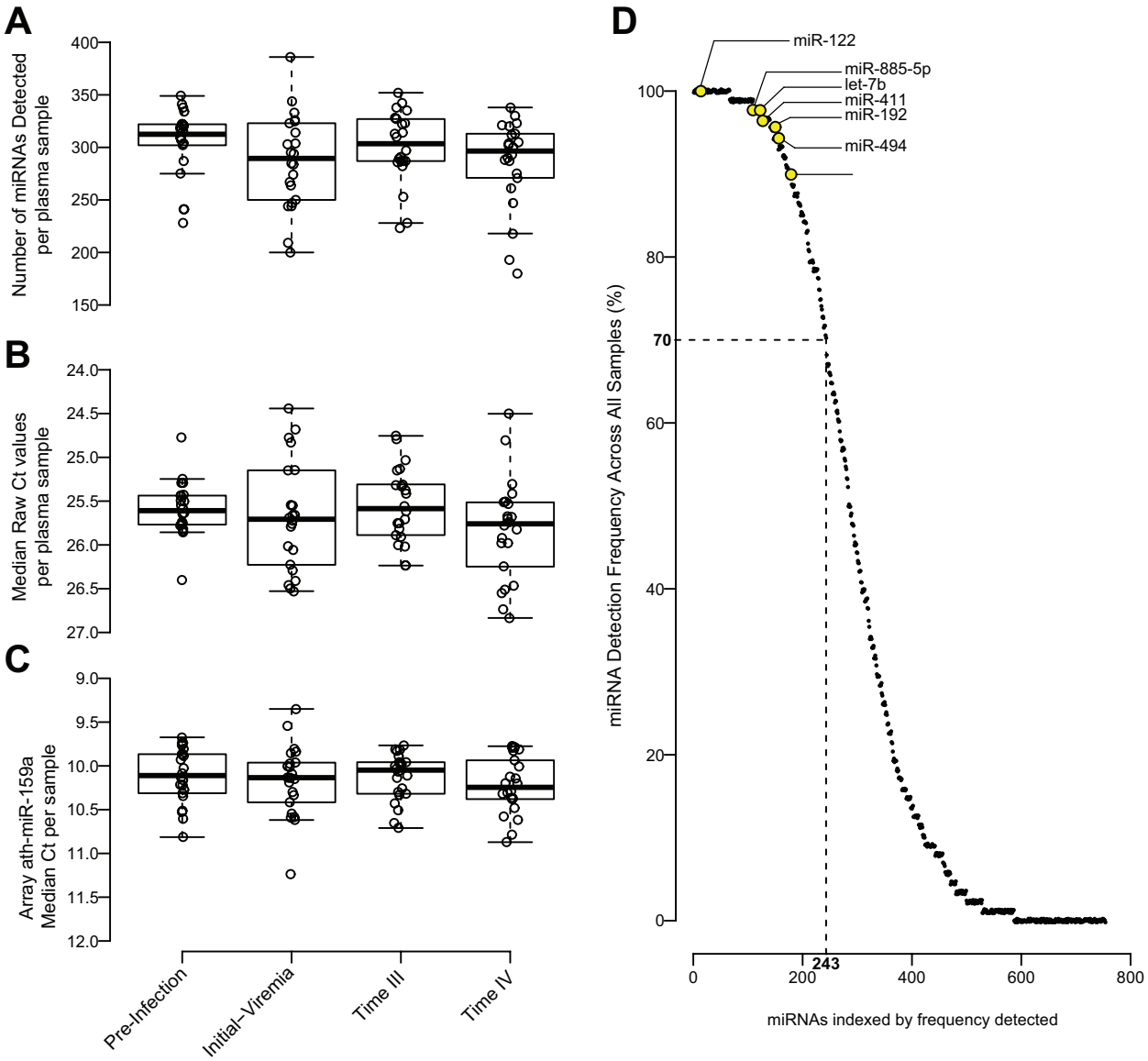
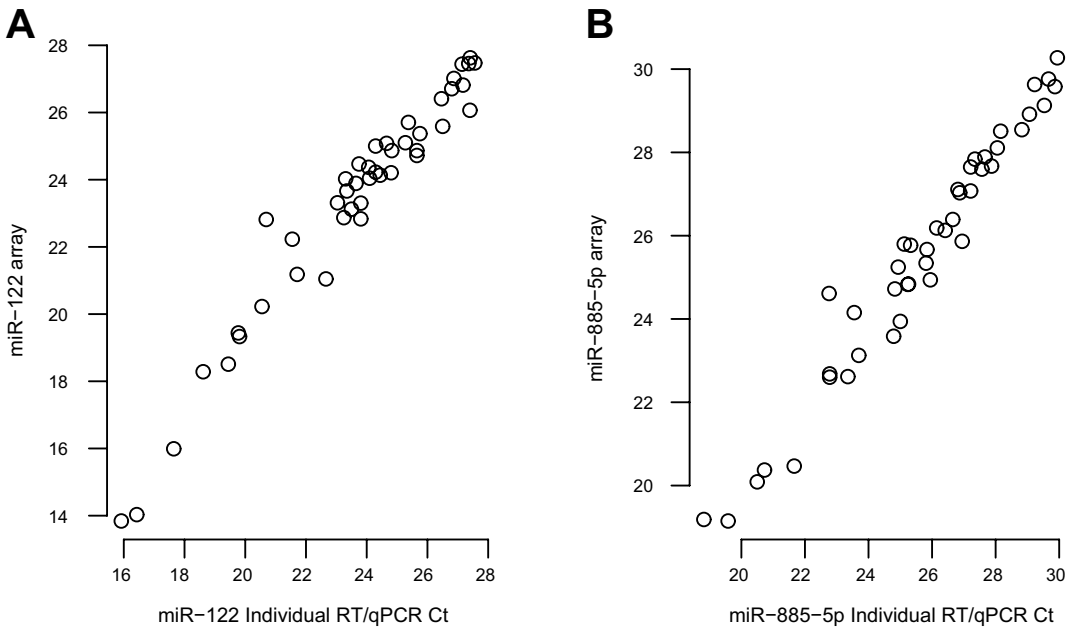
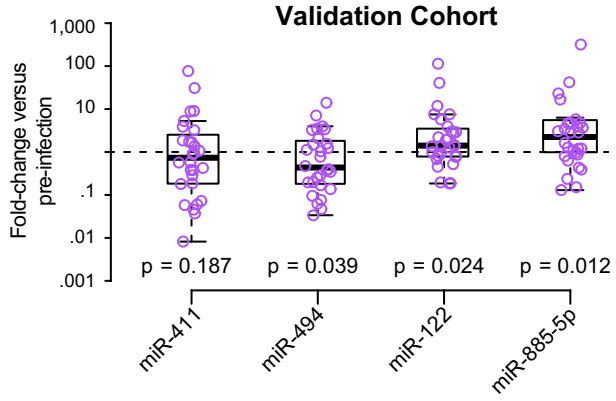


