

SUPPLEMENTARY INFORMATION

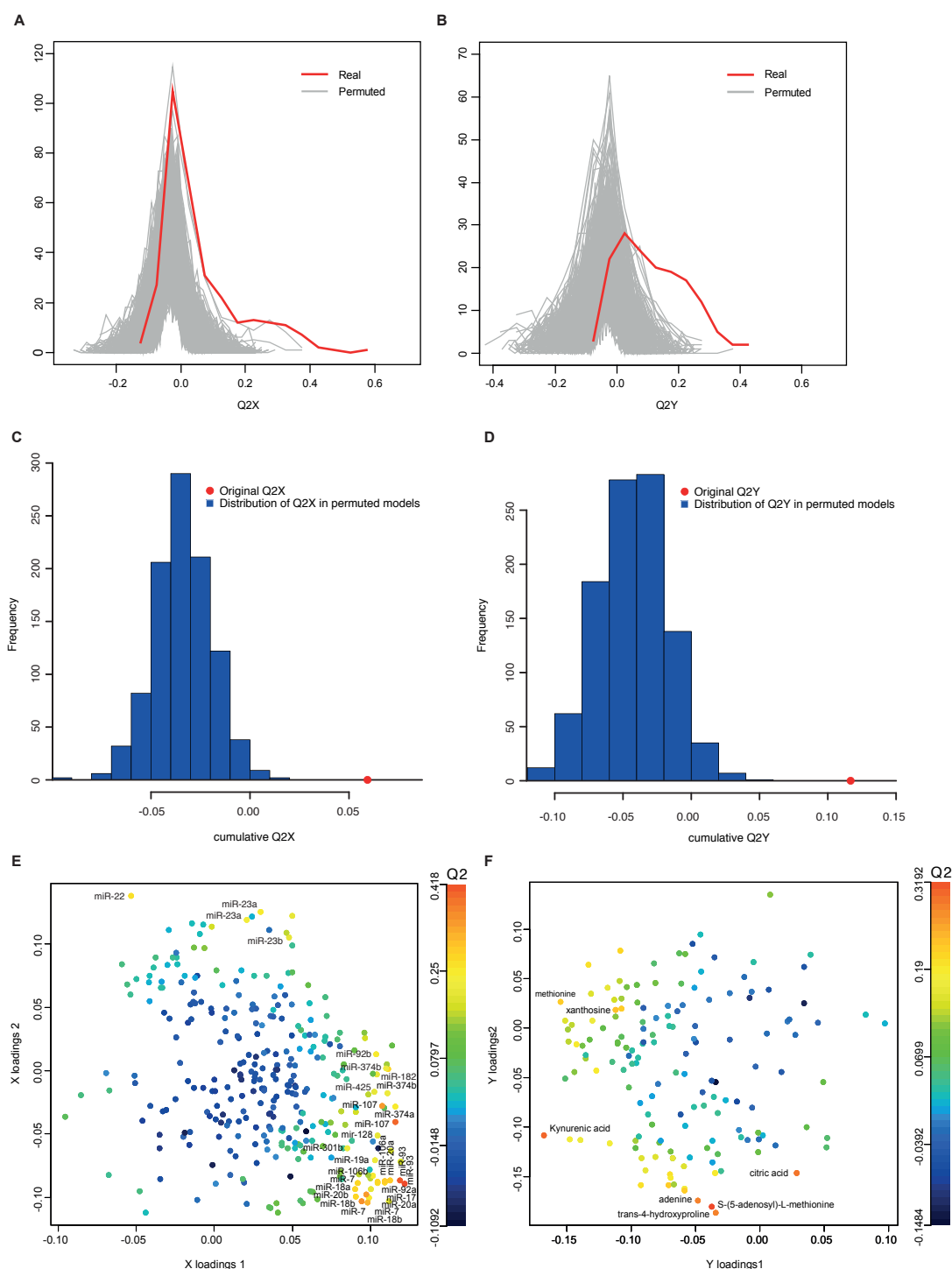


Figure S1. Validation of the O2-PLS model of NCI-60 panel data. Panels A-D: Null distributions for individual variable Q^2X (A) and Q^2Y (B) and cumulative Q^2X (C) and Q^2Y (D) generated from O2PLS models of 1000 datasets randomly created by permuting sample identities. Each of the grey lines corresponds to the distribution of Q^2 values of the variables in the permuted models. The red line corresponds to the distribution of variable Q^2 values in the original model. This analysis indicated that a variable Q^2 greater than 0.26 (metabolites) or 0.3 (miRNAs) was significant. In the cumulative analysis none of the random models reached the Q^2 values of the original model, indicating a significance of $p=0.001$. Panels E/F: O2-PLS model for NCI-60 panel but excluding cell lines derived from hematological cancers, showing loadings for microRNAs (E) and metabolites (F).

