Identifying the Best Predictive SNP in GWAS for Companion Diagnostics

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Abstract: It is now well recognized that the effectiveness and potential risk of a treatment often vary by patient subgroups. A companion diagnostic (CDx) is a diagnostic test co-developed with drugs for the drug safety and effectiveness. Most FDA-approved CDx tests aim for identifying a single, specific predictive SNP, and building ``one drug, one SNP'' model. Predictive biomarkers are of particular importance for clinicians to select right treatment at the right dose for the right person at the right time for the right outcome. Typically, SNPs are ranked in terms of their p-values, and an easy and intuitive way is to select the "best" SNP with the smallest p-value. However, the p-value ordering is sensitive to the noise, and doesn't necessarily correlate with the true ordering of SNPs. Furthermore, to our best knowledge, no work has considered the response profiles of the SNPs. The SNP, even with the smallest p-value, would not be useful for a CDx unless its response profile satisfies certain patterns. In this paper, we first develop a score function to quantify the predictive ability of each candidate SNP. We then formulate the parameters of interest as the minimal difference in predictive ability between a candidate SNP and the best SNP conditional on SNP response profiles satisfying desired patterns. We propose to find the ``best'' SNP based on simultaneous confidence set of parameters of interest built upon the framework of multiple comparison with the best (MCB) controlling per family error rate (PFER). Simulation studies and application in Alzheimer Disease randomized clinical trials will be used to demonstrate the novel discovery and advantage of the proposed framework.