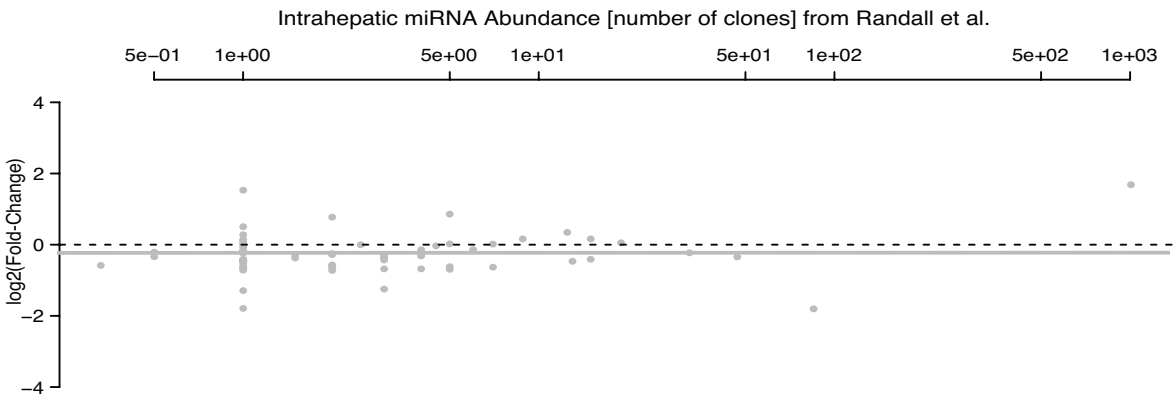
Supplementary Figure 1. Quantitative PCR array performance characteristics indicate that miRNA quantification and detection was unbiased. (A) The number of microRNAs detected per sample and **(B)** the median qPCR crossing threshold (Ct) values among all measured miRNAs per sample are shown across all time points. **(C)** Median Ct values of the externally added control miRNA ath-miR-159a for all samples. Ath-miR-159a was separately included on each array > 10 times to improve the precision of its measurement. **(D)** miRNAs were ordered by their detection frequency (100*the number of samples in which a miRNA was detected divided by the total number of samples) in all samples from participants in the discovery cohort who developed acute HCV infection: 243 miRNAs were detected in > 70% of samples, and these were included in the final unbiased analysis.



Supplementary Figure 2. Validation of qPCR array results using individual RT/qPCR assays for select miRNAs. (A) miR-122 and **(B**) miR-885-5p abundance at pre-infection and initial-viremia time points for all infected individuals in the discovery cohort were confirmed using individual RT/qPCR Cts; qPCR array results compared favorably with individual RT/qPCR results ($r>0.97$, $p<2.2*e-16$ for both).

