

**Supplementary Fig. S1. A.** Representative image of a preparation from a cytological brushing with negative diagnosis for malignancy (Papanicolaou stain, 400x). This patient developed PDAC. B. Representative image of a preparation from a cytological brushing with positive diagnosis for malignancy (Romanowsky stain, 400x). This patient developed CCA.

**Supplementary Fig. S2. A.** Heatmaps showing the mutational profile of paired bile cfDNA and tissue DNA samples from patients with an initial diagnosis of benign stenosis that ended up developing malignancy analyzed with the Pan-Cancer and OCA panels, respectively. Initial diagnosis (Dx), Bilemut diagnosis and final diagnosis are indicated. Asterisks indicate specific mutations that are not included in the Pan-Cancer Panel. **B.** Heatmaps showing the mutational profile of paired bile cfDNA and tissue DNA samples from patients with an initial diagnosis of stenosis of indeterminate origin that ended up developing malignancy analyzed with the Pan-Cancer and OCA panels, respectively. Initial diagnosis (Dx), Bilemut diagnosis and final diagnosis are indicated. Asterisks indicate specific mutations that are not included in the Pan-Cancer Panel. **C.** Analysis of the concordance of mutations detected in the paired bile and tissue samples included in this study.