**KRAS negativity and a longer overall survival in hereditary and familial pancreatic cancer cases.**

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**Abstract.**

Approximately 10-15% of pancreatic ductal adenocarcinoma PDAC cases have a hereditary or familial background. We have previously shown that these cases harbor pathogenic germline mutations in previously described familial cancer genes. Due to the limited

availability of tumor tissue in PDAC, the liquid biopsy is an ideal surrogate to study somatic alterations.

This study aimed to analyze the use of cfDNA as a prognostic and predictive marker in PDAC, to analyze the somatic mutation profile and overall survival of familial or hereditary versus sporadic PDAC cases.

cfDNA was isolated from 1ml of plasma using the Maxwell kit (Promega) and KRAS was detected via BEAMing. the association of KRAS positivity and cfDNA concentration with and clinical variables was assessed using R.

Here we demonstrate for the first time via BEAMing that the majority of hereditary or familial PDAC cases (84%) are negative for a KRAS somatic mutation. Furthermore, we show that KRAS mutation negative cases harbor somatic mutations in potentially druggable genes such as KIT, PDGFR, MET, BRAF and PIK3CA that could be exploited in the clinic. Circulating free DNA (cfDNA) levels correlated with disease status, disease stage and overall survival and appears to be a viable prognostic biomarker in PDAC. Finally, familial or hereditary cases have a longer Overall Survival compared to sporadic cases (10.2 vs. 21.7 months, respectively). Currently, all PDAC patients are treated the same in the clinic with cytotoxic agents, although here we demonstrate that there are different somatic subtypes that could pave the way to personalized treatment.