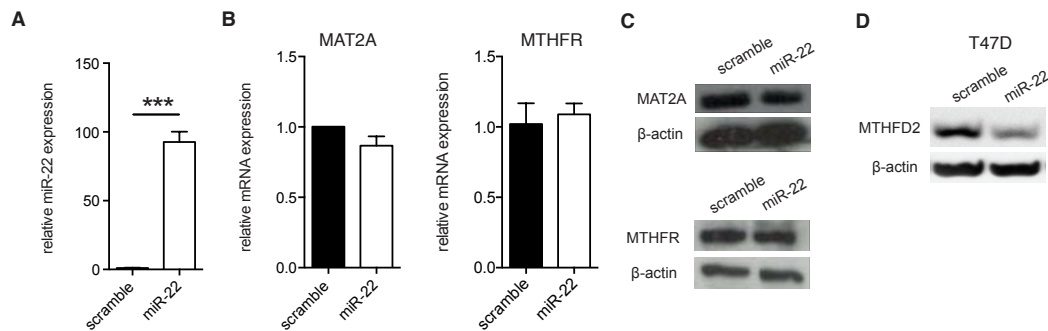


Figure S2. Effect of miR-22 mimic transfection on intracellular levels of the miRNA and on MAT2A and MTHFR expression. (a) qRT-PCR analysis of miR-22 in MCF-7 cells transfected with negative control or miR-22 after 24 hours (n=3). For normalization U6 was used. ;(b) qRT-PCR for MAT2A and MTHFR in miR-22-transfected MCF-7 cells after 48 hours (n=3). For normalization β -actin gene was used.; (c) Immunoblotting analysis of MAT2A and MTHFR in miR-22-transfected MCF-7 cells after 48 hours. (d) Immunoblotting analysis of MTHFD2 in miR-22-transfected T47D cells after 48 hours. Figures show mean $\pm$ s.e.m.

