

Predicting Adverse Cardiovascular Events for Tyrosine Kinase Inhibitors From Molecular Features

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Cardiotoxicity is a major concern for the FDA when examining new drug applications (NDAs) for the family of anti-cancer tyrosine kinase inhibitors (TKIs). Despite their therapeutic effect, many TKIs are associated with adverse cardiovascular events (ACEs), including hypertension, decreased ejection fraction, and cardiac failure. Some TKIs are associated with these side effects, while others are not, and little is known about the molecular mechanisms underlying these discrepancies. By integrating different types of molecular data collected by the LINCS consortium, and by others, on the response of human cells to treatment with TKIs, we developed machine learning classifiers that can reliably predict the likelihood that a newly developed TKI will induce cardio-toxicity. We use drug-kinase binding data from an enzyme-linked immunosorbant assay (ELISA), L1000 transcriptional profiling of cancer cell lines, and RNA-seq transcriptional profiling of cardiomyocytes, to identify kinase targets and transcriptional signatures associated with cardiovascular toxicity, thereby unraveling the mechanisms underlying the toxic effects of certain TKIs. The biomarkers we discovered can help determine if newly developed TKIs are likely to induce cardiac complications, suggest mechanisms for such toxicities, to guide further research and assist in regulatory vetting before such adverse events appear in patients.