Title: “Personalized medicine of VEGF-targeting therapies: a multiscale modeling approach for developing predictive biomarkers from gene expression data”

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Abstract: A major obstacle in oncology drug development is the ineffectiveness of therapies in some patients due to inter-individual tumor heterogeneity. Some molecular biomarkers have proven useful, but these kinds of markers are still unable to accurately predict all responsive and nonresponsive patients. Computational models can aid in the development of predictive biomarkers by providing a source of simulated data that can be used to find robust, multivariate markers. Here, we present a method for generating and testing predictive biomarkers that incorporates patient-specific gene expression data into mathematical models of ligand-receptor interactions and drug pharmacokinetics. We applied the method to the vascular endothelial growth factor (VEGF) family using a model of the transport of two VEGF-A isoforms, two PlGF isoforms, and soluble VEGF-R1 throughout the body, along with the binding of these ligands to receptors and extracellular matrix in normal and tumor tissue. We added population variability by varying the protein production rates according to gene expression data for the 5 genes (VEGFA, PGF, FLT1, KDR, NRP1) from the breast, prostate, and kidney cancer TCGA datasets. In this way, we create a population of virtual patient models, and we use this population to simulate clinical trials. In particular, we simulated the addition of two antibodies to the in silico patient population: one that binds VEGF-A (Avastin), and one that binds NRP1. We showed that within breast cancer, the triple-negative subtype was more likely than other breast cancer subtypes to respond to VEGF inhibition. We also showed that the expression changes in kidney cancer made VEGF inhibition broadly successful across many patients, whereas in breast and prostate cancers, responsive subsets made up a smaller proportion of patients, in keeping with the observed outcomes of clinical trials. Across tumor types, multivariate biomarkers were better able to predict treatment response than the best expression-based univariate biomarkers. Using the population models, we considered the impact of effects of attributing gene expression variability to endothelial cells instead of tumor cells. Our results provide a framework that can be generalized to other drugs and other diseases; available matched gene expression and clinical outcome data can be used to validate the predicted biomarkers.