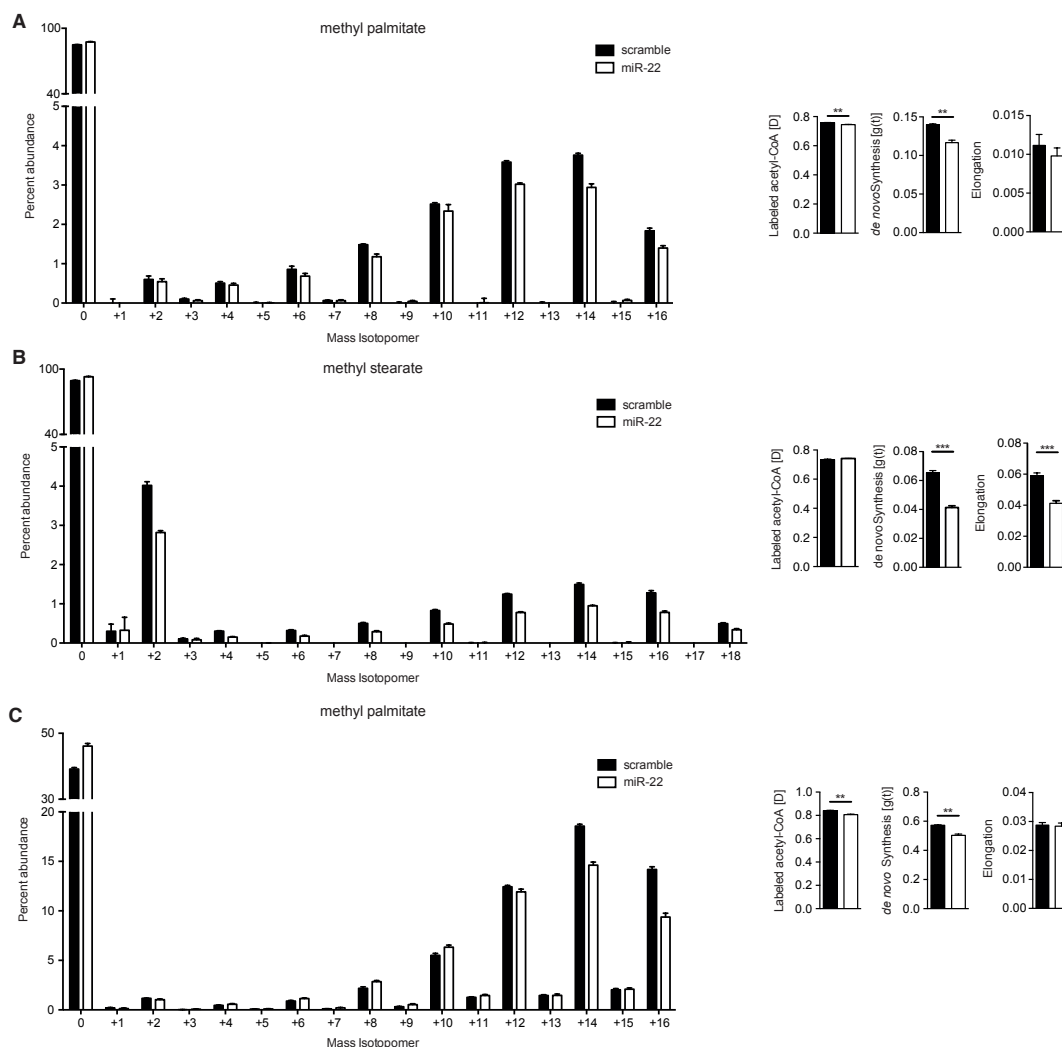


Figure S3. Effect of miR-22 mimic transfection on lipid synthesis. Mass isotopomer distributions (MID) of transesterified fatty acids from lipids corrected for natural isotope abundance following labeling with $U-^{13}C_6$ -glucose (mean $\pm$ s.e.m., n=3) and their estimated ISA parameters (mean $\pm$ s.e.m., n=4); (a) and (b) 5 hour incubation with labeled substrate; c) 48 hour labeling. Asterisks note p-values after a Student's t-test. ** $p < 0.01$, *** $p < 0.001$

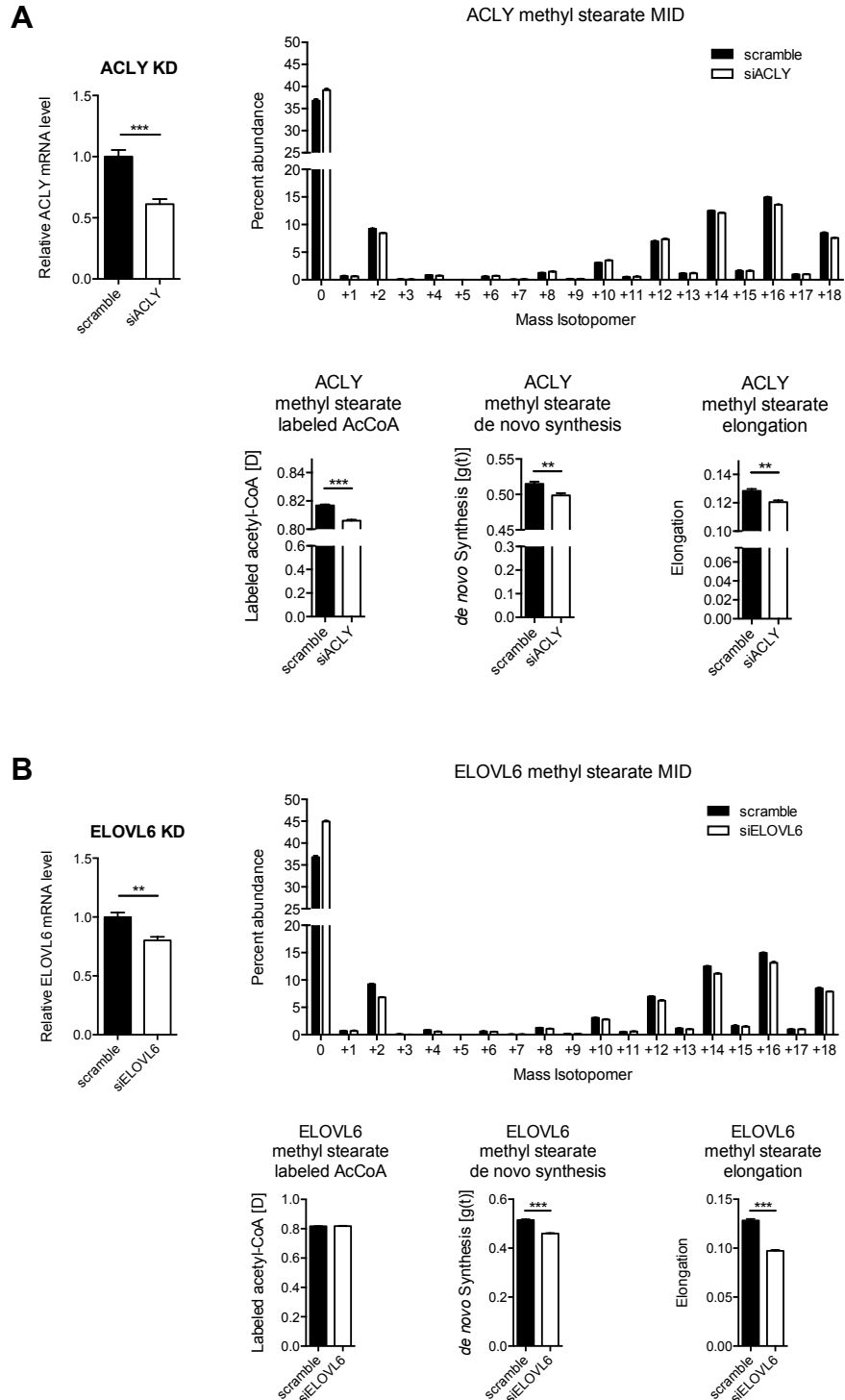


Figure S4. Isotopomer Spectral Analysis of stearate after siRNA silencing of ACLY and ELOVL6. Levels of target mRNA (to show target knockdown efficiency), mass isotopomer distribution (MID) of measured stearate transesterified from lipids, and estimated ISA parameters for stearate transesterified from lipids in MCF-7 cells transfected with either (a) siACLY or (b) siELOVL6, and incubated with U-¹³C₆-glucose for 48 hours. Data are shown as mean $\pm$ s.e.m., n=5; Asterisks note p-values after a Student's t-test. ** p<0.01, *** p<0.001

