HIGH BLOOD LEVELS OF TRANSCRIPTION FACTORS SIGNALING EPITHELIAL-TO-MESENCHYMAL TRANSITION (EMT-TFS) FOR THE DIAGNOSIS OF COLORECTAL (CRC) AND PANCREATIC (PC) CANCER

CHALLENGE
CRC is the second most frequent cause of cancer-related death worldwide. Different screening tests are available and effective in reducing CRC-specific mortality. Though direct detection of lesions by colonic inspection remains the gold standard tool of screening, its high invasiveness, cost and non-uniform benefits across different areas of the colon have paved the way to other approaches. Some options indirectly detect lesions by analysis of occult blood in the stool or by molecular screening of multiple DNA modifications released from neoplastic cells in the blood. Although the burden of CRC mortality has been reduced by CRC screening, the impact on cancer incidence ultimately depends on test sensitivity of pre-malignant lesions.

Pancreatic cancer is an uncommon but deadly disease with an yearly incidence of 12.4/100000 and surviving rate at 5 years of 7.7%. It is the only major cancer with a rising mortality rate making it to become the second leading cause of cancer-related deaths in the United States by 2030. Unfortunately no clinically useful test exists to identify early pancreatic cancer or high-grade pancreatic intraepithelial lesions. It is estimated that with early detection, survival rate can increase 6-fold. Hence, the need for noninvasive, discriminatory biomarkers for early PC detection is urgent.

THE TECHNOLOGY
It has been shown that cancer intravasation in humans is coupled with the epithelial to mesenchymal transition (EMT), a process driven by transcription factors (TFs) whose detection is therefore expected to provide diagnostic and prognostic clues.

We found that the amount of a panel of TFs-mRNA molecules connected to the EMT in the blood of cancer patients exceeds that measured in healthy subjects. Hence, we developed and IP protected a robust PCR-based molecular test measuring circulating levels of EMT-TFs mRNA to identify colorectal and pancreatic cancer patients and pre-cancerous advanced colonic lesions without the need to separate the circulating tumor cells from the pool of circulating blood mononuclear cells.

Our proof of concept and verification study (case-control, hospital based) included 250 CRC patients plus 50 patients with high-grade dysplasia adenoma, 221 control subjects (comprising 188 with clean colonoscopy and 43 with hyperplastic polyps), 140 patients with diminutive adenoma, and 50 patients with inflammatory bowel disease. A total of 50 patients with PC were also enrolled. Overall CRC patients including those with high-grade dysplasia adenoma were detected with 88% sensitivity and 70% specificity, while those with PC with sensitivity and specificity of 99% and 73%, respectively. For its span of applicability, the competitive values of its specificity and sensitivity and its operational simplicity, our method has the potential to become the in-vitro screening test for early, non-invasive detection of both CRC and PC.

FIGURE: ROC curves for the diagnosis of HGD, CRC and of PC by the leading EMT marker TWIST1. Diagnostic improvements due to additional EMT-TF mRNA signatures are not shown.
APPLICABILITY/FIELDS OF APPLICATION
Our PCR-based method is a new, highly performant in-vitro blood test for the early detection of advanced precancerous colonic lesions, and for CRC and PC diagnosis. Our invention has therefore the potential to become a widely used, non-invasive, inexpensive method for CRC and PC opportunistic screening, for the early diagnosis of both tumors and has possible application as a prognostication tool.
Indeed, the availability of the highly sensitive and specific EMT-TFs panel for early diagnosis of these two cancers would have a significant impact on health systems in terms of cost-effectiveness.

COMMERCIAL OPPORTUNITY
EMT-TFs panel is likely to become a simple technology for liquid biopsy aimed at CRC and PC diagnosis. We therefore seek a commercial partner interested in developing our promising test, under a license, co-development agreement or creation of a spin-off company.

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PATENT SITUATION
The technology is covered by a granted European patent (EP2883962) and an international application WO2015091575 in the regional phase.

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