



## Scientific Abstract

### SU2C-Dutch Cancer Society Colorectal Cancer Early Detection Dream Team: “Molecular Early Detection of Colorectal Cancer”



*[This abstract was provided by the scientists when their application was accepted.]*

**Background:** With over 1.2 million new cases and over 608,000 deaths annually, colorectal cancer (CRC) is the third most common cancer and the third highest cause of cancer death in the developed world. The most effective strategy to handle this problem is early detection of disease. Yet, surprisingly, most emphasis and budget in cancer research are devoted to new treatments of metastasized cancer.

**Aim of the project:** The MEDOCC project aims to improve the current stool assay for CRC screening, i.e. immunochemical fecal occult blood test (FIT) (work package 1 (WP1)) and improve the identification of high-risk stage II CRC patients who may benefit from systemic therapy by molecular detection and monitoring of residual disease (work package 2 (WP2)). To this end we will further develop, validate and evaluate diagnostic performance and cost-effectiveness of biomarkers already developed by our team members and translate these assays into clinical applications.

**Methods:** 1) While FIT can reduce CRC mortality by 30%, its performance can be improved as detecting hemoglobin in stool is not cancer specific and the current test still misses approximately 30% of carcinomas and 70% of pre-malignant lesions. In WP1 we will further develop four promoter CpG island methylation markers (*SFRP2*, *NDRG4*, *TFPI2* and *PHACTR3*) identified by team members into sensitive and specific nanotechnology based-assays for analysis of stool subsamples. In addition, we are in the process of validating and selecting the best performing protein biomarkers out of 134 candidates identified by in-depth proteomics (LC-MS/MS) analysis of stool samples from CRC cases, adenoma cases and controls. The best combination of DNA methylation and/or protein biomarkers will be evaluated against the gold standard FIT within the context of the Dutch CRC population screening program (cross-sectional screening trial with a paired design, n=10,000).

2) Identifying those stage II CRC patients at high risk of developing metastatic disease remains a challenge. MEDOCC dream team members have shown proof of principle for somatic mutations and personalized rearrangements as biomarkers of residual disease, and for methylation markers to identify high risk stage II CRC patients. In WP2 we will validate these findings in a prospective multicenter observational study (n=1,000) by analyzing circulating tumor DNA (liquid biopsies), employing sensitive technologies such as PARE (Personalized Analysis of Rearranged Ends), BEAMing, Digital Karyotyping and nanotechnology based-methylation assays and correlate these measurements with disease-free and overall survival.





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**Expected results:** The MEDOCC project will yield 1) a cost-effective biomarker test for stool-based population screening for CRC that is ready for implementation and 2) prospective clinical validation of the prognostic relevance of (circulating) tumor DNA in stage II CRC, ready for a subsequent biomarker driven intervention study.