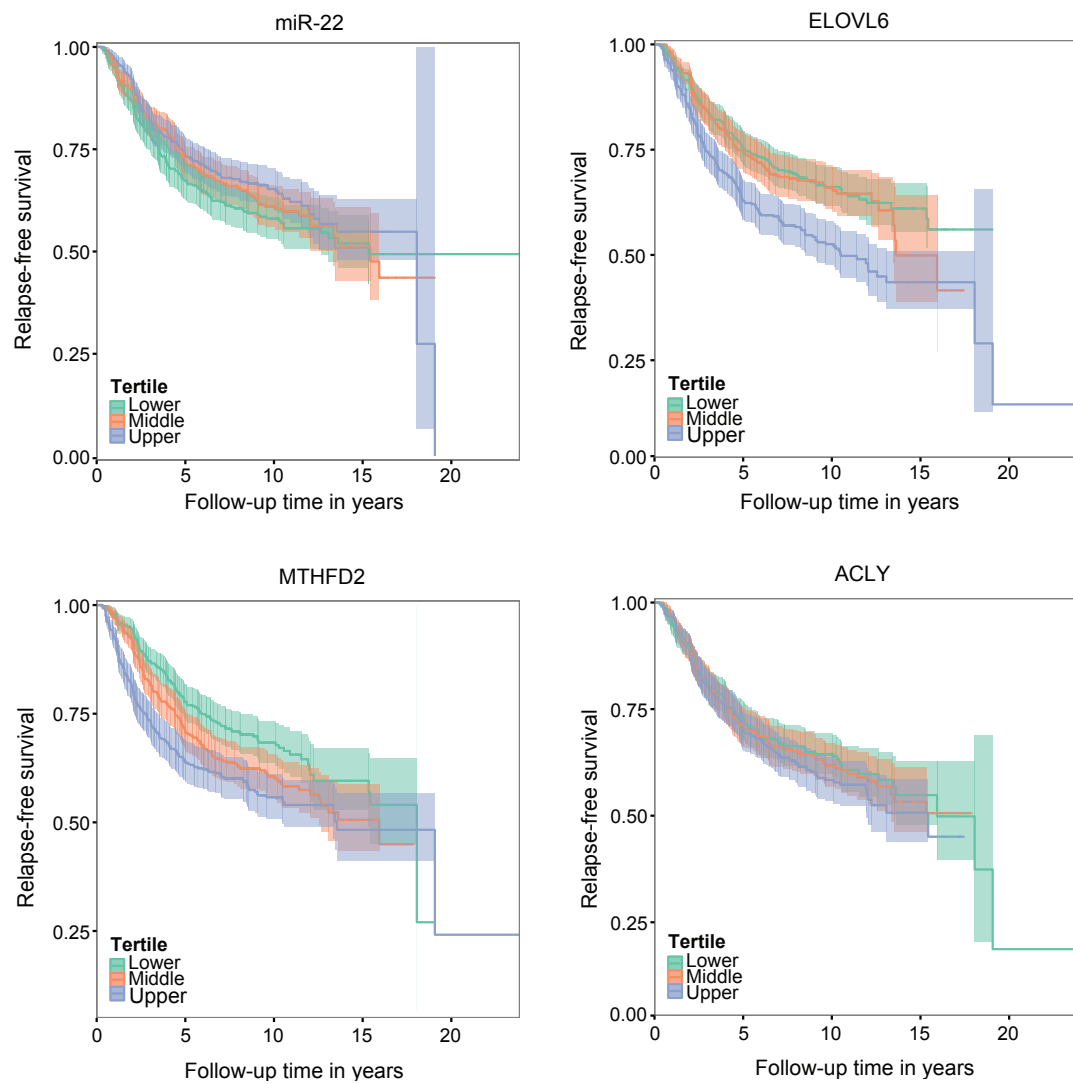


Figure S5. Relapse-free survival stratified by expression of miR-22, ELOVL6, ACLY, and MTHFD2. Kaplan-Meier analysis of relapse-free survival stratified by expression tertiles of miR-22 and the three miR-22 target genes combining 10 independent patient data sets. Survival curves show 95% CIs.

