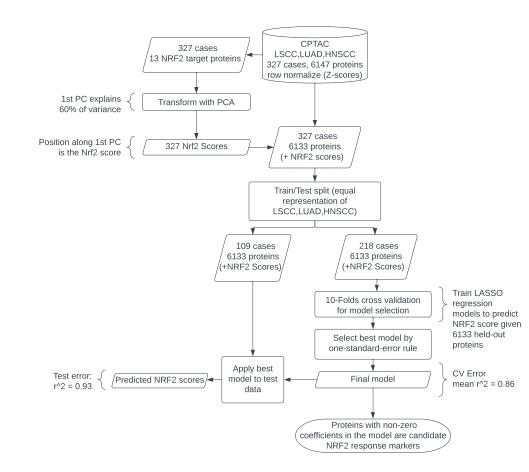
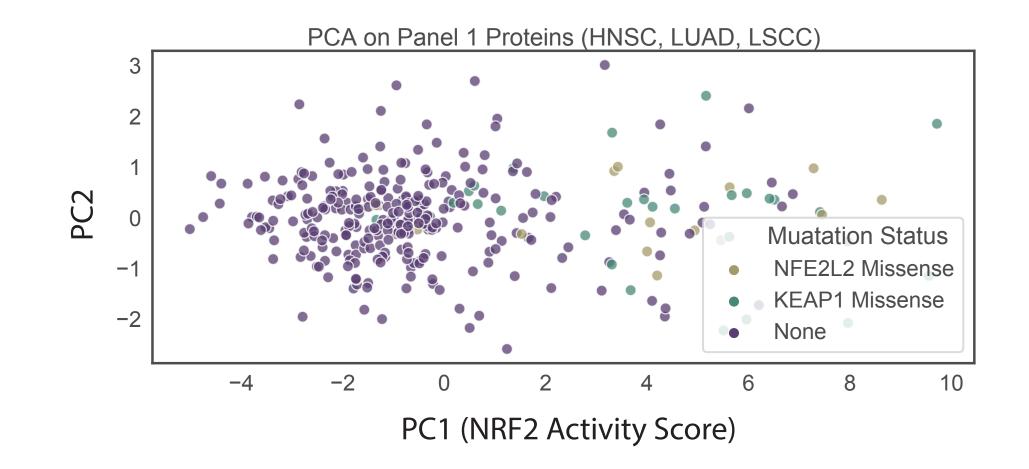
## Number of Proteins with CV < 20%</th> OIS-PRM DDA 0 50 100

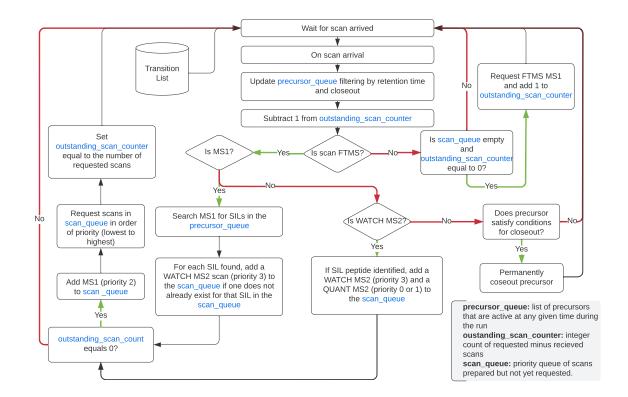
**OIS-PRM Improves Sensitivity over DDA**. OIS-PRM quantifies more proteins than does DDA (172 vs. 47) a with a coefficient of variation (CV) less than 20%. See main figure 1.



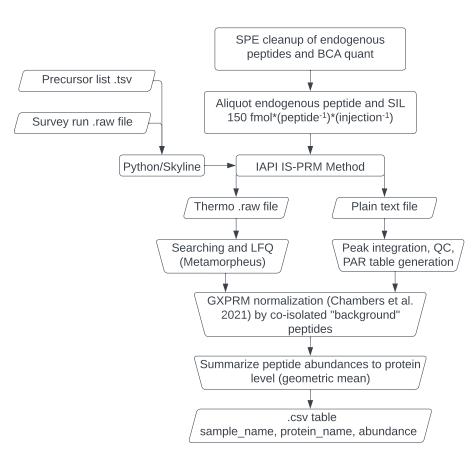
**CPTAC Analysis.** Schema of NRF2 pathway analysis from CPTAC cohorts for HNSCC, LUSC, and LUAD. See main figure 2.



