IN SILICO PREDICTION OF ORAL BIOAVAILABILITY. **M. Lawless**, J. DiBella, M. B. Bolger, R.D. Clark, M. Waldman, V. Lukacova; Simulations Plus, Inc., Lancaster, CA.

BACKGROUND: Oral bioavailability (F%) is an important pharmacokinetic property that can determine the fate of a compound in clinical trials. Predicting F% directly from the 2D structure of the molecule prior to first-in-human dosing is highly desirable.
METHODS: A database of 62 drugs, primarily metabolized by cytochrome P450 (CYP) enzymes, including their F% and dose was created. Artificial neural network ensemble (ANNE) models based on 2D molecular structures were used to predict aqueous and biorelevant solubility, pKa, logD, gastrointestinal permeability, fraction unbound in human plasma, and blood to plasma concentration ratio. A hierarchical set of models was used to determine CYP metabolism. First, classification models predicted whether each compound was a substrate for each of five major CYP isoforms (1A2, 2C9, 2C19, 2D6, and 3A4). Next, sites of metabolism were predicted for those compounds that were projected to be substrates. Finally, Km and V_{max} predictions were made for each predicted site of metabolism. These predictions were used as inputs for physiologically based pharmacokinetic (PBPK) models implemented within GastroPlus™.
RESULTS: All of the drugs were predicted to be well absorbed. All molecules were correctly predicted to be substrates of the CYPs associated with their major clearance pathways. Furthermore, these pathways had the highest predicted CYP intrinsic clearance in 42 of the 62 molecules. Overall, 68% of the molecules were predicted within 2-fold of their reported F%.
CONCLUSION: *In silico* tools predicting F% from 2D molecular structures can play an important role in anticipating challenges prior to initiating clinical development. Refining ANNE models based on the chemical space of interest is one strategy for improving prediction of F%.