

INFORMATION FOR HEALTHCARE PROFESSIONALS

DO YOU TREAT NODE NEGATIVE CRC PATIENTS?

As a healthcare professional that diagnoses, operates on and/or treats colorectal cancer patients, you know that node-negative patients often pose a clinical dilemma. With up to 30% of them experiencing disease recurrence, what do you do? Do you treat them? Which ones? The new Previstage™ GCC Colorectal Cancer Staging Test may help you make more confident decisions for those patients. The test detects in the lymph nodes removed during the CRC surgery the expression or absence of expression of guanylyl cyclase C (GCC or GUCY2C) mRNA, a cellular marker that is expressed in colorectal cells, both normal and cancerous, but never in normal tissue in other parts of the body.

THE CLINICAL DILEMMA OF NODE NEGATIVE CRC PATIENTS

The current method of staging colorectal cancer consists of examining, using a microscope, very small sections of lymph nodes, surgically removed from patients. This histopathological method can detect one cancer cell in 200 normal cells, and is limited to analyzing a small percent of the available tissue (as little as 0.1%), which can lead to missed metastases. With this traditional method, up to 30% of patients thought to have disease confined to the colon return with recurrent disease, presumably through occult metastases not reported due to lymph node understaging.

ASCO does not recommend routine adjuvant chemotherapy (CT) for patients with stage II CRC, but it may be considered for “high-risk” cases. The NCCN guidelines recommend to consider adjuvant CT for “low risk” T3/N0/M0, and to treat “high risk” T3/N0/M0 and all T4/N0/M0. How do you use these guidelines? Which node negative patients do you consider for treatment?

A NEW SOLUTION TO THE CLINICAL DILEMMA

The Previstage™ GCC Colorectal Cancer Staging Test is the first test that can molecularly assess the presence or absence of CRC metastases in the lymph nodes. Based on the detection and amplification of minute quantities of GCC mRNA, Previstage™ GCC employs a technology that has been shown to be up to 100,000 times more sensitive than microscopic methods, and provides physicians with a significantly more sensitive tool for staging patients with colorectal cancer.



In an educational session held during the 2009 Gastrointestinal Cancers Symposium (ASCO GI) on *Molecular Markers and Prognosis of Patients with Colorectal Cancer*, when a patient is found to have GCC positive lymph nodes, it was suggested that he or she could be considered as a stage III patient.

PUBLICATIONS AND STUDIES SUPPORTING THE GCC PROGNOSTIC VALUE

Dr. Scott Waldman, at the Thomas Jefferson University, first identified in the early 1990's the potential clinical value of the guanylyl cyclase C (“GCC”) gene expression in staging colorectal cancer. GCC is a transmembrane receptor protein found exclusively in cells lining the intestine from the duodenum to the rectum. It is involved in multiple functions including water transport, crypt morphology and suppression of tumorigenesis. It is expressed in colorectal cells, both normal and cancerous, but not in normal cells outside the intestine. In early research, GCC mRNA has shown to be highly accurate in detecting the spread and recurrence of colorectal cancer, respectively in lymph nodes and blood, thereby representing a significant improvement over traditional detection methods. To date, over 50 peer-reviewed journal articles have been published on the relationship between GCC mRNA and colorectal cancer. A selected list of these can be found on DiagnoCure’s website at www.diagnocurelabs.com.

The U.S. National Institutes of Health provided grants totaling over \$10 million to Dr. Waldman for two prospective 5-year multicenter studies on GCC mRNA in CRC. The first study was performed with over 400 enrolled patients from 9 different sites to identify the prognostic value of GCC. It was published in February 2009 in the *Journal of the American Medical Association* [Feb 18, 2009, Vol. 301, No. 7] by researchers at Thomas Jefferson University. The study strongly supports the clinical utility of identifying GCC mRNA in the lymph nodes to more accurately predict risk of disease recurrence in node negative CRC patients. In a group of 257 CRC stage I and II patients, when GCC was considered independently from other factors such as T4, patients whose nodes were GCC positive were 4.7 times more likely to develop disease recurrence than those whose nodes were GCC negative, and 3.3 times more likely to die within three years. In fact, patients with GCC positive nodes had a risk of recurrence and survival rate comparable to that of stage III patients.

PREVISTAGE™ GCC IS AVAILABLE FROM DIAGNOCURE ONCOLOGY LABORATORIES

DiagnoCure owns the exclusive worldwide diagnostic rights to the GCC marker. In 2008, DiagnoCure completed the development of a GCC colorectal cancer staging test and in late summer 2008, the Company launched its new laboratory-developed Previstage™ GCC Colorectal Cancer Staging Test. The test is performed by DiagnoCure Oncology Laboratories, a CLIA-certified service laboratory located in West Chester, Pennsylvania.

Dr. Waldman's study is an important validation of the clinical use of the GCC marker for the identification of patients who have metastatic colorectal cancer and for predicting risk of disease recurrence. DiagnoCure's Previstage™ GCC Colorectal Cancer Staging test was developed to detect the same marker as evaluated in the study. The Previstage™ GCC test, however, uses all of the advances in technologies and methodologies that have emerged since the study was first initiated.

Previstage™ GCC is calibrated against histopathology positive lymph nodes of stage III patients to establish the cut-off that distinguishes GCC positive patients (cancer cells detected) from GCC negative patients (no cancer cells detected). The validation of DiagnoCure's test resulted in 22% of pN0 patients to be GCC positive. In comparison, the GCC testing used in Dr. Waldman's study was calibrated to maximize the Negative Predictive Value in terms of recurrence, which means a lower cut-off was used to distinguish between GCC positive and GCC negative patients, resulting in 87.5% of pN0 patients to be GCC positive.

Using qRT-PCR technology, Previstage™ GCC is performed on the lymph nodes that have been embedded in paraffin by your hospital pathologist. Normally, only half of each lymph node that was removed during the surgery (12 nodes minimum) is necessary to perform the test. The other half is sent back to your pathologist. Standard turn-around time is seven business days. The patient report indicates the numbers of GCC positive lymph nodes, negative lymph nodes and uninterpretable lymph nodes.

Previstage™ GCC is a laboratory-developed test, and it was determined to have an analytical sensitivity of 92% and analytical specificity of 98%.

PATIENT ASSISTANCE PROGRAM

DiagnoCure Patient Billing is a free service that works with the patient and the insurance carrier to determine coverage availability for the Previstage™ GCC Colorectal Cancer Staging Test.

From the request for the Previstage™ GCC Colorectal Cancer Staging Test to the resolution of the claim, a DiagnoCure Patient Billing representative is available to assist the patient through this process. Since DiagnoCure wants to make sure that every patient who can benefit from the Previstage™ GCC Colorectal Cancer Staging Test can have access to it, a patient may also be eligible for the Uninsured Patient Assistance Program.

TO LEARN MORE ABOUT PREVISTAGE™ GCC

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The Previstage™ GCC Colorectal Cancer Staging Test is a laboratory-developed test. It was developed and its characteristics were determined by DiagnoCure Oncology Laboratories, which is certified under U.S. CLIA regulations as a high-complexity laboratory.