Supplementary Tables (Excel files)

Supplementary Table 1. Clinical characteristics of individual tumors from each patient. Tumors and normal samples are listed, with the normal tissues listed next to the matched resected tumor. Tumor size represents the greatest dimension.

Supplementary Table 2. Whole Exome Sequencing results for multiple primary lung cancers. For each patient, the cancer cell fraction (ccf) of any mutation that was found in at least one sample is reported for every sample.

Supplementary Table 3. Summary of WES and poly-G data. For each tumor across individual patients, the number of shared and total mutations identified by WES is noted, along with the fraction of cell divisions shared according to the poly-G data analysis.

Supplementary Figure legends:

Supplementary Figure 1.

a, Schematics of the relative location of all normal samples and corresponding tumors in our cohort. **b,** Schematic of the tumor locations in patient III-4. **c,** Lineage tracing of patient III-4 with a known germline *T790M-EGFR* mutation, identified by Whole Exome Sequencing. The germline *EGFR* mutation found in normal lung tissue is denoted at the top of the tree. Numbers on branches are mutations that accumulated between two nodes, with known cancer-associated *EGFR* mutations highlighted next to the branch.

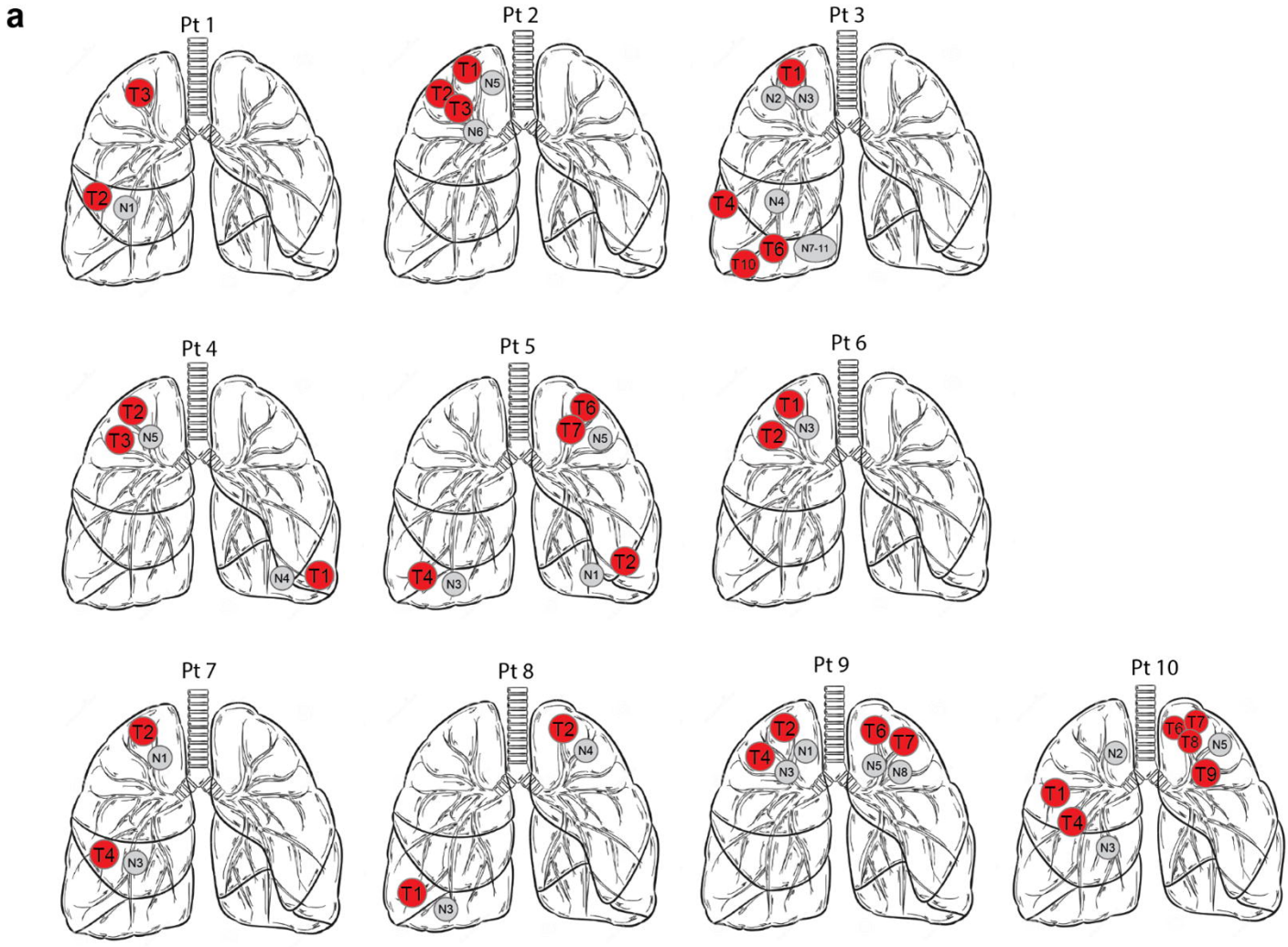
Supplementary Figure 2.

