



May 16, 2014

To: submissions@nccn.org

Re: Submission Request – Colon Cancer

Submitted by:

Name: Amy P. Sing, MD, Senior Director, Medical Affairs

Company: Genomic Health Inc. (a CLIA-certified laboratory)

Address: 301 Penobscot Drive, Redwood City CA 94063

Phone: (650) 569-2035

E-mail: asing@genomichealth.com

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NCCN Guidelines Panel: Colon/Rectal/Anal Cancers- June 9, 2014

On behalf of Genomic Health Inc., I respectfully request the **NCCN Colon/Rectal/Anal Cancers Panel** to review the enclosed data for inclusion of the **Oncotype DX[®] Colon Cancer Assay** in the postsurgical recurrence risk assessment of patients with mismatch repair proficient (MMR-P) T3N0M0 stage II colon cancer.

Specific Changes: Recommend the Oncotype DX Colon Cancer Assay as a component of the postsurgical T3N0M0 MMR-P stage II colon cancer recurrence risk assessment in COL-D as an additional bullet (Proposed bullet: The panel recommends that Oncotype DX Colon Cancer assay be considered for all patients with T3 MMR-P stage II colon cancer to better inform the individualized adjuvant treatment discussion).

FDA Clearance: FDA clearance is not required for this assay because the assay is performed in the central laboratory at Genomic Health that is regulated and certified under the Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists (CAP).

Rationale: Inclusion of this assay (analytically and clinically validated in over 3,000 patients¹⁻⁶) in the treatment decision algorithm for patients with T3N0M0 MMR-P stage II colon cancer will reduce variability of recurrence risk assessment, offer an independent quantitative risk estimate that will lead to a more informed, individualized discussion and treatment decision for the patient, and increase confidence of physicians and patients by incorporating individualized estimates of recurrence risk and expected absolute treatment benefit.

The following articles are submitted in support of this proposed change.

Analytical validation studies:

1. Clark-Langone KM, Wu JY, Sangli C, et al. Biomarker discovery for colon cancer using a 761 gene RT-PCR assay. *BMC Genomics*. 2007;8:279-97.
2. O'Connell MJ, Lavery I, Yothers G, et al. Relationship between tumor gene expression and recurrence in four independent studies of stage II/III colon cancer patients treated with surgery alone and surgery plus adjuvant fluorouracil plus leucovorin. *J Clin Oncol*. 2010;28(25):3937-44.
3. Clark-Langone et al. Translating tumor biology into personalized treatment planning: analytical performance characteristics of the Oncotype DX[®] Colon Cancer Assay. *BMC Cancer*. 2010, 10:691.

Clinical validation studies:

4. Gray, R. et al. Validation study of a quantitative multi-gene RT-PCR assay as a predictor of recurrence in stage II colon cancer patients. *J Clin Oncol*. 2011; 29(35):4611-9.
5. Venook, A et al. Biologic Determinants of Tumor Recurrence in Stage II Colon Cancer: Validation Study of the 12-Gene Recurrence Score in Cancer and Leukemia Group B (CALGB) 9581. *J Clin Oncol*. 2013; 31(10):1775-81.
6. Yothers, G et al. Validation of the 12-gene colon cancer Recurrence Score in NSABP C-07 as a predictor of recurrence in stage II and III colon cancer patients treated with 5-FU/LV and 5-FU/LV+oxaliplatin. *J Clin Oncol* 2013;31(36):4512-9.

Clinical utility studies:

7. Hornberger J, Lyman GH, Chien R, Meropol NJ. A multigene prognostic assay for selection of adjuvant chemotherapy in patients with t3, stage II colon cancer: impact on quality-adjusted life expectancy and costs. *Value Health*. 2012 Dec;15(8):1014-21.
8. Cartwright T, Chao C, Lee M, Lopatin M, Bentley T, Broder M, Chang E, Effect of the 12-Gene Colon Cancer Assay Results on Adjuvant Treatment Recommendations in Patients with Stage II Colon Cancer. *Current Medical Research & Opinion*. 2014; 30(2):321-8.
9. Brenner B, Lopatin M, Lee M, Geva R, Beny A, Dror Y, Steiner M, Hubert A, Idelevich E, Liebermann N. Impact of the 12-Gene Colon Cancer Recurrence Score[®] Assay on Clinical Decision-Making for Adjuvant Therapy in Stage II Colon Cancer Patients in Israel. Presented at: European Cancer Congress; September 2013; Amsterdam, Netherlands. Abstract #2382.
10. Srivastava G, Renfro LA, Behrens RJ et al. Prospective Multicenter Study of the Impact of Oncotype DX Colon Cancer Assay Results on Treatment Recommendations in Stage II Colon Cancer Patients. *The Oncologist*. 2014; 19 (5).

Sincerely,



Amy P. Sing, MD
Senior Director, Medical Affairs

Additional Information:

Clinical Utility: Since the 2011 NCCN Task Force publication the assay has demonstrated clinical utility to physicians, patients, society and payers in three clinical utility studies.

- Overall testing resulted in less frequent recommendations for both 5-FU and 5-FU + oxaliplatin chemotherapy which is in line with both the NCCN and ASCO guidelines recommendations
 - Three clinical utility studies have shown consistency regarding the assay's impact on physician's treatment recommendations. Treatment recommendations changed on average 35% of the time (29% - 45%).⁸⁻¹⁰
 - Consistency was also seen across the studies in the percentage of recommendations for increasing and decreasing treatment intensity.
 - The prospective MCCRC study showed the assay influenced treatment recommendations for the majority of physicians and increased confidence in their treatment recommendations.⁹
 - Physicians reported the assay provided additional clinically relevant information and they often decreased or increased their treatment intensity recommendations based on the assay.⁹
- Patient decisional conflict was significantly reduced reflecting less uncertainty and more clarity and satisfaction.
 - The majority of patients reported the Recurrence Score result influenced their treatment decision with intensity changes seen in both directions.
 - Patient's post-assay decisions showed improved alignment with their physician recommendation. Demonstrating better agreement between physician and patient on the course of treatment.
- From a societal view the prospective MCCRC study showed use of the 12 gene assay increases quality-adjusted survival and that it is cost-saving for patients with stage II, T3, MMR-P colon cancer.
- Similar to the *Oncotype DX Breast Cancer Assay*, health economic analyses suggest use of the test will potentially reduce overall cost by reducing chemotherapy use.⁷

In summary, *Oncotype DX* guided treatment decisions improve outcomes for patients and society. The consistent high rate of decision change likely reflects how the quantitative information provided by the Recurrence Score result is clinically meaningful to physicians and patients, and addresses lack of confidence in the conventional risk assessment utilizing clinical and pathologic characteristics.