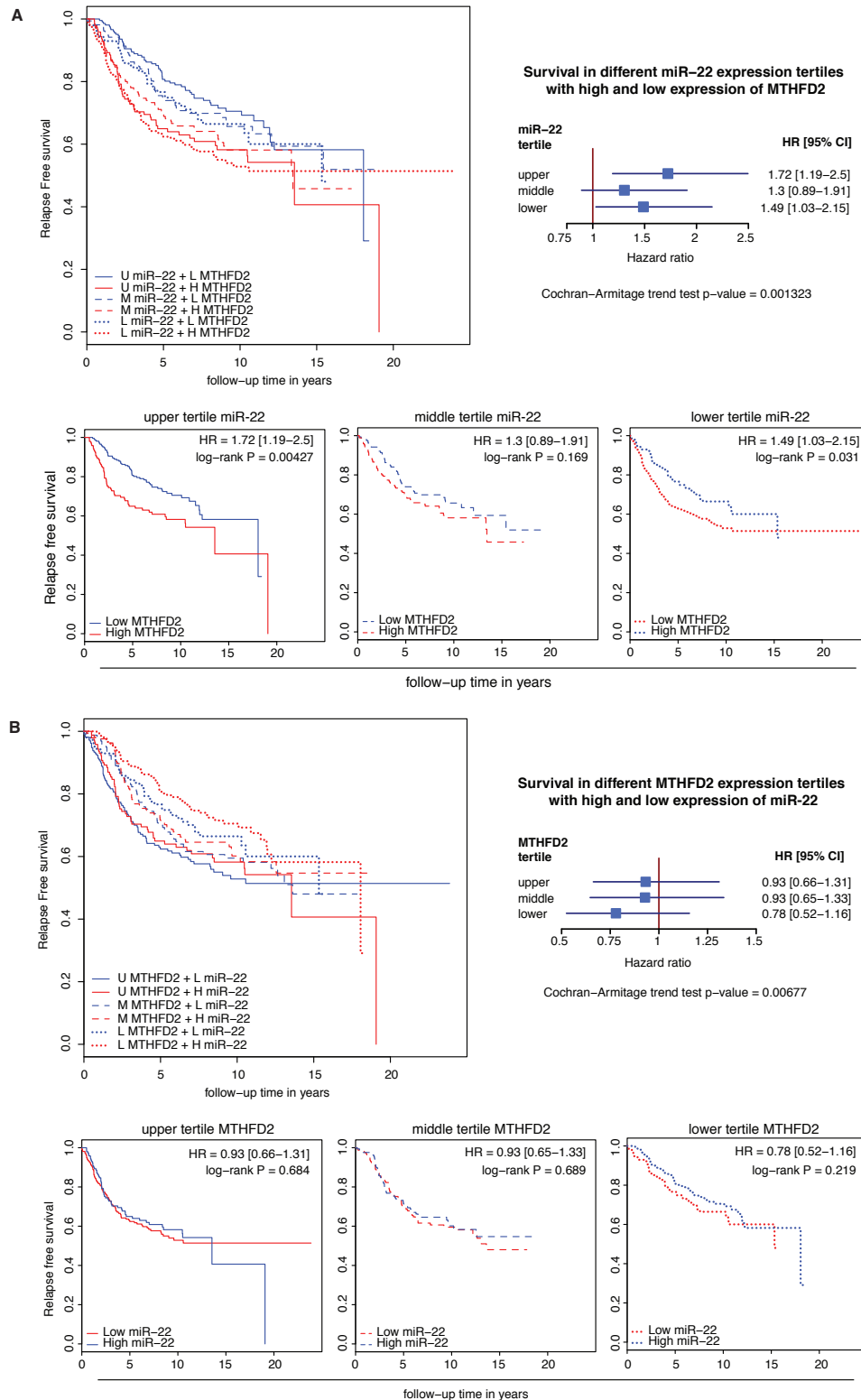


Figure S6. Effect modification on patient outcomes between miR-22 and MTHFD2. (a) Kaplan-Meier analysis of relapse-free survival stratified by expression tertiles of miR-22, i.e. survival modifier (U, M and L are upper, middle and lower tertiles, respectively), and upper and lower expression tertiles of MTHFD2 (H and L are high and low expression groups according to upper and lower tertiles, respectively). (b) Kaplan-Meier analysis of relapse-free survival stratified by expression tertiles of MTHFD2, i.e. survival modifiers, and upper and lower expression tertiles of miR-22. The extent of effect modification was determined by the Cochran-Armitage trend test.

