**Supplementary Figure 1. The patient enrollment process of the studied cohort.**

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**Supplementary Figure 2. Mutation plot of patients with unknown primary using somatic mutations detected in plasma samples.** Top mutated genes were shown. The gene alteration types were indicated by the color on the right.



**Supplementary Figure 3. The ratio of CUP, ESCC, lung cancer, colorectal cancer patients with different pathway gene alterations.** (A) the ratio of CUP, ESCC, lung cancer, colorectal cancer patients with TP53 and RTK-RAS pathway gene alterations.(B) the ratio of CUP, ESCC, lung cancer, colorectal cancer patients with HRR pathway gene alterations.WT: wild type; MUT: mutated ESCC: Esophageal squamous cell cancer. ns: not significant; \*\*\*: p˂0.001; \* p˂0.05. p value was calculated using Fisher’s exact test.

