

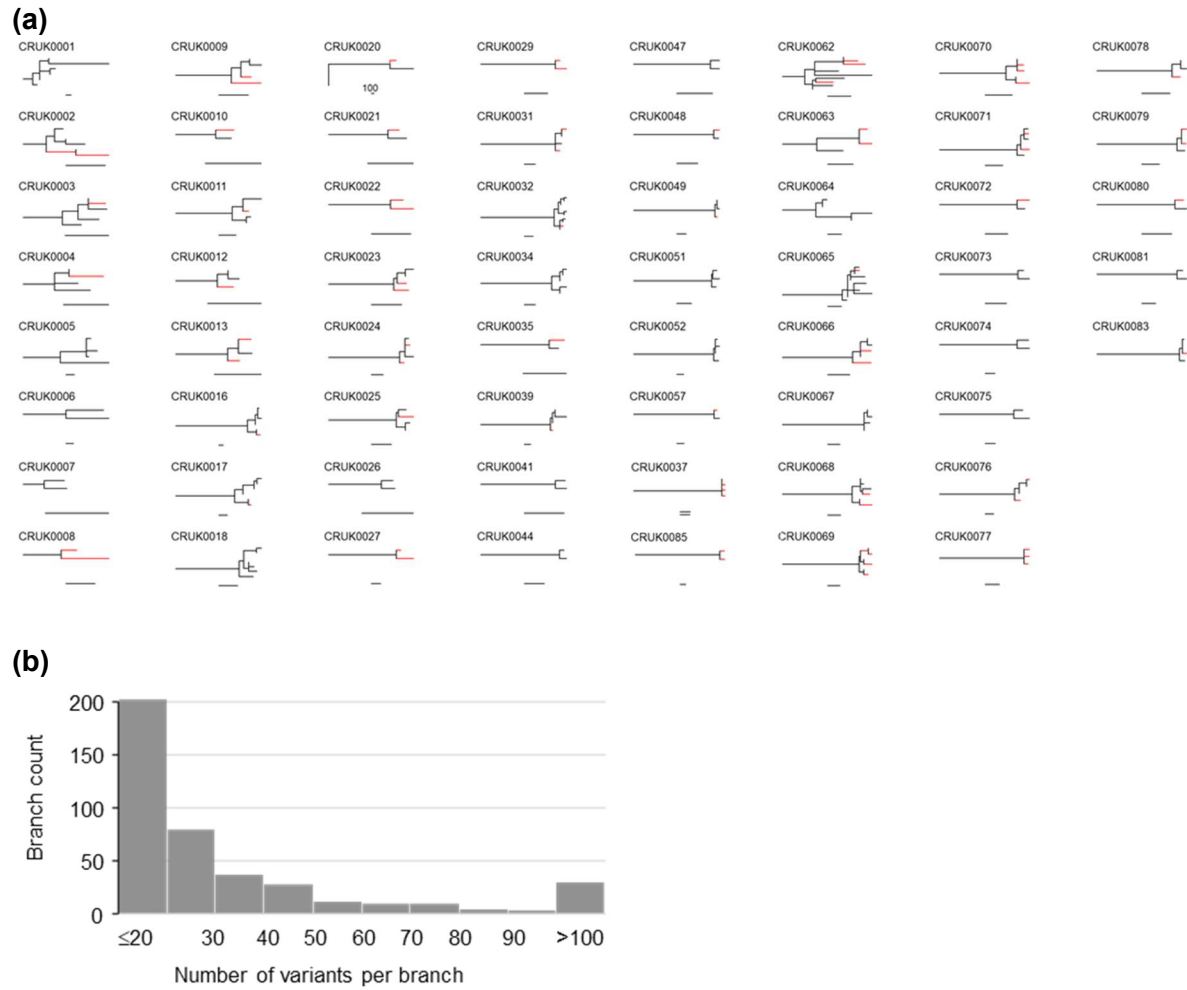


Figure S1. Clone phylogenies from data in Jamal-Hanjani et al. (2017). (a) Only phylogenies with >1 tip were included. Branches with <20 variants were combined for signature detection (see **Methods**). Combined branches were shown with red. The scale bar is equal to 100 variants in each case. (b) The number of variants in individual branches of all the clone phylogenies that are shown in panel a.

