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NCCN Guidelines Panel: Pancreatic Adenocarcinoma.

Specific Changes:

1) On page PANC-1, please revise the algorithm bullet point for germline testing under "No metastatic disease" to: "Germline testing if diagnosis is confirmed, or if individual meets testing criteria based on family history[f]".

   [f]Germline testing is recommended for any patient with confirmed pancreatic cancer, or with a first-degree relative with pancreatic cancer, or who meets the testing criteria in the NCCN Guidelines for Genetic/Familial High-Risk Assessment Breast, Ovarian and Pancreatic Cancer. For details, see page [new section proposed below].

2) Rather than providing the necessary genetic testing details in a footnote and the Discussion section, consider taking the approach utilized by other NCCN panels to organize the details of information related to hereditary genetic testing in a new section containing the following content:
   a. A recommendation for testing utilizing a comprehensive multi-gene panel, which should at a minimum include the genes *ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, TP53*. This list is taken from footnote m, page CRIT-3 of the NCCN Guideline for Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic Cancer.
   b. The table currently appearing on page MS-54 of the Discussion, along with bullet points briefly addressing the additional relevant information currently included in the Discussion, i.e., the positive data from pancreatic cancer screening trials and existing recommendations to test unaffected first-degree relatives of pancreatic cancer patients in cases where it was not possible to test the affected individual.

Rationale:

Regarding #1, some individuals whose evaluation does not result in a pancreatic cancer diagnosis may still be at increased risk due to personal or family factors, and many are likely to be appropriate candidates for germline testing. The NCCN Panel for Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic (page CRIT-3) recommends germline testing for all first-degree relatives of pancreatic cancer patients who were not themselves tested, as well as individuals meeting other criteria (pages CRIT-1 and CRIT-2). Identification of a germline

mutation in a patient who does not yet have a pancreatic cancer diagnosis can guide screening recommendations for pancreatic and other cancers.

Regarding #2, the NCCN Pancreatic Adenocarcinoma guidelines provide valuable information relevant to germline testing for pancreatic cancer patients. However, most of this content is in the Discussion section, as opposed to being included in the main body of the recommendations. Other NCCN cancer treatment panels have highlighted genetic/familial risk assessment more prominently to emphasize its importance in routine clinical care. This will become increasingly relevant in pancreatic cancer, as evidence mounts supporting the value of targeted therapies, as well as the efficacy of screening protocols for individuals at high risk due to genetic mutations and/or their family history. For examples, please see pages GAST-D (1 thru 7) in the NCCN guidelines for Gastric Cancer or pages ME-A (1 and 2) in the NCCN guidelines for Cutaneous Melanoma.

Regarding #2a, healthcare providers ordering genetic testing for newly diagnosed pancreatic cancer patients will benefit from the provision of a list of the genes that should be included on a panel. The NCCN Panel for Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic (page CRIT-3) offers a concise list of genes relevant to pancreatic cancer. Given the wide variability of hereditary cancer panels for germline testing, a concise list of the genes relevant to pancreatic cancer will help treating providers ensure that patients have access to the most appropriate genetic testing relevant to their clinical situation.

The following references are submitted in support of these proposed changes:

Ajani JA, et al. NCCN Clinical Practice Guidelines in Oncology®: Gastric Cancer. V 4.2019. Dec 20. Available at http://www.nccn.org.

Daly M et al. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. V 1.2020. Dec 4. Available at http://www.nccn.org.

Goggins M, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. 2020 69:7-17. PMID: 31672839.

Swetter, SM, et al. NCCN Clinical Practice Guidelines in Oncology®: Cutaneous Melanoma. V 2.2020 April 9. Available at http://www.nccn.org.

Sincerely,

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