

## Gene Signatures May Help in Colon Cancer Stage II Treatment Decision



By Larry Hand | October 28, 2015

NEW YORK (Reuters Health) - Researchers in Canada and China have developed eight cancer hallmark-based gene signature sets (CSS sets) that may help to decide if patients with stage II colorectal cancer (CRC) should be treated with adjuvant chemotherapy after surgery.

"The most important question for stage II colon cancer is if the patients should be treated or not. This question has been debated more than 20 years," said Dr. Edwin Wang, of the National Research Council Canada and McGill University, Montreal, Quebec.

"These results give a clear answer to this question: a small fraction of the patients are high-risk patients who do need adjuvant treatment. The cancer hallmark-based gene signature assay is able to identify these high-risk patients who do gain survival benefit with (fluorouracil)-based adjuvant chemotherapy," he told Reuters Health by email.

Dr. Wang and colleagues analyzed 13 public microarray datasets with more than 1,000 stage II CRC samples. They applied their previously developed Multiple Survival Screening (MSS, here: <http://bit.ly/1R0YfeR>) algorithm to identify predictive gene signatures, focusing on genes associated with cancer hallmarks, such as evasion of growth suppressors, resistance of cell death, and metastasis.

They randomly selected one of the cohorts to run MSS and perform a survival test and group survival-specific genes based on cancer hallmark-associated Gene Ontology (GO) terms, including cell cycle and apoptosis. They focused on 60-100 modulated genes between recurred and nonrecurred samples to develop a cancer hallmark GO-defined gene group. They generated 1 million random gene sets of 30 genes each.

From that, they collected 1,000-5,000 random gene sets that could distinguish low-risk and high-risk groups "across more than 90% of the 36 random data sets for a cancer hallmark GO-defined gene group ( $p < 0.005$ )." They then used MSS to find gene signatures.

They identified eight cancer hallmark gene signatures and tested them in the 12 other cohorts and found that the signatures predicted prognosis but not adjuvant treatment benefits.

The researchers then built CSS sets from the originally tested cohort and another cohort and found that for predicting low risk, they obtained best results when four of the eight signatures had consensus. For predicting high risk, they obtained best results when all eight signatures agreed.

After testing the CSS sets in 767 samples from the other 11 cohorts, they found, "The CSS sets assigned 60%, 28%, and 12%, respectively, of all the stage II disease into low-, intermediate-, and high-risk groups, with 5-year relapse-free survival rates of 94%, 78%, and 45%, respectively ( $p = 0.02$  to  $p < 0.001$ ). . . . We also significantly increased the prediction accuracy for high-risk samples to 55%."

The 94% rate for low-risk prediction is higher than those from two commercially available assays, Oncotype DX (87%) and ColoPrint (88%), and the 55% rate for high-risk prediction is also higher than Oncotype DX (22%) and ColoPrint (22-26%), the researchers write.

"The cancer hallmark-based gene signature assay has been successfully validated in 11 independent patient

cohorts, suggesting that the signatures are stable and clinically useful. It is rare that gene signatures have been validated in so many independent patient cohorts in the past," Dr. Wang said.

"The cancer hallmark-based gene signature assay helps in determining which patients are low- or high-risk. Clinicians will be confident that the predicted low-risk patients should not be given adjuvant chemotherapy. Roughly 60% of the patients predicted to be low-risk will be able to avoid over-treatment, which is a serious problem in clinics," he added.

"In particular, if clinicians apply (fluorouracil)-based adjuvant treatment, we showed that the predicted high-risk patients significantly gained survival benefit (tumor recurrence reduced for 30-40% for five years)," he said.

Gene-expression profiling has matured, he added, and technology is widely available.

Dr. Greg Yothers, of the University of Pittsburgh and NRG Oncology, Pittsburgh, Pennsylvania, and colleagues write in an accompanying editorial, "The novel approach of using combinations of gene ontology term-associated signatures has great promise for use in other cancer disease sites and potentially for other diseases with genetic association. This scientific contribution is important even if the present stage II colon cancer results are never widely adopted in the clinic."

He and his colleagues pointed out, however, that neither the new study nor three clinical trials on the other two assays evaluated any chemotherapy containing oxaliplatin, which "a significant portion of patients with stage II colon cancer" received in the U.S. That may point to a need for a clinical trial of oxaliplatin, he and his colleagues write.

Comparing the newly identified signatures with Oncotype DX and ColoPrint may not be fair because of the different methodologies used to derive the assays, they say.

Dr. Yothers told Reuters Health by email that the newly identified signatures might be adaptable in the clinic "after a Clinical Laboratory Improvement Amendments (CLIA) approved assay is developed and validated."

He added, however, "The technology is available, but I'm not sure the financial incentive exists for any party to follow through and make the assay widely available."

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