

Supplementary Figure 1. Pan-TRK IHC in four cases identified as having NTRK fusions by OncoPanel analysis shows strong cytoplasmic staining confirming the presence of functional TRK fusion protein (40×). Top left image demonstrates the specificity of TRK staining, which is present only in neoplastic cells, whereas adjacent normal crypts are negative.

Supplementary Figure 2A. Two cases of *ALK* fusion in our cohort shared clinical and molecular features but differed in their microsatellite status. Both tumors were *APC* wild-type (wt) and contained biallelic *RNF43* frameshift (fs) mutations. B. Copy number variation by chromosome is color-coded for two *ALK* fusion-associated colon cancers in our cohort. *ALK*+MMR-D cancer (top) displays a diploid genome, whereas *ALK*+MSS cancer (bottom) displays frequent copy number gains and losses. *ALK* fusion breakpoints are shown in both profiles (arrow). The vertical axis is the ratio of the number of reads for each specimen and a panel of normals in log base 2 scale. A value of 0 denotes no difference from normal (diploid).

Supplementary Figure 3A. MMR-D RTK fusion CRC cases display a diploid genome similar to those in other MMR-D cases: *BRAF* V600E+mutated and Lynch syndrome. Copy number profile plots of RTK fusions or Wnt fusions with MSS CRC show extensive gains and losses and are shown for comparison. 3B. All MMR-D subgroups: *BRAF* V600E+, Lynch syndrome and RTK fusion show a significantly higher homopolymer indel rate (top) and TMB (bottom) than do MSS tumors with either RTK fusions or Wnt fusions.

Supplementary Figure. 4. Histologic analysis with hematoxylin and eosin *stained slides* for two patients with *NTRK1-LMNA* fusions. Morphological analysis shows: A. mucinous and B. medullary histology.