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NCCN Guidelines Panel:	Genetic/Familial High Risk Assessment: Colorectal

Specific Change: For the algorithm on page LS-2, remove "Consider LS-specific testing (4 MMR genes and EPCAM)" in the arm when "no tumor available or insufficient tumor" and recommend proceeding directly to multi-gene testing.

FDA Clearance: Not applicable.

Rationale: Tumor screening to direct germline testing for LS can be useful in guiding gene specific testing. However, in the absence of information from tumor testing it is unlikely that clinical presentation can adequately distinguish between LS and other hereditary colorectal cancer conditions, which significantly limits the value of testing only for LS instead of proceeding directly to multi-gene/syndrome testing. Studies demonstrate that up to 5.6% of patients who met NCCN Lynch syndrome testing criteria are found to have a mutation in genes other than one of the 5 LS genes. Removing the "Consider LS-specific testing (4 MMR genes and EPCAM)" step leads to a more straightforward algorithm and allows the provider to more efficiently reach a clinical diagnosis and implement appropriate management in a timely fashion.

The following articles are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

References:

1. Yurgelun MB, et al. Identification of a Variety of Mutations in Cancer Predisposition Genes in Patients with Suspected Lynch Syndrome. *Gastroenterology*. 2015 149:604-13.PMID: 25980754

2. Shirts BH, et al. Improving performance of multigene panels for genomic analysis of cancer predisposition. *Genet Med*. 2016 18:974-81. PMID: 26845104.

3. Chubb D, et al. Genetic diagnosis of high-penetrance susceptibility for colorectal cancer (CRC) is achievable for a high proportion of familial CRC by exome sequencing. *J Clin Oncol*. 2015 33:426-32. PMID: 25559809.

Sincerely,

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