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NCCN Guidelines Panel: Colon/Rectal/Anal Cancers

On behalf of HalioDx, I respectfully request the NCCN® Colon Cancer Guidelines Panel to consider the updates below for inclusion of the Immunoscore® assay to measure the tumor immune response in the post-surgical pathologic review of patients diagnosed with colon cancer.

Requested Updates :
1) **Add the evaluation of immune response as a recommendation for risk assessment of early colon cancer patients to the *Principles of Pathologic Review* section (COL-B 2 of 8), indicating the relation of immune response with outcome in early stage colon cancer, and that this evaluation should be performed via a validated test such as Immunoscore®.**
2) **Amend the *Principles of Pathologic Review* section (COL-B 4 of 8) by adding immune response testing via a validated test such as Immunoscore® indicating that i) Stage II patients with a high immune response (Immunoscore-High tumors) have a good prognosis regardless MMR/MSI status and might be spared chemotherapy ii) immune response assessment in Stage III patients refines prognosis in both low-risk (T1-3/N1) and high-risk (T4/N2) groups and iii) immune response assessment may help guide the chemotherapy duration for Stage III patients**
3) **Amend the *Principles of Risk Assessment for Stage II Disease* (COL-F) by adding immune response testing (see COL-B 4 of 8)**
4) **Amend the *Principles of Adjuvant Therapy* (COL-G 1 of 2) to indicate that a benefit of 6 months is superior to 3 months of FOLFOX in stage III patients with Immunoscore-High tumors (among both low- and high-risk subgroups), whereas no significant benefit is indicated for patients with Immunoscore-Low tumors.**

FDA Clearance: FDA clearance is not required for the Immunoscore® assay as it is performed in a central laboratory which is regulated and certified under the Clinical Laboratory Improvement Amendments (CLIA).

Rationale:

- The clinical relevance of the interaction between a patient's immune system and their cancer is widely recognized. The World Health Organization (WHO) recently introduced immune response as an essential and desirable diagnostic criterion for CRC alongside standard histological parameters, indicating that assessment of immune response at the tumor site is now a complementary tool to standard staging procedures. The WHO referenced Immunoscore validation data as evidence of the immune response prognostic power in colon cancer[1-2]. Immunoscore testing allows standardized and accurate evaluation of immune response by quantifying CD3+ and CD8+ lymphocytes in specific regions of the tumor (core and invasive margin)[3].

- A large international multicenter study (>2600 TNM stage I-III colon cancer patients) led by the Society for Immunotherapy of Cancer (SITC)[1-2] has validated Immunoscore[4-8] as a strong predictor of Time To Recurrence (TTR), Overall Survival (OS) and Disease Free Survival (DFS), independently of existing clinicopathological risk parameters, including T-stage, N-stage, sex, grade of differentiation, MRR/MSI status, mucinous colloid type, sidedness and LVI/PNI. Immunoscore imparted the highest relative contribution to survival prediction out of all parameters. Therefore, Immunoscore further refines the prognosis of early stage cancer patients when used in conjunction with the TNM classification system.

- A sub-analysis of the SITC stage II cohort (n=1434) demonstrated that Immunoscore was significantly and independently predictor of survival (TTR, DFS and OS). Immunoscore re-stratified patient prognosis within MSI and MSS subsets[1]. Among high-risk untreated Stage II patients, Immunoscore had the greatest relative

contribution to prediction of OS (60%) of all risk parameters[9]; 69.5% of those patients had tumors classified as Immunoscore-High, with 5Y TTR statistically similar to that observed in the low-risk patients (p=0.42) but significantly superior to that of the Immunoscore-Low patients (p<0.00001). The 5-year recurrence rates of patients with Immunoscore-High tumors were similar for untreated patients and for patients who received adjuvant chemotherapy (p=0.37). In a recent analysis, similar results were obtained for the subgroup of high-risk patients with T4 tumors, where 65.4% of these patient tumors were classified as Immunoscore-High, which correlated with favorable outcomes (87.5% 5YR TTR)[10]. Therefore, the Immunoscore can identify a large group of stage II patients with sufficiently low risk of recurrence, such that the absolute benefit of adjuvant chemotherapy is unlikely to outweigh the risks of toxicities.

