

OMED Colorectal Cancer Screening Committee Meeting

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Title: Epigenetic Markers and FIT

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Noninvasive screening techniques to detect early stage colorectal cancer (CRC) and precursor lesions target exfoliated molecular markers specific to the carcinogenesis pathways and phenotypic markers, like hemoglobin, which are not pathway specific. To date, the performance of these pathway and non-pathway associated approaches have been compared^{1,2} using optical colonoscopy as the reference method. With the discovery of CRC associated epigenetic and mutation markers that are commonly found in advanced adenomas (AA) and CRC, multiple panels of high specificity markers are being studied for colorectal neoplasm detection in tissue and stool specimens. Adding FIT, similarly driven to high specificity and incorporated into the same stool sample collection process for additive detection of CRC, potentially broadens the coverage of a multi-target stool test panel at a small decrement to specificity and small increase in cost.

Quantitative types of FIT, which can be analyzed in central laboratories using automated equipment for consistency and that have regulatory approval for single stool testing, are appealing for use with stool DNA (sDNA) testing. Earlier work examining the low sensitivity but commonly used gFOBT, Hemoccult, showed no additive benefit to sDNA testing alone.¹ However, subsequent work looking at the high sensitivity gFOBT, HemoccultSensa, which is equivalent to some FIT tests, did show additive detection of CRC to an older sDNA test multi target panel² (+16%), but minimal additive detection of AA (+7%). Combined specificity decreased to 80% (-4%). Most recently, an sDNA test using Vimentin and BRAF together identified 71% of sessile serrated adenomas (specificity 90%) while HOSensa found 7% at 95% specificity and was not additive to Vimentin+BRAF.³

Current work by Exact Sciences with sequencing of methylated marker candidates on tissue DNA extracted from CRC, AA, and normal epithelia has demonstrated that several marker combinations are complementary and provide coverage of nearly 100% of CRC and adenomas with preserved high specificity. The combination of two such markers, for example, Vimentin and BMP3, can be driven to 100% specificity and still yield high sensitivity in tissue samples for CRC (82%) and AA (95%) detection. While stool performance of optimal marker combinations awaits testing, the incorporation of a single FIT set at 98-100% specificity appears promising and may add 5-10% to CRC detection to such a multi target panel. This may be especially so for later stage CRC, which may lose expression of some hypermethylated markers. No improvement of AA detection is anticipated.

This is ongoing work and Exact's final multi-target panel may include two or more of epigenetic markers, k-ras mutations and FIT all driven to very high specificity. Exact's test will be examined in average risk patients in a multi-site, point-in-time, cross-sectional blinded pivotal screening study. The study will compare Exact's test with a separate standard single event FIT performed on the same stool sample and analyzed according to manufacturer's instructions. Optical colonoscopy on all subjects will be the reference method. The study provides a unique opportunity to prospectively assess the screening performance of optimized sDNA and FIT testing alone and in combination; it will begin in early 2011.

1. Imperiale et al, NEJM 2004; 351:2704-14 2. Ahlquist et al, AIM 2008; 149:441-50. 3. Ahlquist et al, DDW, New Orleans, 2010.