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Date of request:	November 10, 2016
NCCN Guidelines Panel:	Genetic/Familial High Risk Assessment: Colorectal

Specific Change: On page GENE-3, add the following to the "Examples of clinical scenarios where multi-gene testing should be considered" in Table 3:

- Patients with a personal diagnosis of pancreatic cancer, regardless of family history, and patients with a family history of pancreatic and other cancers (especially melanoma, breast and colorectal) who do not definitively meet testing criteria strongly suggestive of a specific hereditary cancer syndrome.

Also, on page HRS-1, add the following bullet point bullet point under "CRITERIA FOR FURTHER EVALUATION FOR HIGH-RISK SYNDROMES":

- Patients with a personal diagnosis of pancreatic cancer, and patients with a family history of pancreatic and other cancers (especially melanoma, breast and colorectal)

FDA Clearance: Not applicable.

Rationale: Pancreatic cancer is a feature of multiple hereditary cancer syndromes, including those that are the primary focus of this panel. A growing body of literature has demonstrated that 3.8% to 21.9% of pancreatic cancer patients carry clinically significant germline pathogenic variants in inherited cancer genes, with the higher percentages in those with a family history of pancreatic (8.0%), breast (10.7%), colorectal cancer (11.1%), or Ashkenazi Jewish ancestry (4.6% to 19.2%). It is important to highlight the importance of testing all pancreatic cancer patients, and to emphasize that a family history of a wide range of cancers increases the likelihood of finding a clinically significant germline mutation. The large, and growing, number of genes with a demonstrated pancreatic cancer association points to a multi-gene panel as the most appropriate testing option in the majority of cases.

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.

Germline mutation prevalence studies:

1. Catts ZA, et al. Statewide Retrospective Review of Familial Pancreatic Cancer in Delaware, and Frequency of Genetic Mutations in Pancreatic Cancer Kindreds. Ann Surg Oncol. 2016 23:1729-35. PMID: 26727920.

2. Ferrone CR, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol. 2009 27:433-8. PMID: 19064968.

3. Grant RC, et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015 148:556-64. PMID: 25479140.

4. Holter S, et al. Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients With Pancreatic Adenocarcinoma. J Clin Oncol. 2015 33:3124-9. PMID: 25940717.

5. Hu C, et al. Prevalence of Pathogenic Mutations in Cancer Predisposition Genes among Pancreatic Cancer Patients. Cancer Epidemiol Biomarkers Prev. 2016 25:207-11. PMID: 26483394.

6. Lucas AL, et al. BRCA1 and BRCA2 germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts. Cancer. 2014 120:1960-7. PMID: 24737347.

7. Salo-Mullen EE, et al. Identification of germline genetic mutations in patients with pancreatic cancer. Cancer. 2015 121:4382-8. PMID: 26440929.

8. Yang XR, et al. Multiple rare variants in high-risk pancreatic cancer-related genes may increase risk for pancreatic cancer in a subset of patients with and without germline CDKN2A mutations. Hum Genet. 2016 135:1241-1249. PMID: 27449771.

9. Zhen DB, et al. BRCA1, BRCA2, PALB2, and CDKN2A mutations in familial pancreatic cancer: a PACGENE study. Genet Med. 2015 17:569-77. Epub 2014 Nov 20. PMID: 25356972.

Sincerely,

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