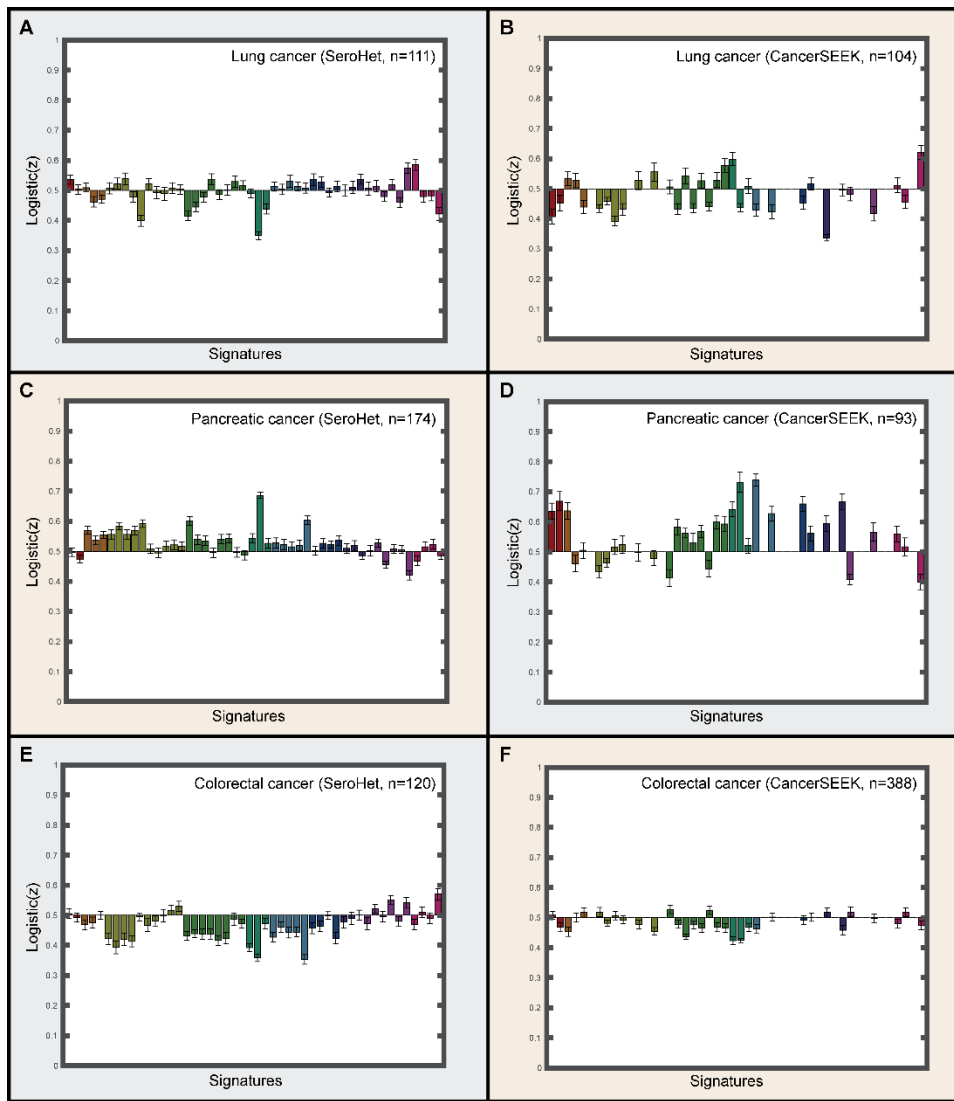


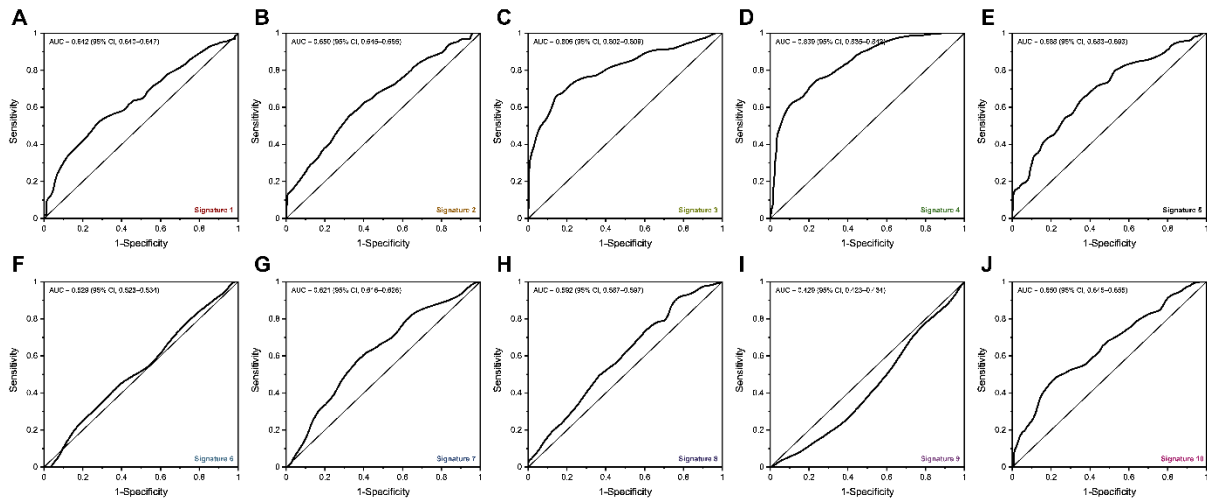
**Figure S1. Signature-wise standard deviation for patient metadata.** Standard deviation of signature-wise  $\log_2$  fold changes is presented. Sex and smoking exhibited the largest standard deviation, while family history of malignancy exhibited the smallest standard deviation.



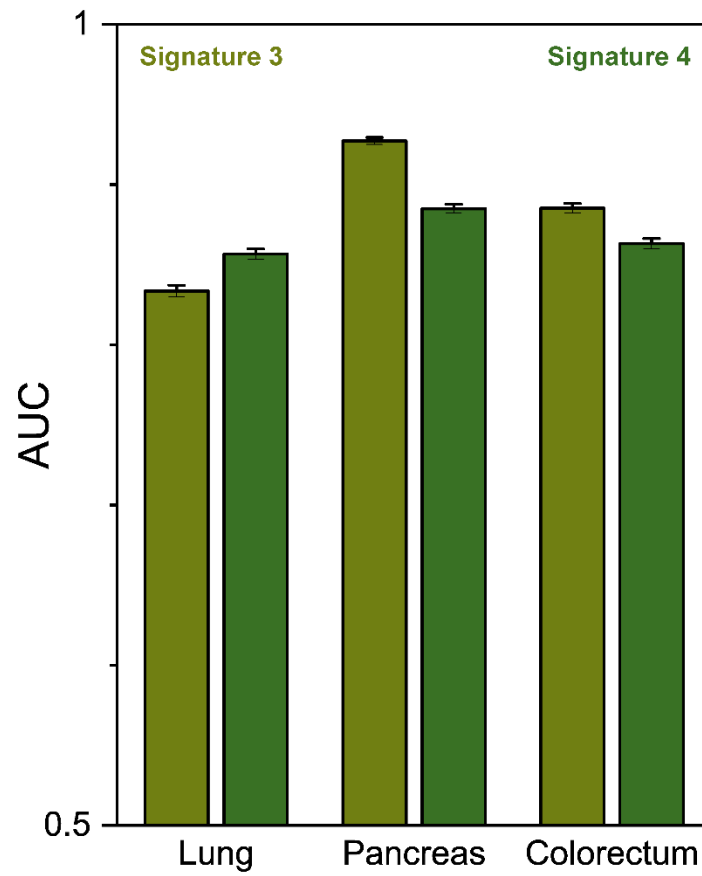
**Figure S2. Correlation of seroprotein profiles between SeroHet and CancerSEEK cohorts.** The Spearman's  $\rho$  was 0.716 (p-value < 0.001), indicating the high correlation between the seroprotein concentration profiles of cancer patients between the two cohorts. Each dot represents individual seroprotein markers and is color-coded based on its SeroHet signature membership.



