

Medical Rationale

Colorectal cancer (CRC) affects approximately 6% of the population and is the second leading cause of cancer related death in the United States and in Europe (5,6). CRC is the third most common cancer diagnosed in men and women. In the US, approximately 150,000 men and women are estimated to be diagnosed with CRC and approximately 50,000 will die from CRC in 2008. Costs for direct medical treatment of CRC in the US have been estimated to amount to \$8.3 billion in 2007. Survival is markedly better when CRC is diagnosed in early stages: Five-year survival is 90% when CRC is still localized (i.e. stage I/II), 68% for regional disease (i. e. stage III), and only 10% when distant metastases are detected (i. e. stage IV) (6). Given today's treatment options for CRC, patient outcomes could potentially be greatly improved if more cancers were detected in early stages. Several studies have demonstrated a reduction of mortality associated with early detection of disease through CRC screening. For example, it has been demonstrated that biennial FOBT decreases CRC mortality by 14% (7). However, less than 50% of the screening population has recently been tested using any of the recommended screening options. (8). Given the mortality reduction associated with early detection of disease, there is now general agreement that average-risk adults aged 50 and older should be screened for CRC.

Current CRC screening guidelines include FOBT, flexible sigmoidoscopy (alone or with FOBT), double contrast barium enema, or colonoscopy (9). Recently, a stool DNA test based on known DNA alterations in the sequence of events leading to colorectal carcinogenesis has been included in the guidelines. Non-invasive screening is mostly conducted using FOBT, which while inexpensive, exhibits a low compliance rate (around 12% in the US) due to its use restrictions, perceived inconvenience and lack of consumer acceptance. The gold standard procedure for CRC detection is colonoscopy; it exhibits excellent performance characteristics, but has a limited utility as a first line screen due to its high cost, healthcare delivery resource limitations, and inadequate patient acceptance. From public health as well as health economics perspectives, the poor adoption of current screening options limits the effectiveness of CRC screening initiatives; as stated by Sidney Winawer, MD, "the best test is the one that gets done" (10). It is believed that a blood based, first-line screening assay capable of detecting individuals with CRC colorectal disease, confirmed by colonoscopy, would have greater utility for population screening. Such a blood-based test for CRC screening is not yet available.

The *m*SEPT9 biomarker is proposed to be useful as a test to indicate the presence of CRC. The test would be provided in the form a simple blood draw as part of a routine physical exam thereby improving access to screening for the general population. The *m*SEPT9 assay has been optimized for cancer detection as a first product in Epigenomics' pipeline of CRC screening and diagnostic products, reflecting that CRC detection is

the primary target of the test.