On an Expanded Framework for Personalized Cancer Treatment: Beyond Pharmacogenomics

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Cancer has been a perennial challenge to clinicians and researchers for more than a century. The current clinical approach of 'standard-dose-for-all' and subsequent titration through *trial-and-error* causes severe toxicity in some patients while proving insufficient to others as patients vary genetically as well as phenotypically. The much anticipated pharmacogenomics has been losing its sheen as a sole predictor of clinical outcome. The manifestation of gene (upstream causal variable) to clinical outcome (downstream response variable) proceeds through various stages; several biochemical processes interfere and manipulate the overall outcome. Given the complexity of biological processes and amount of available information, prediction of clinical response through simple deductive reasoning or through pharmacogenomics is infeasible. To address this challenge, we developed a multidisciplinary quantitative approach, empowered by systems theoretic methodology, to serve as a decision-support mechanism for physicians to quantitatively predict the response and adjust dosage for each individual patient.

The first step in treatment planning is the classification of patients into subgroups that are susceptible to extreme responses. To this end, we designed a metabolomics-based approach to study the global metabolic fingerprint in pre-dose samples and characteristic changes due to drug dosing in post-dose samples. The full set of metabolites was correlated to the observed clinical response using data analysis and modeling to identify differentially expressed metabolites in various response groups. The discovered biomarkers, together with our model, aid in identifying patients' risk profiles well in advance, even before commencing their treatment.

Once patients are divided into subgroups, the next crucial step is to predict optimal dosage for individual patients. Several classes of models, including kinetic, pharmacological and population balance models, were developed for the dynamic prediction of drug distribution, reaction and cellular interaction. Unlike physical sciences, the variability in these systems is extremely high (c.v. as high as 100%). Hence, we identified parameters using population approaches such as non-linear mixed effect modeling and Bayesian hierarchical modeling. To circumvent the scarcity of clinical data, we employed a global sensitivity analysis based model-reduction technique and improved the information content by optimal DoE techniques. The identified individual patient model was used to determine optimal dosage through robust model predictive control. To enable the translation of our framework into clinical practice, we developed one-of-its's-kind software, christened *nEqualsOne*. It shows a great potential to serve as a decision-support tool to enhance the decision-making capabilities of practicing clinicians and improve the survival and quality-of-life among cancer patients. The generic nature of the framework assures a broader impact in other areas of healthcare and consequently bears wide socioeconomic implications.