- Two large prospective-retrospective biomarker studies of randomized, controlled trials of stage III cancer patient samples validated the Immunoscore prognostic performance, specifically the ability of the assay to identify patient recurrence within the low- (T1-3,N1) and high-risk (T4 and/or N2) clinical groups more accurately[11-12]. In addition to consistent prognostic performance in both studies, the Immunoscore biomarker study of IDEA-France showed that patients with tumors classified as Immunoscore-High benefitted from 6 months vs 3 months of FOLFOX, with significantly higher DFS in both low-risk (p=0.0003) and high-risk (p=0.006) patient clinical subgroups. Conversely, in patients with tumors classified as Immunoscore-Low, no significant difference was observed in DFS for patients receiving either 6 or 3 months of chemotherapy (p=0.27)[12]. An additional analysis of Stage III patients further suggests that patients with a better pre-existing immunity (Immunoscore-High) do benefit the most from chemotherapy, even in low-risk patients[13].

- Based on this evidence, and as a further support, the 2020 European Society for Medical Oncology (ESMO) Clinical Guidelines for Localised Colon Cancer consider Immunoscore to refine the prognosis of early colon cancer patients in conjunction with the TNM scoring and thus adjust the chemotherapy decision-making process[14].

Altogether, these data support the addition of Immunoscore as a critical component of clinical decision making for patients with early stage colon cancer by providing prognostic and predictive information to help guiding treatment decisions.

Thank you for your review of this submission.

Sincerely,

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VP Global Medical, Regulatory & Quality

HalioDx

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

1. Pagès F et al. International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. *Lancet*. 2018 May 26;391(10135):2128-2139. doi:10.1016/S0140-6736(18)30789-X *(IF: 59.1)*

2. Pagès F, et al. Quantifying Immunoscore performance. *Lancet*. 2018 Nov 3;392(10158):1624-1625. doi: 10.1016/S0140-6736(18)32385-7

3. Marliot F, et al. Analytical validation of the Immunoscore and its associated prognostic value in patients with colon cancer*. J Immunother Cancer.* 2020 May;8(1):e000272. doi: 10.1136/jitc-2019-000272.

4. Galon J, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006 313:1960-4 doi: 10.1126/science.1129139 *(IF: 41.1)*

5. Pagès F, et al. The in situ cytotoxic and memory T cells predict outcome in early-stage colorectal cancer patients. *J Clin Oncol* 2009. 27(35):5944-51. doi: 10.1200/JCO.2008.19.6147 *(IF: 26.3)*

6. Mlecnik B, et al. Histopathologic-based prognostic factors of colorectal cancers are associated with the state of the local immune reaction. *J Clin Oncol*. 2011 Feb 20;29(6):610-8. doi: 10.1200/JCO.2010.30.5425 *(IF: 26.3)*

7. Mlecnik B, et al. Integrative Analyses of Colorectal Cancer Show Immunoscore Is a Stronger Predictor of Patient Survival Than Microsatellite Instability. *Immunity*. 2016 Mar 15;44(3):698-711 doi: 10.1016/j.immuni.2016.02.025. *(IF: 20.7)*

8. Zhang X, et al. The prognostic value of Immunoscore in patients with cancer: A pooled analysis of 10,328 patients. *Int J Biol Markers.* 2020 doi:10.1177/1724600820927409

9. Galon J et al. Immunoscore clinical utility to identify good prognostic colon cancer stage II patients with high-risk clinico-pathological features for whom adjuvant treatment may be avoided. *J Clin Oncol* 37, no. 4_suppl (February 01, 2019) 487-487. doi: 10.1200/JCO.2019.37.4_suppl.487 *Presented at ASCO GI 2019*

10. Galon J et al. Immunoscore as a parameter predicting time to recurrence and disease-free survival in T4N0 stage II colon cancer patients. *J Clin Oncol* 38: 2020 (suppl; abstr 4105). Doi: 10.1200/JCO.2020.38.15_suppl.4105 *Presented at ASCO 2020*

11. Sinicrope FA, et al. Contribution of Immunoscore and Molecular Features to Survival Prediction in Stage III Colon Cancer. *JNCI Cancer Spectr.* 2020;4(3):pkaa023. doi:10.1093/jncics/pkaa023

12. Pagès F, et al. Prognostic and predictive value of the Immunoscore in stage III colon cancer patients treated with oxaliplatin in the prospective IDEA France PRODIGE-GERCOR cohort study. *Ann Oncol.* 2020;31(7):921-929. doi:10.1016/j.annonc.2020.03.310 *(IF: 14.2)*

13. Mlecnik B, et al. Multicenter international SITC study of the consensus Immunoscore for the prediction of survival and response to chemotherapy in Stage III colon cancer *J Clin Oncol* 2020 *(IF: 26.3)* In Press

14. Argiles G et al. Localised Colon Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. *Ann Oncol.* 2020 doi: https://doi.org/10.1016/j.annonc.2020.06.022