The clinical antipsychotic trial of intervention effectiveness study compared the effectiveness of five antipsychotic medications in 1493 patients with schizophrenia. DNA was available from 750 patients. In this 18-month trial, discontinuation was used as a measure of effectiveness. Findings indicated that discontinuation rates were high with no differences between medications overall. However, certain drugs were better or worse on an individual level. Prior to examining the associations between clinical and genetic data, a central record of hypotheses tested was established to track ongoing statistical testing. Gene variants that influence dose response were identified and a dose adjustment phase was established to define optimized dose. The identified gene variants had no effect on the optimized dose. However, there are gene variants that relate more closely to the etiology of schizophrenia and the functioning of antipsychotic drugs. These gene variants were associated with drug discontinuation using an annotation system that allows for the interpretation of large amounts of p-values in the context of genomic features. Using a post association annotation system, three SNPs approached study-wide significance. Two of the three were synonymous SNPs in exon 8 of GRM7, which were associated with discontinuation from ziprasidone due to inefficacy. The third SNP in intro 2 RIMS1 was associated with discontinuation from quetiapine due to inefficacy. Next steps include, besides replication and functional evaluation, identifying genes that affect weight gain on atypical antipsychotic medications.

To clarify the genesis of false negatives, an example was provided in which the SCN1A polymorphism in an epilepsy pharmacogenetic trial reached significance using a candidate gene approach but it would fail to achieve significance in the context of a genome-wide association study. The use of a genetic annotation system would aid in the prevention of such false negatives in large-scale genome-wide association studies.