Introduction

In an ever-growing biological landscape, there is an imperative need for biomarkers that can effectively capture the inherent dynamics of complex disease states. Current biomarkers often adhere to a ‘one-of-a-kind’ approach, which means that the information content is a measure of a single variable (mutation status and/or information content) rather than a spectrum of variables that provide clearly identifiable signals to different response categories. To address these limitations, a biomarker was recently de- veloped to assess KRAS dependency across diverse cancer cohorts, a pivotal metric in evaluating drug efficacy (Tsai et al., 2023). In this study, the authors introduce the K20 model, which incorporates 20 key features, including gene expression-patterns and KRAS mutation status. The model achieved an AUC of 0.74 during validation, enabling accurate predictions of KRAS dependency in both mutant and wild-type cell lines. When applied to TCGA datasets, it efficaciously identified subgroups with heightened KRAS dependency, demonstrating its potential to elucidate molecular and tumor biology.

Herein, we evaluated the performance of the K20 model. Our re-inplementation demonstrates reproducibility and robustness of the K20 model, underscores the continued need for a new generation of biomarkers capable of delivering on the promise of predicting patient response to KRAS therapies.

Methods

Data

KRAS dependency scores from DEPTOM2 RNA screens (DepMap) • RNA expression profiles and KRAS mutation status from TCGA

KRAS expression profiles of LUNG, PAAD, COAD, READ cancer from TCGA

Models

1. ElasticNet Regression combining both KRAS expression and mutation status
2. XGBoost Regression with optimization of alpha, gamma parameters
3. Linear Regression on 1 feature
4. Logistic Regression on 5 features
5. Logistic Regression on 1 feature
6. L1 ElasticNet Regression

Results

Table 1. ROC AUC of different models. The K20 AUC was calculated using non-removed data available in (5), (6), (10) or (10+13)

Model | Dataset | AUC
--- | --- | ---
K20 Regression | KRAS dependency and KRAS mutation | 0.926 ± 0.033
K20 Regression | KRAS mutation only | 0.892 ± 0.067
L1 ElasticNet Regression | KRAS dependency and mutation | 0.898 ± 0.067

Figure 6. ResponderID™ KRAS: A Novel RNA-based Biomarker Framework for Guiding KRAS Therapeutic Development and Clinical Adoption

Figure 3. ResponderID Expression: A screenshot of the models for predictive visualization in gene expression data.

Figure 4. ResponderID™ KRAS: Biology-Driven Machine Learning to Personalize KRAS Inhibitor Therapeutics

Table 1. Genialis KRAS Dependency Modeling from DepMap

Figure 1. Figure 2. Figure 3. Figure 4. Figure 5. Figure 6.