New noninvasive test for colorectal cancer shows promise

October 16 2012

A new noninvasive test for colorectal cancer screening demonstrated high sensitivity for detecting colorectal cancer, in particular precancers that are most likely to develop into cancer, according to data presented at the 11th Annual AACR International Conference on Frontiers in Cancer Prevention Research, held here Oct. 16-19, 2012.

"This test measures different kinds of DNA changes, known as methylation and mutation, along with a measure of fecal blood. By combining these measures, we can look for the kinds of biological changes that are most frequently found in precancers and cancers in the colon," said Graham P. Lidgard, Ph.D., senior vice president of research and development and chief science officer at Exact Sciences, which developed the test and sponsored the study.

Lidgard and colleagues analyzed 1,003 patient samples from 36 study sites and developed an analytic algorithm for the novel, automated stool DNA-based test platform, which generated a positive or negative result for each patient. The specimens were collected either before colonoscopy bowel preparation in screening and surveillance patients or at least seven days post-colonoscopy from patients with colorectal cancer and large precancers.

The control group included 796 patients with negative colonoscopies or small polyps (less than 1 cm), and the case group included 207 patients with confirmed colorectal cancer or precancers.

"By analyzing samples with confirmed diagnoses from colonoscopy, we were able to build an analytic algorithm that combines our 11 stool-based biomarkers into a single result," Lidgard said. "Through this study, we were able to demonstrate a high detection rate for both cancers and precancers using our automated analytic platform and algorithm."

The researchers reported that the test detected 98 percent of all cancers as well as 83 percent of precursors with high-grade dysplasia and 57 percent of precursors 1 cm or larger overall, at 90 percent nominal specificity.

"We are encouraged by the results of this study for detecting cancer and cancer precursors, especially the precursor lesions with high-grade dysplasia, an abnormality broadly recognized as being associated with a higher risk for progression to cancer itself," Lidgard said. "Current screening tests using only fecal occult blood are biologically limited in their ability to detect precursors to colorectal cancer."

Exact Sciences is involved in a large colorectal cancer screening study collecting samples from more than 10,000 patients prior to screening colonoscopy. The company plans to apply for FDA approval after completing the study.

More information:

Abstract:

B12 An optimized molecular stool test for colorectal cancer screening: Evaluation of an automated analytic platform and logistic algorithm.
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We have demonstrated that colorectal cancer (CRC) and advanced pre-cancers can be detected non-invasively by a manual multi-target stool DNA-based test (sDNA-MT) comprising exfoliated DNA markers (methylated BMP3 and NDRG4, mutant KRAS (7 mutations, codons 12, 13), plus β-actin) and fecal hemoglobin (Hb) (Lidgard, Gastroenterology 2012;142(5);S-770). We now report the clinical performance of this sDNA-MT test using an optimized automated analytic platform and logistic algorithm. This platform could facilitate the routine performance of sDNA-MT for CRC screening by molecular diagnostics capable clinical laboratories.

Method: Stool samples were collected from 1003 subjects at 36 study sites after informed consent and prior to colonoscopy bowel preparation from those presenting for average risk CRC screening (283) or surveillance (176) at 2 sites. From referred subjects with CRC, Advanced Adenoma (AA) or Sessile Serrate Adenoma ≥ 1 cm, (SSA) stool was collected at least 7 days post-colonoscopy and prior to surgery or chemo-radiation (135; 21 sites) and similarly for subjects with no neoplastic findings on colonoscopy (Neg) (409; 13 sites). The study population included: cases (207), 58% male, median age 65 yrs. (38-87), CRC (93), AA (84), SSA ≥ 1 cm (30) and controls (796), 42% male, median age 65 yrs. (50-84), Neg (641) and non-advanced adenomas (NA) (155).

Stool sample collection and DNA isolation were previously described. Automated methylation, mutation and actin assays were performed with a Hamilton STARlet fluid handler (Hamilton Robotics, Reno NV), and QuARTS (Quantitative Allele-specific Real-time Target and Signal amplification) run on an ABI 7500 FastDx real time thermal cycler (Applied Biosystems, Foster City, CA). Fecal Hb (ng/ml buffer) analysis

was performed by automated sandwich ELISA. A "Positive" or "Negative" result was determined with an algorithm that included the methylation and mutation results and a logistic regression score, which combines DNA marker results with Hb and actin results. Algorithm results exceeding a threshold were called "Positive". The algorithm provided good discriminative ability, stability, sensitivity and specificity. Robustness was tested with computer simulations and statistical techniques (leave-one-out and 10-fold cross validation).

Results: At a 90% nominal specificity, sDNA-MT sensitivity was 98% for CRC (91/93) [Stage: I , 95% (20/21), II, 100% (23/23), III 96% (26/27), IV 100% (7/7) and I-III combined 97% (69/71)], 57% (65/114) for precursors ≥1 cm (AA, SSA) , and 86% (12/14) for precursors with high grade dysplasia. CRC patients were typically referred to colonoscopy for symptoms and test sensitivity may be elevated relative to that seen with screening.

Conclusion: With this study using a novel automated sDNA-MT analytic platform with logistic algorithm, we corroborate our earlier findings using a manual process and demonstrate a platform that allows testing to be performed routinely by molecular diagnostic capable laboratories. The high sensitivity of sDNA-MT for CRC across all stages and for advanced precursors with high-grade dysplasia could lead to improved non-invasive CRC screening performance with wide accessibility to patients. A large multi-site pivotal CRC screening study (DeeP-C study clinicaltrials.gov, NCT01397747) to support such use is underway.

Provided by American Association for Cancer Research