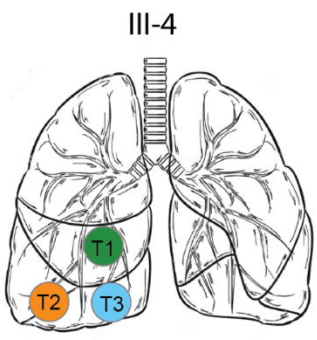
a, IGV tracks for the patients harboring germline variants, showing the germline *EGFR* mutations in the normal samples as well as tumors. Patient 4 also shows *EGFR G873E* on same read as *L858R* in the tumor samples, indicating that the two mutations are *in cis*. **b,** Phylogenetic tree from patient 6, with a germline variant identified by WES. The germline *EGFR* mutation that is shared among tumors from the same individual is shown in magenta. Numbers on branches are mutations that accumulated between two nodes. **c,** Phylogenetic tree from patient predicted to be independent by WES. As observed in patients with a germline *EGFR* mutation, there is no intersection between the branches, but unlike these patients, there is no germline mutation shown in magenta.

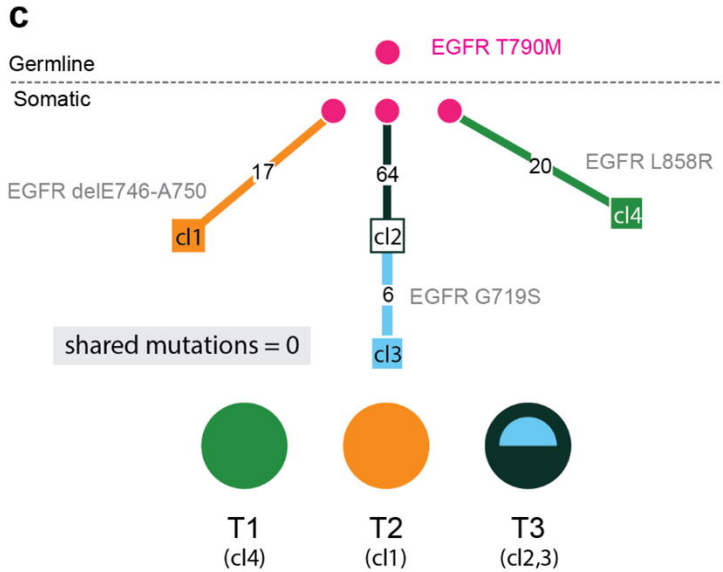
Supplementary Figure 3.

a-b,d-e Quantification of ten replicates of Figure 2d-e, g-h. EGFR autophosphorylation at Y845 was normalized to vinculin loading control, then phosphorylation was normalized to total EGFR expression in that sample, and finally normalized to the average signal within an experiment for comparison across experiments. AKT phosphorylation at S473 was normalized to vinculin loading control, and then to the average signal within an experiment. Error bars are SEM. False Discovery Rate q-values were corrected for multiple comparisons by the Benjamini, Krieger and Yekutieli procedure. * $q<0.05$ **c,** Representative images of a soft agar colony formation assay corresponding to Figure 2f.

