One focus of precision medicine is to use a patient's germline to modulate a therapeutic drug dose to the patient's own specific metabolism rate. Patients classified as ultra-rapid metabolizers of drug metabolizing enzymes (DME) may require a higher than recommended dose to maintain the drug's efficacious dose while poor metabolizers may require a lower dose to avoid adverse effects. In this investigation, a four-tier activity scoring system (AS) was compared to the genotypic information provided by a two-tier activity scoring system (2TAS). Patients were genotyped for 138 DME SNPs: 88 associated with cytochrome P450 SNPs and 24 are associated with Phase 2 and transport enzymes. The genotypic information obtained from the two-tier activity scoring system was compared to the four-tier activity scoring system to determine a score for each SNP. The genotypic responders were categorized into the following genotypes: homozygous reference allele, heterozygote, and homozygous alternate allele. A score of 1.0 is given to the homozygous reference allele, 0.5 to the heterozygote, and 0.0 to the homozygous alternate allele given a score of 0.0. However, in this new variation, the scores were applied across all SNPs and summed in order to convert alphabetic designations to numeric for further analysis by various biostatistical methods. The two-tier activity scoring system measures only the enzymes defined by the alternate allele thus allowing us to view each SNP individually. The four-tier activity scoring system measures the total activity of all SNPs which act together. For example, while the CYP2D6*4 haplotype contains rs3892097 or g.1846G>A (the transition of G to A at base pair 1846), the CYP2D6*11 haplotype contains rs201377835 (g.882G>C), rs16947 (c.*40T>G), and 2 additional SNPs at base pair 159 and 236, respectively. This combination of SNPs is associated with ultra-rapid metabolizer (URM) and may require a higher than recommended dose to maintain the drug's efficacious dose. This combination of SNPs is associated with poor metabolizer (PM) and may require a lower dose to avoid adverse effects.

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### RESULTS

The three most statistically significant principal components are shown. The mixed model CYP SNPs and Phase 2 and transporters were used to calculate the sum scores. The sum scores were then analyzed for their ability to accurately predict the phenotype. The sum scores of one PHH lot and N = the total of all sum scores across all lots. H is an information statistic index and typical values are 1.5 to 3.5. D is a dominance index and would give more weight to dominant sum scores. The sum score varied from 1.5 (pompering with impaired and poor metabolators) to 2.0 (pompering with more extensive or normal metabolators). The sum score of 2.00 falls at the top of the range of a diverse population. 93% is the PC1 and the Reciprocal Index is 0.0025, both of which show the lack of optimized variability using the sum score method. The application of these alpha diversity indices allows for the determination of the sum score method with almost 93% agreement of the European Caucasians. Genotypes indicating varied alleles are naturally present in lesser amounts in the worldwide population. While the sum score method did not suffer from the diversity of genome scoring, there are still issues:

a) Does the sum score method lead to adequate diversity of genotypes?

b) Are the results from these alpha diversity indices just reflecting the typical variations in the worldwide population regarding variant allele?

### CONCLUSIONS

The sum score method allowed for visualization of genetic variant comparisons with end point testing of DME metabolites. The sum score method allowed for the observation of a distinct compartment of genetic variants data with the formation of a significant CME metabolites.

### REFERENCES / ACKNOWLEDGEMENTS


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