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

Specific Changes:

On page GENE-1, modify the second bullet point as follows:

- The majority of patients meeting assessment and testing criteria for inherited colorectal/GI cancer risk have personal and/or family histories that could be explained by multiple genes or syndromes. In these cases, multi-gene testing with a comprehensive cancer panel (see definition on page GENE-2) is likely to be the more efficient and/or cost-effective than single gene/syndrome testing.

On page GENE-3, modify the second bullet point under Examples of clinical scenarios for which multi-gene testing SHOULD NOT be considered:

- As first line testing in rare cases where the personal and family history is unambiguously suggestive of a single known hereditary syndrome with highly distinctive clinical features that do not overlap with other syndromes.

Rationale: The overwhelming preponderance of evidence from studies of multi-gene/syndrome panel testing demonstrates that a significant fraction of patients carry pathogenic variants in genes other than those which would have been predicted based on expert assessment of the available clinical history. Given that comprehensive cancer panel testing is almost always more efficient and cost-effective than more narrowly targeted or sequential testing strategies, there are very few patients for whom this is not the most appropriate approach. This should be emphasized appropriately in the guidelines.

References:

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Pearlman R, et al. Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer. JAMA Oncol. 2017 3:464-471. PMID: 27978560.

Rosenthal ET, et al. Clinical testing with a panel of 25 genes associated with increased cancer risk results in a significant increase in clinically significant findings across a broad range of cancer histories. Cancer Genet. 2017 218-219:58-68. PMID: 29153097.

Stanich PP, et al. Prevalence of Germline Mutations in Polyposis and Colorectal Cancer-Associated Genes in Patients With Multiple Colorectal Polyps. Clin Gastroenterol Hepatol. 2019 17:2008-2015. PMID: 30557735.

Yurgelun MB, et al. Identification of a Variety of Mutations in Cancer Predisposition Genes in Patients With Suspected Lynch Syndrome. Gastroenterology. 2015 149:604-613. PMID: 25980754.

Sincerely,

Royce (Terry) Adkins, MD

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