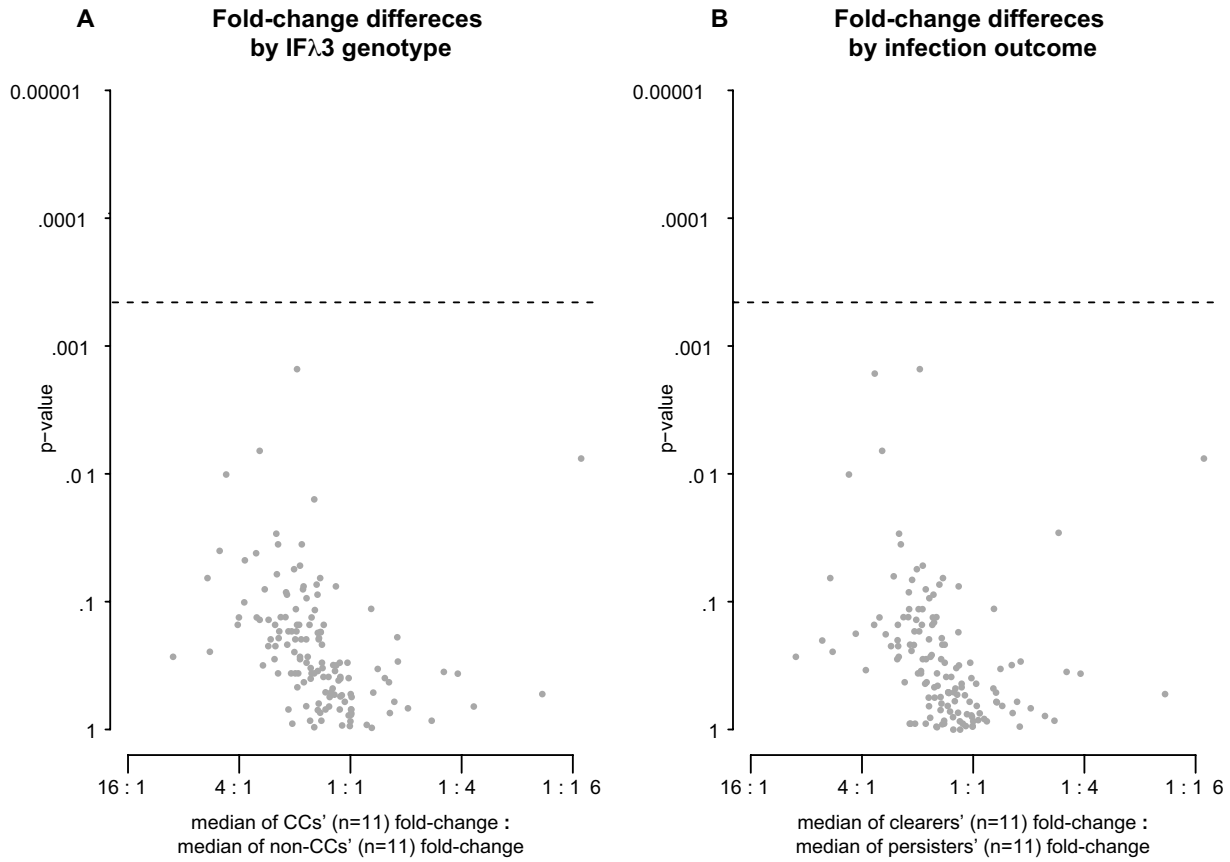


Supplementary Figure 3. Validation of the plasma miRNA signature of acute HCV in a separate cohort. Boxplots with individual values show the changes in circulating miRNA abundance for miR-411, miR-494, miR-122, and miR-885-5p between pre-viremia and initial viremia in 28 participants of the UFO study. P-values generated by the non-parametric Wilcoxon rank-sum test are shown for the plotted miRNAs.



Supplementary Figure 4. Plasma miRNA abundance is not related to intrahepatic miRNA abundance. The plasma miRNA abundance at initial viremia for each of 70 miRNAs (y-axes) was compared to the intrahepatic abundance of the same miRNAs (x-axes), based on previously published data[1].

[1] Randall G, Panis M, Cooper JD, Tellinghuisen TL, Sukhodolets KE, Pfeffer S, et al. Cellular cofactors affecting hepatitis C virus infection and replication. Proc Natl Acad Sci U S A 2007;104:12884–9. doi:10.1073/pnas.0704894104.



Supplementary Figure 5. Changes in miRNA abundance did not significantly differ by *IFNL3* genotype or infection outcome. Fold-changes between pre-infection and initial viremia were separated into groups according to **(A)** *IFNL3* genotype or **(B)** infection outcome and each group was assigned a median fold change (n=11 for CC, nonCC [CT or TT], clearers, and persisters). The volcano plots depict the differences in the median fold-changes between each group in the x-axes in the form of a ratio (higher fold-change in the non-CTs or persisters to the left). In the y-axis is shown the uncorrected p-value of the change in miRNA abundance. The dashed lines indicate the threshold for significance.