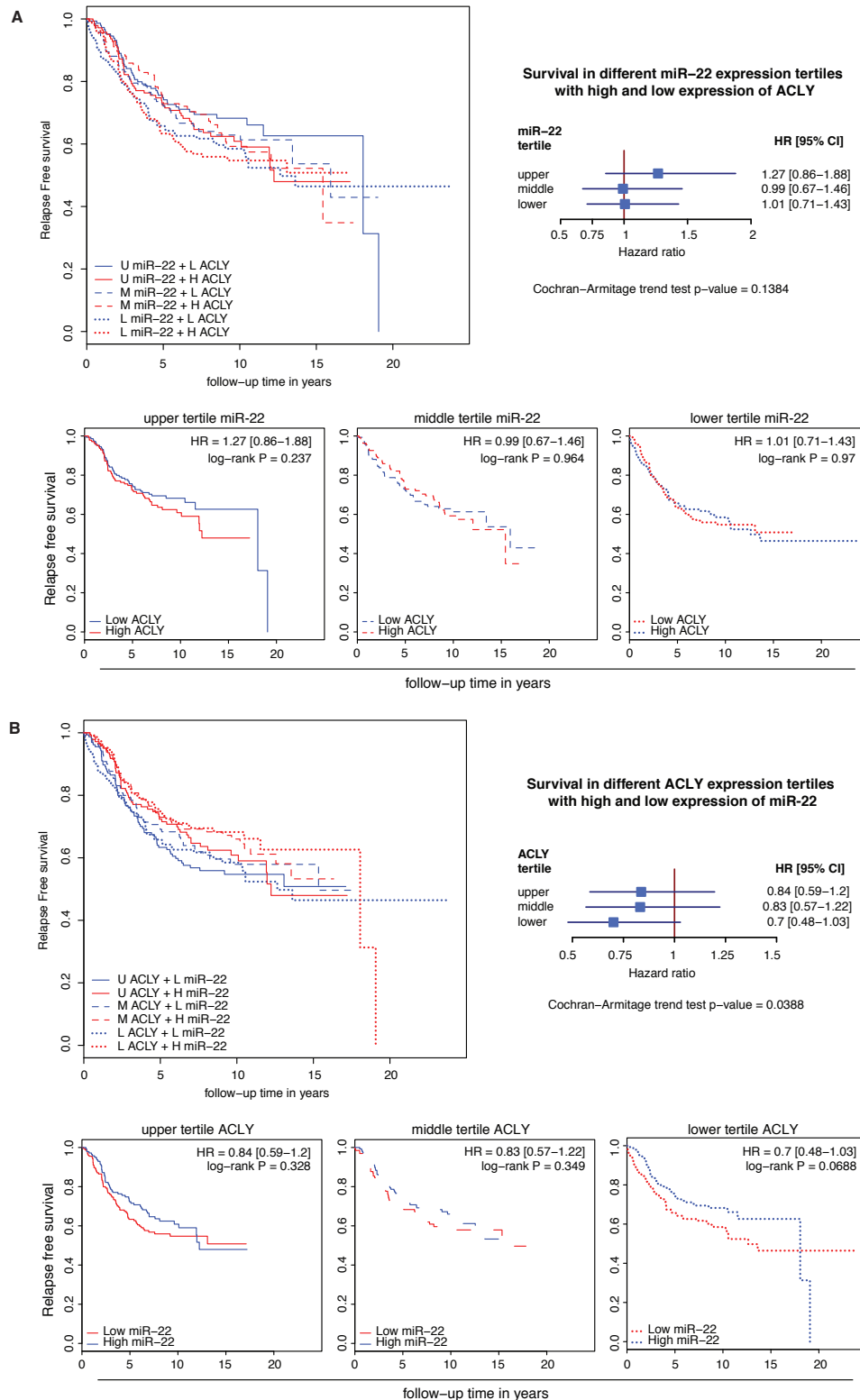
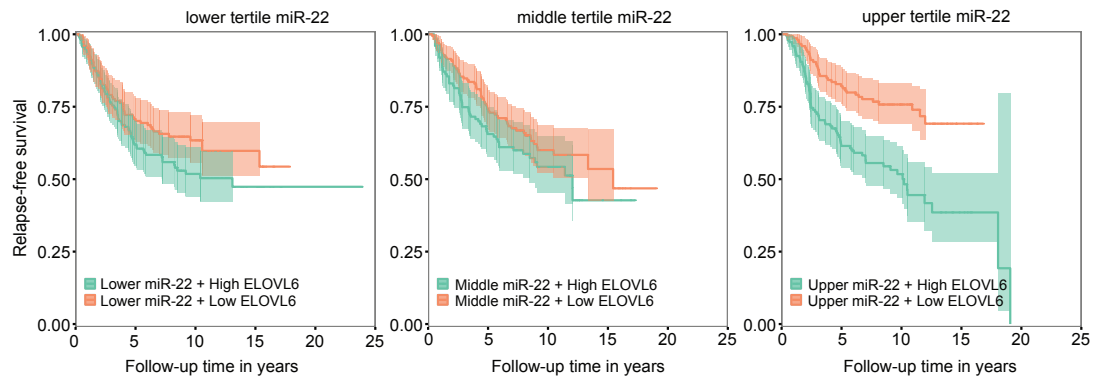


Figure S7. Effect modification on patient outcomes between miR-22 and ACLY. (a) Kaplan-Meier analysis of relapse-free survival stratified by expression tertiles of miR-22, i.e. survival modifier (U, M and L are upper, middle and lower tertiles, respectively), and upper and lower expression tertiles of ACLY (H and L are high and low expression groups according to upper and lower tertiles, respectively). (b) Kaplan-Meier analysis of relapse-free survival stratified by expression tertiles of ACLY, i.e. survival modifiers, and upper and lower expression tertiles of miR-22. The extent of effect modification was determined by the Cochran-Armitage trend test.

