SUPPLEMENTARY FIGURES AND TABLE LEGENDS

Supplementary Figure 1: Validation of mRNA knockdown of candidate genes in the RNAi screen. Relative mRNA levels are shown for each individual siGENOME siRNA (siG-#) used in the RNAi screen compared to siNTC control in NCI-H838 cells after three days of knockdown. Data for *FGD4*, *PYROXD1*, and *YARS2* are not shown since they were expressed too low to accurately measure their gene expression levels (data not shown). Mean +/- S.D. is shown.

Supplementary Figure 2: LDHB is not selectively overexpressed in KRAS mutant colon cancer. (A) Average relative *LDHB* $\log_2$ mRNA expression +/- S.D. in KRAS wild-type or KRAS mutant colon cancer cell lines. (B) Immunoblot of LDHB and LDHA in colon cancer cell lines that are KRAS wild-type or KRAS mutant. (C) Correlation analysis between the average $\log_2$ expression of glycolysis signature genes and RAS signature genes in individual colon tumors (n = 227). *P*-value for Pearson correlation is a one-tailed *t*-test.

Supplementary Figure 3: RNAi of KRAS to determine cellular dependence on proliferation and effects on *LDHB* expression. (A) Relative cell proliferation (from CellTiter Glo assay, CTG) of NSCLC cell lines using pooled siRNA against KRAS. Cells whose proliferation was reduced to 50% or lower relative to siNTC control (red dashed line) were considered dependent on KRAS expression. KRAS status indicates whether the cells are KRAS wild-type (WT), mutant (mut), or amplified (amp). (B) KRAS knockdown does not affect *LDHB* mRNA expression. Relative *LDHB* mRNA expression

is shown three days after KRAS RNAi with three independent siRNAs. Representative knockdown of *KRAS* expression in NCI-H838 cells is shown in Supplemental Figure 1; siKRAS-1 did not inhibit *KRAS* expression and thus is not shown here.

Supplementary Figure 4: LDHB expression and dependence in lung adenocarcinoma cell lines containing various oncogenic drivers. (A) Immunoblot analysis of LDHB and LDHA expression in lung adenocarcinoma cell lines containing the indicated oncogenic mutation. For quantitative analysis LDHB expression was normalized to the TUBULIN control. Mut represents mutant, amp represents amplified, and fus represents fusion. (B) Relative cell proliferation (using CellTiter-Glo assay) of lung adenocarcinoma cell lines using two independent LDHB siRNA oligos compared to siNTC control. The various cell lines differ in the oncogenic driver and levels of LDHB as indicated. (C) Immunoblot analysis of LDHB following siRNA knockdown in the indicated cell lines. TUBULIN serves as a loading control.

Supplementary Figure 5: LDHB expression correlates with poor overall survival in lung tumors. (A, B) Kaplan-Meier survival data for lung cancer patients, separated by LDHB IHC score. Patients with high LDHB expression (n = 99; IHC score of 2 or 3) had a worse overall survival compared to patients with low LDHB expression (n = 71; IHC score 0 or 1) for a 5-year survival (A) or overall survival (B), as measured by death or being censored from the study. (C) Kaplan-Meier survival data for KRAS wild-type lung cancer patients separated by *LDHB* expression as determined by microarray (n = 137 tumors). Patients with high LDHB expression (above mean *LDHB* expression of all

tumors) had poorer overall survival when compared to patients with low LDHB expression (below mean *LDHB* expression of all tumors) for 5 year survival.

Supplementary Table 1. Significance and frequency of KRAS (chr12:25249446-25295121) amplification across multiple cancer types. Data is extracted from Tumorscape (www.broadinstitute.org/tumorscape).

Supplementary Table 2. KRAS mutation status and copy number of KRAS and LDHB in NSCLC cell lines.

Supplementary Table 3. Characteristics and history for the different cohorts of lung cancer patients used in the LDHB and survival correlation analysis. Only those patients with complete study details are shown.