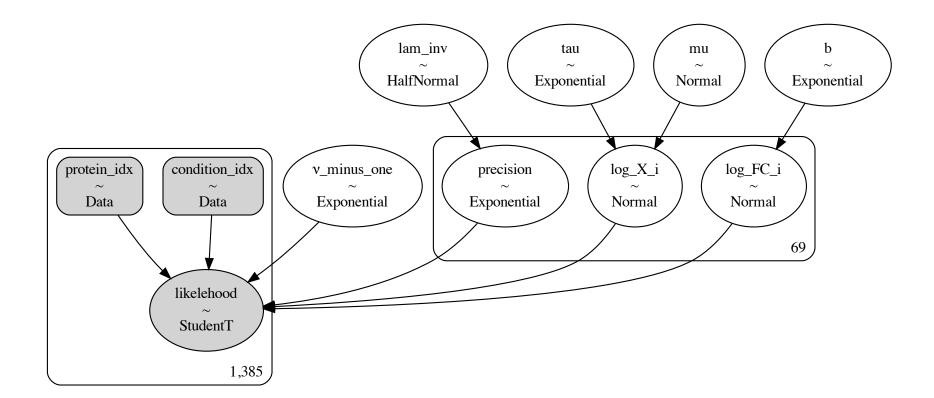
CPTAC NRF2 Targets Expression PCA Plot: A PCA plot of the CPTAC data from figure 2C but demarking mutation status rather than cancer type



**OIS-PRM Algorithm**. Schematic of the OIS-PRM data acquisition algorithm as detailed in supplemental methods.

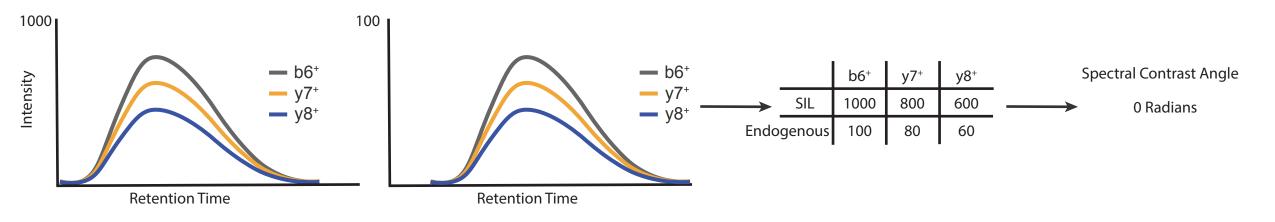


**OIS-PRM Analysis Pipeline.** Schematic of the data analysis pipeline for OIS-PRM and SureQuant<sup>™</sup> experiments as detailed in supplemental methods.



**NRF2 Target Expression Model.** Plate diagram for hierarchical Bayesian model used to estimate posterior distributions for mean fold changes in the expression of NRF2 targets between NRF2 active and inactive cell lines and tumors. Detailed in supplemental methods.

## Spectral Contrast Angle Between SIL and Endogneous With Interference on y8<sup>+</sup> lon SIL (Peptide) Endogenous (light) Peptide 1000 100 Interfered Ion **—** b6<sup>+</sup> **—** b6<sup>+</sup> Spectral Contrast Angle Intensity b6+ v7+ y8+ — y7+ — y7+ SIL 1000 800 600 $\approx \pi/10$ Radians **—** y8<sup>+</sup> — v8⁺ 120 Endogenous 100 80 **Retention Time Retention Time** Spectral Contrast Angle Between SIL and Endogneous Absent Interference SIL (Peptide) Endogenous (light) Peptide



Use of Spectral Contrast Angles to Detect Interference: Spectral contrast angles between the endogenous and internal standard peptides are used to detect interefered transitions.