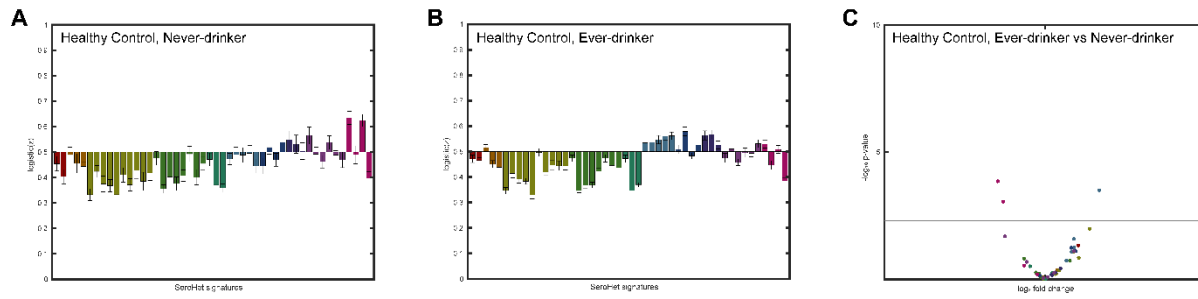
**Figure S3. Seroprotein profiles by cancer types in SeroHet and CancerSEEK cohorts.** A–F. Logistic(z) values of cancer patients with lung, pancreatic, or colorectal cancers within each cohort. SeroHet signatures are color-coded. High correlation between SeroHet and CancerSEEK cohorts are evident in all cancer types. Error bar, 95% CI.



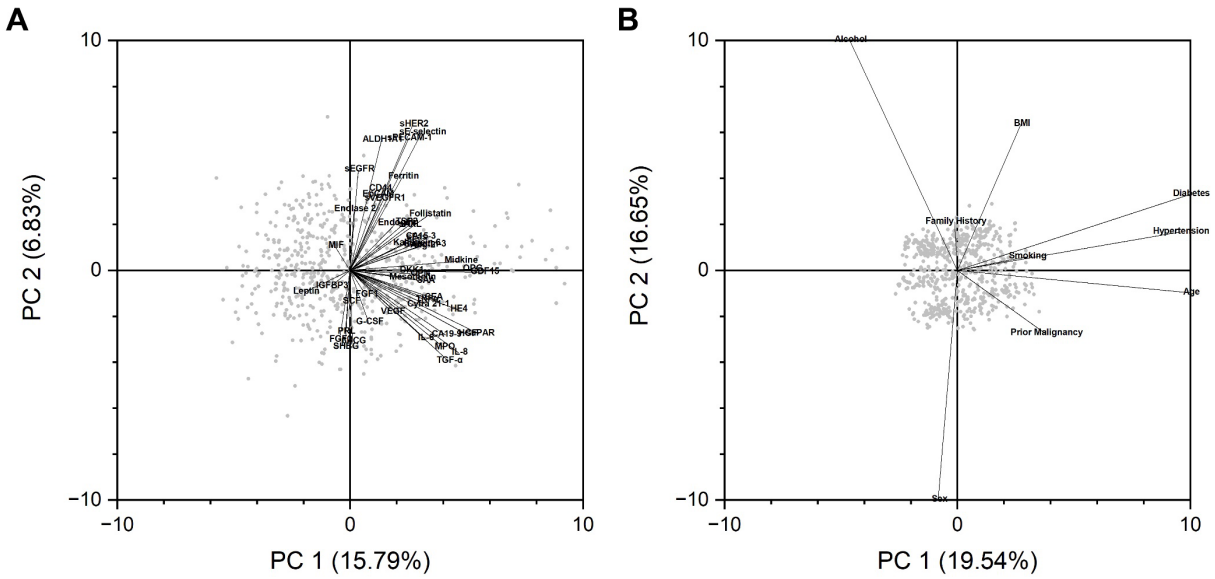
**Figure S4. ROC curves of AJCC stage I cancer detection using each SeroHet signature. A–J. AUC values for each SeroHet signature as well as their 95% CI are indicated in the upper left. SeroHet signature 3 and 4 were highly diagnostic of AJCC stage I cancer detection.**



**Figure S5. Performance of SeroHet signatures 3 and 4-based cancer detection by cancer type.** AUC values are represented as individual bar. Error bar, 95% CI.



**Figure S6. Comparison between seroprotein concentration profiles of healthy never-drinkers and ever-drinkers.** A. Seroprotein signatures of healthy individuals without the history of alcohol consumption. B. Seroprotein signatures of healthy individuals with the history of alcohol consumption. C. Volcano plot between seroprotein signatures of healthy ever-drinkers and never-drinkers. Horizontal line represents the Bonferroni-corrected threshold for p-value at a target family-wise error rate of 0.05.



**Figure S7. Principal component analysis of the cohort.** A. Principal component analysis was performed on the serum protein markers. Grey dot indicates each individual, and the black line indicates each serum protein marker with regards to the first and the second principal component. B. Principal component analysis was performed on the patient metadata. Grey dot indicates each individual, and the black line indicates each clinical parameters with regards to the first and the second principal component.