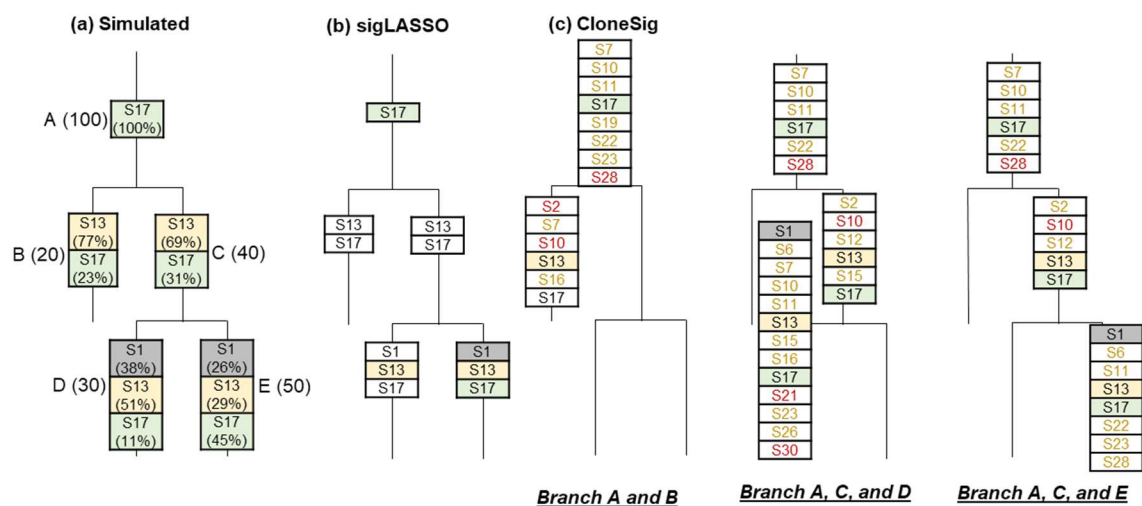


Figure S2. Mutational signatures detected by sigLASSO and CloneSig. (a) Model clone phylogeny and simulated mutational signatures (see **Figure 2a** for the detail). (b and c) mutational signatures inferred by sigLASSO (b) and CloneSigs (c). (c) Since CloneSigs can be used only for a linear tree, we independently analyzed mutations from branches A and B, branches A, C, and D, and branches A, C, and E. Incorrectly detected signatures are shown with red (>5% estimated relative activity) and yellow (0.1% - 5% estimated relative activity) letters, and correct signatures not detected are shown in white boxes with black letters.

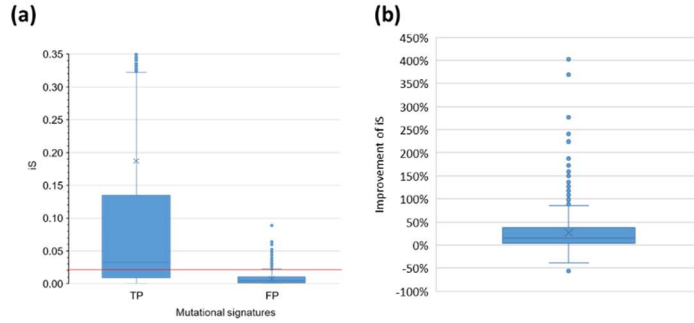


Figure S3. The pattern of iS values. (a) iS values for correct (TP) and incorrect (FP) signatures. The red line indicates iS of 0.02. (b) Difference of iS before and after applying *PhyloSignare*. We summed up iS values from all signatures detected from each branch of a phylogeny (overall iS). We computed the overall iS for each phylogeny and compared the values between before and after applying *PhyloSignare*. For each phylogeny, we calculated the difference of overall iS after applying *PhyloSignare* from the value before applying *PhyloSignare*, which was then divided by the value before applying *PhyloSignare* to normalize it. QP was used for the signature detection, and the iS was calculated for these signatures. All the simulated datasets were used (see **Methods**). A cross in a box is a mean and a center line is a median. A box represents the range between first and third quartile. The whiskers indicate 1.5× interquartile range box limits. The outliers are represented by dots.

