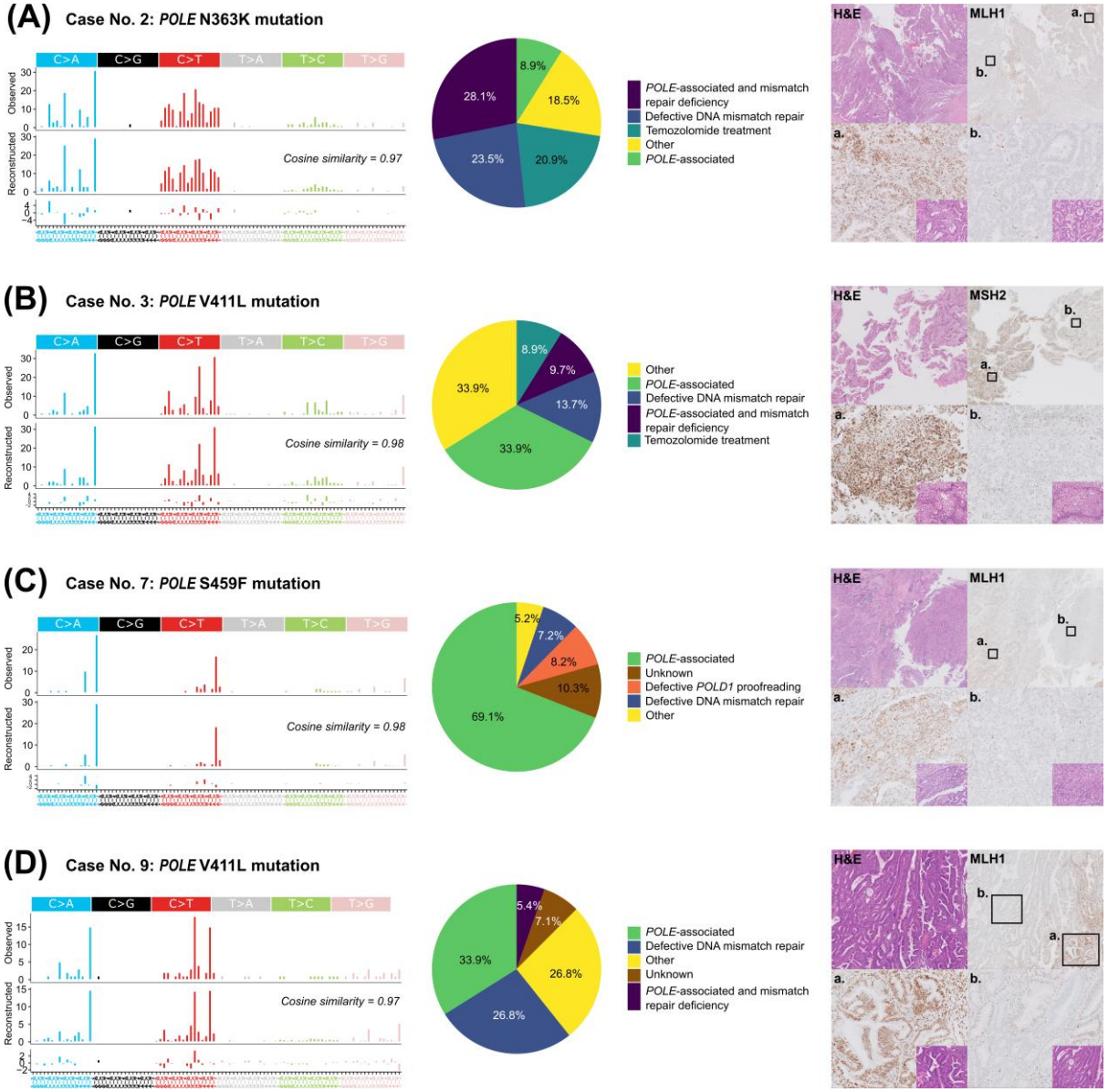


Supplementary Fig. S3. Mutational signature profiles in *POLE*-mutated tumors with subclonal mismatch repair protein loss. (A–D) For each case, the left panel displays the observed (top), reconstructed (middle), and residual difference (bottom) SBS spectra across 96 trinucleotide contexts, grouped by six substitution classes. Cosine similarity between the observed and reconstructed profiles is indicated. The pie charts show the relative contributions of the refitted COSMIC SBS signatures. The right panel shows representative H&E and MMR protein IHC images; inset (a) highlights an area of intact MMR protein expression, and inset (b) highlights an area of subclonal MMR protein loss. Etiologic labels reproduce the COSMIC-associated annotations of computationally attributed signatures and do not indicate documented clinical exposure in an individual patient. Cosine similarity quantifies reconstruction of the observed spectrum and does not by itself establish the biological accuracy of each attributed signature. SBS, single base substitution; COSMIC, Catalogue of Somatic Mutations in Cancer; H&E, hematoxylin and eosin; MMR, mismatch repair; IHC, immunohistochemistry.