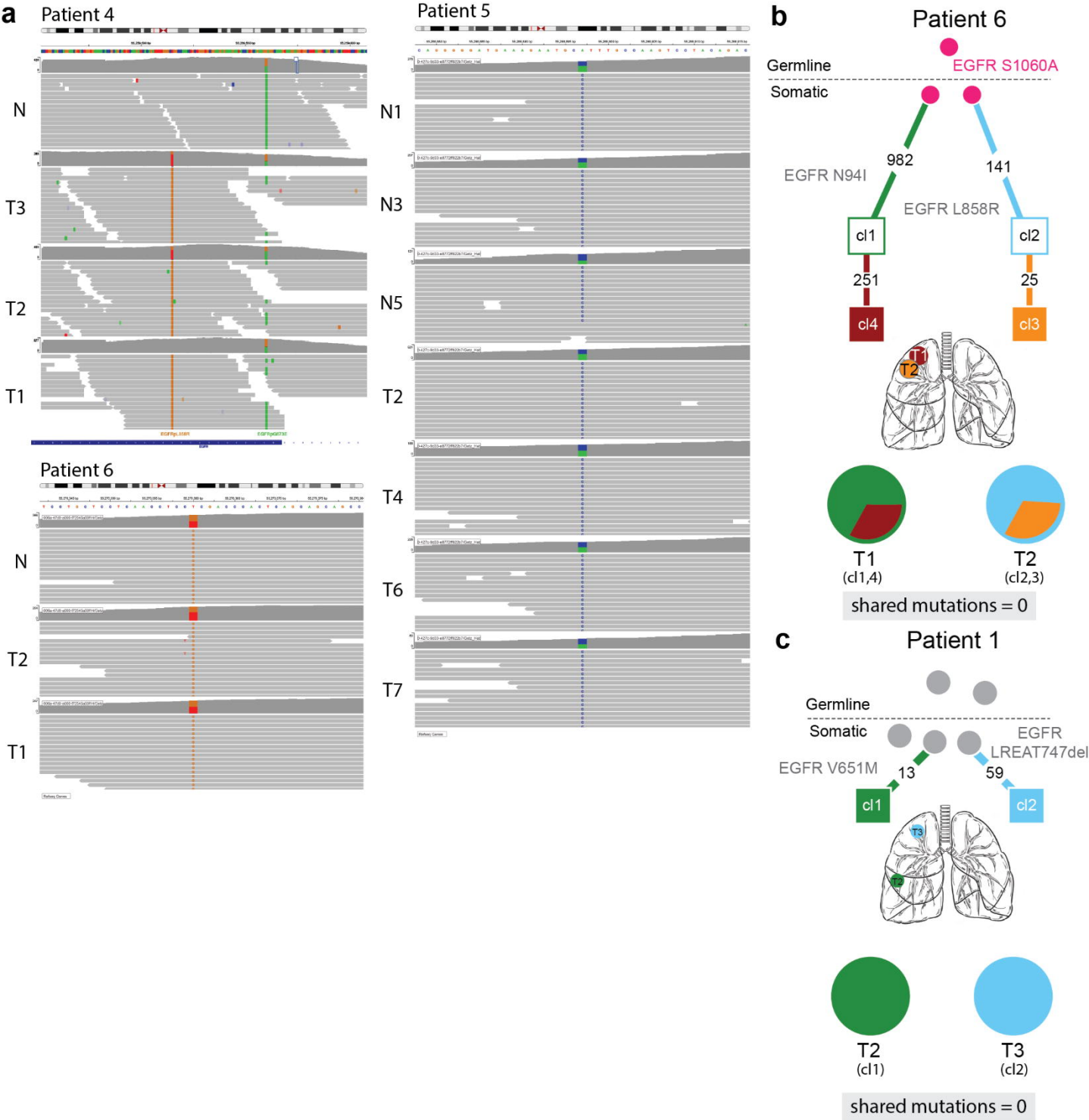
Supplementary Figure 1







Supplementary Figure 2



Supplementary Figure 3