



**Supplementary Figure 7:** Illustration of branching model used in our manuscript (A) and alternative model in which a lineage descended from the most recent common ancestor (MRCA) of the initial sample is selected by therapy to be progenitor of the recurrent sample (“selection model”) (B). Shaded blue/red region represents tumor growth, branches represent ancestry of individual cells sampled at the two time points, and yellow loops are drawn around the cells sampled. Though we use bulk sequencing data, this diagram shows individual cellular lineages to illustrate possible relationships. The two models differ in the mutational patterns (see Methods, “Evolutionary Model”) than can be achieved with a single mutational event. Specifically, only the branching model allows a mutation to be clonal in the initial sample and absent from the recurrence, while only the selection model allows a mutation to be subclonal in the initial sample and clonal in the recurrence. (C) Scatterplot/histogram of mutational patterns that distinguish the two models. Each point represents a single patient (red: hypermutated relapse; blue: non-hypermutated relapse). The x-axis gives the number of mutations that follow a single-event pattern unique to the selection model, and the y-axis gives the number that follow a single-event pattern unique to the branching model. Most points lie along the y-axis, indicating that the branching model provides a better overall explanation of the cohort. (D) Correlation between mutation load and age of primary GBM WES-based on TCGA samples. (E) Distribution of estimated time before diagnosis when the initial and recurrent lineages diverged, in years (median and 95% credible interval for each patient).