A Survival in different miR-22 expression tertiles with high and low expression of ELOVL6



B Survival in different ELOVL6 expression tertiles with high and low expression of miR-22

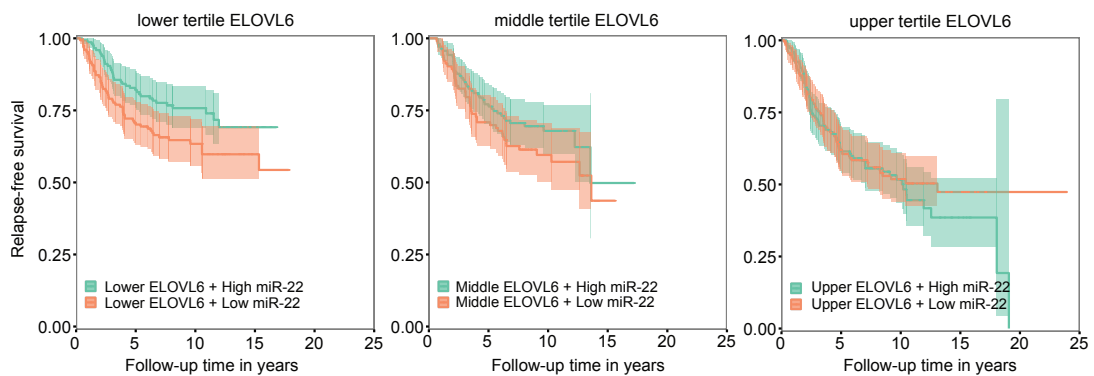
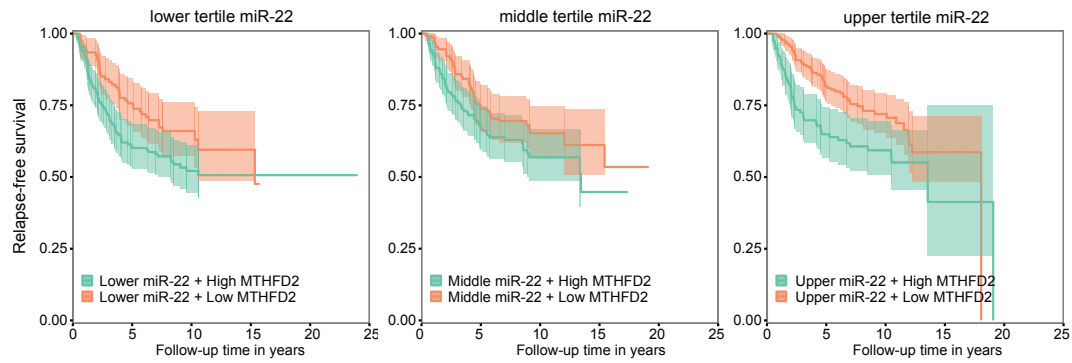


Figure S8. Effect modification on relapse-free survival by expression levels of miR-22 and ELOVL6. Kaplan-Meier analysis of relapse-free survival stratified by expression tertiles of (a) miR-22, i.e. survival modifier, and upper and lower expression tertiles of ELOVL6 (b) Kaplan-Meier analysis of relapse-free survival stratified by expression tertiles of ELOVL6, i.e. survival modifiers, and upper and lower expression tertiles of miR-22. (U, M and L are upper, middle and lower tertiles, respectively; H and L are high and low expression groups according to upper and lower tertiles, respectively). Survival curves show 95% CIs.

A Survival in different miR-22 expression tertiles with high and low expression of MTHFD2



B Survival in different MTHFD2 expression tertiles with high and low expression of miR-22

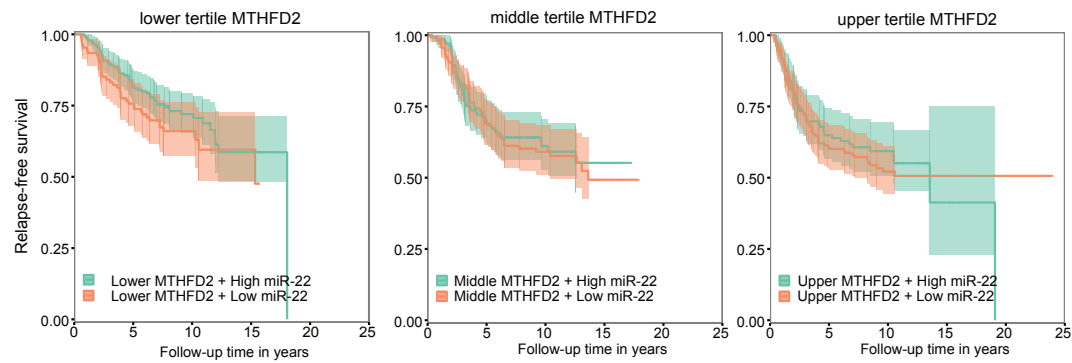
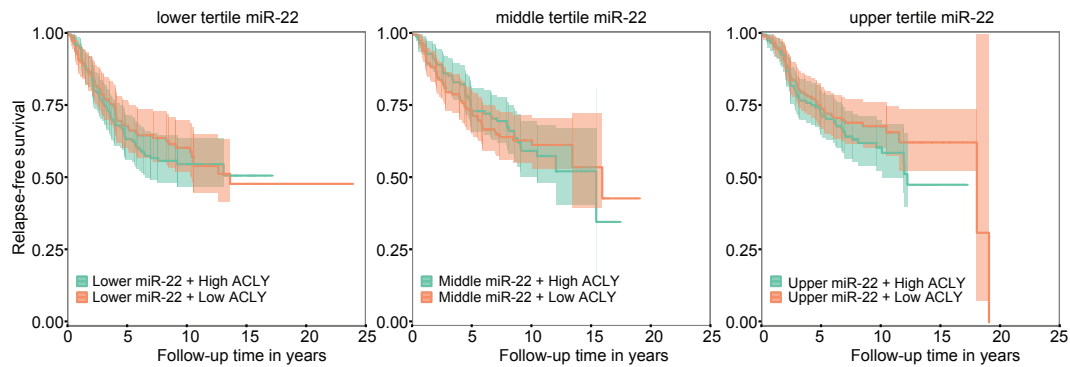