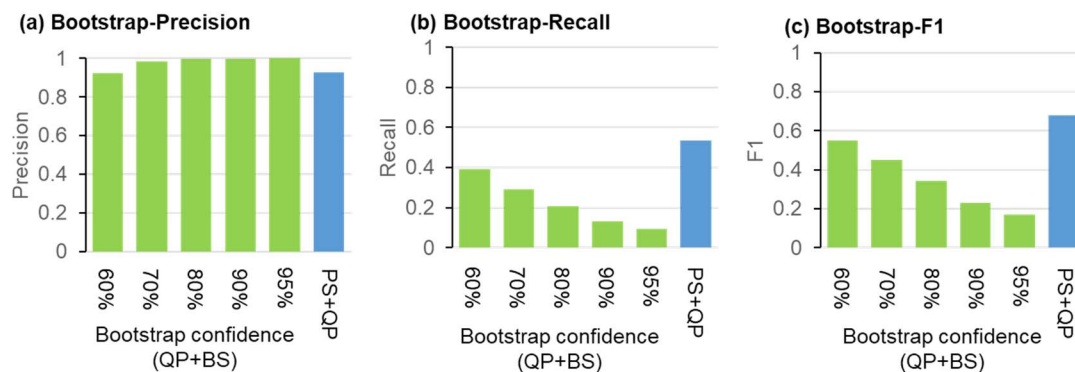


Figure S4: Comparison between *PhyloSignare* and bootstrapping approaches. (a) Precision, (b) recall, and (c) F1 score for all the signatures across all datasets for the bootstrap approach with QP [QP+BS] and QP coupled with *PhyloSignare* (PS+QP). For the bootstrapping approach, signatures that were detected with 60%, 70%, 80%, 90%, and 95% bootstrap confidence are shown. Signatures were pooled across all datasets in the computation.

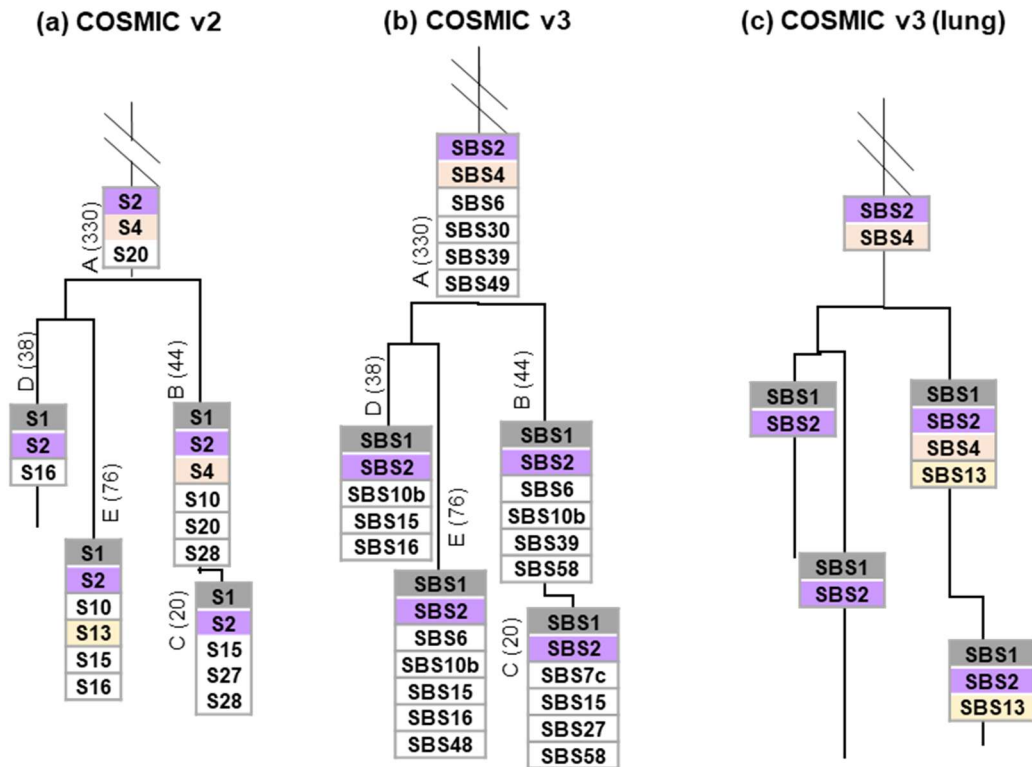


Figure S5. *PhyloSignare* inferences on CRUK0025 patient data. The mutational signatures identified for different branches (A – F) are shown. The number in the parentheses is the variant count for each branch. QP was coupled with *PhyloSignare*. (a) All COSMIC v2 signatures were used. (b) All COSMIC v3 signatures were used. (c) COSMIC v3 signatures that are known to be found in lung cancer were used. Detected signatures that are not expected for lung cancer are shown within white boxes.