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NCCN Guidelines Panel: Colon/Rectal/Anal Cancers

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 Recurrence Score® assay** in the postsurgical recurrence risk assessment of patients with mismatch repair proficient (MMR-P) T3N0M0 stage II colon cancer.

Specific Changes: Request that the Oncotype DX Colon Recurrence Score assay be included as a prognostic factor as part of the "pathological stage" (page COL-3), in a manner similar to MSI, MMR, and MSS, in the routine post-surgical work-up for patients diagnosed with stage II, T3, MMR-P colon cancer.

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 3,600 patients[1-7]) in the treatment decision algorithm for patients with T3N0M0 MMR-P stage II colon cancer will reduce variability of recurrence risk assessment and offer an independent quantitative risk estimate that will lead to a more informed, individualized discussion and treatment decision for each patient.

Since the time of the previous submission request in 2014, data from an additional clinical validation study were reported.[7] This study, conducted in patients with both stage II (n=247) and stage III (n=350), showed that the continuous Recurrence Score result was significantly associated with relapse-free interval after adjustment for disease stage ($p<0.001$), consistent with findings from prior studies.
Three clinical utility studies have demonstrated that testing results in less frequent recommendation for chemotherapy (both 5-FU and 5-FU + oxaliplatin),[8-10] in line with the NCCN and ASCO guideline recommendations. On average, treatment recommendations change 35% (range 29%-45%) of the time with use of the assay. 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. Shared decision making is realized when both physician and patient contribute to care decisions based on all available information. In this regard, the individualized risk assessment provided by the Recurrence Score assay, used in conjunction with clinicopathologic features, supports shared decision making and increase confidence in the treatment decision for both patient and physician.[8]

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

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. [Gene discovery]
2. O'Connell MJ, Lavery I, Yothers G, et al. Relationship between tumor gene expression and recurrence in four independent studies of patients with stage II/III colon cancer treated with surgery alone or surgery plus

adjuvant fluorouracil plus leucovorin. *J Clin Oncol.* 2010;28(25):3937-3944. [Gene set refinement and early analytic validation]
3. Clark-Langone KM, Sangli C, Krishnakumar J, Watson D. Translating tumor biology into personalized treatment planning: analytical performance characteristics of the Oncotype DX Colon Cancer Assay. *BMC Cancer.* 2010;10:691. [Analytic validation]
4. Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. *J Clin Oncol.* 2011;29(35):4611-4619. [QUASAR study; clinical validation in stage II colon cancer]
5. Venook AP, Niedzwiecki D, Lopatin M, 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(14):1775-1781. [CALGB 9581; confirmatory study in stage II colon cancer that was consistent with QUASAR]
6. Yothers G, O'Connell MJ, Lee M, et al. Validation of the 12-gene colon cancer Recurrence Score in NSABP C-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin. *J Clin Oncol.* 2013;31(36):4512-4519. [NSABP C-07; clinical validation in stage II & III colon cancer]
7. Yamanaka T, Oki E, Yamazaki K, et al. 12-gene Recurrence Score assay stratifies the recurrence risk in stage II/III colon cancer with surgery alone: The SUNRISE study. *J Clin Oncol.* 2016;34(24):2906-2913. [SUNRISE study; clinical validation in stage II & III colon cancer; first validation in stage III colon cancer without chemotherapy]

Clinical utility studies:
8. Brenner B, Geva R, Rothney M, et al. Impact of the 12-gene colon cancer assay on clinical decision making for adjuvant therapy in stage ii colon cancer patients. *Value Health.* 2016;19(1):82-87. [Retrospective analysis demonstrating changes in treatment recommendations for patients with stage II, T3, MMR-P colon cancer that were consistent with Recurrence Score result]
9. Cartwright T, Chao C, Lee M, et al. Effect of the 12-gene colon cancer assay results on adjuvant treatment recommendations in patients with stage II colon cancer. *Curr Med Res Opin.* 2014;30(2):321-328. [29% change in treatment recommendations for patients with stage II colon cancer]
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. *Oncologist.* 2014;19(5):492-497. [45% change in treatment recommendations for patients with stage II, T3, MMR-P colon cancer]

Sincerely,

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