Figure S9. Effect modification on relapse-free survival by expression levels of miR-22 and MTHFD2. Kaplan-Meier analysis of relapse-free survival stratified by expression tertiles of (a) miR-22, i.e. survival modifier, and upper and lower expression tertiles of MTHFD2 (b) Kaplan-Meier analysis of relapse-free survival stratified by expression tertiles of MTHFD2, i.e. survival modifiers, and upper and lower expression tertiles of miR-22. (U, M and L are upper, middle and lower tertiles, respectively; H and L are high and low expression groups according to upper and lower tertiles, respectively). Survival curves show 95% CIs.

A Survival in different miR-22 expression tertiles with high and low expression of ACLY



B Survival in different ACLY expression tertiles with high and low expression of miR-22

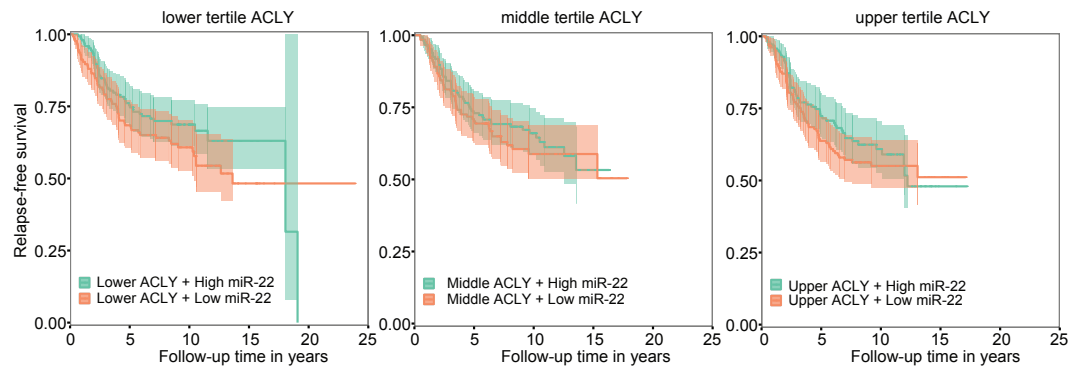


Figure S10. Effect modification on relapse-free survival by expression levels of miR-22 and ACLY. Kaplan-Meier analysis of relapse-free survival stratified by expression tertiles of (a) miR-22, i.e. survival modifier, and upper and lower expression tertiles of ACLY (b) Kaplan-Meier analysis of relapse-free survival stratified by expression tertiles of ACLY, i.e. survival modifiers, and upper and lower expression tertiles of miR-22. (U, M and L are upper, middle and lower tertiles, respectively; H and L are high and low expression groups according to upper and lower tertiles, respectively). Survival curves show 95% CIs.

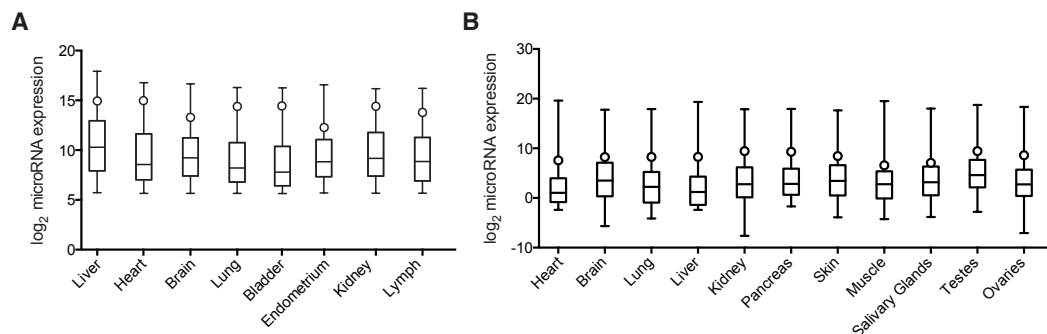


Figure S11. Expression pattern of miR-22 in normal human tissues. Boxplots displaying microRNA expression levels, with miR-22 expression levels identified by the open circle, in various tissues based on (a) Microarray data (Meiri et al, 2010) (b) next-generation sequencing data (Kuchen et al, 2010).