Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ESOPH-1 External Request: Submission from Foundation Medicine (08/26/20) to add the following statement to the Workup: "If metastatic disease is suspected, consider comprehensive genomic profiling via a validated NGS assay for the identification of MSI, TMB, MMR mutations, HER2 (ERBB2) alterations, and NTRK gene fusions (as opposed to sequential testing of single biomarkers or use of limited molecular diagnostic panels (≤50 genes))."	Based on a review of the data and discussion, the panel did not use the language proposed in the submission. However, the panel supported adding the following recommendation to the Workup: "If sufficient tissue is available after the above testing has been completed, next generation sequencing (NGS) may be considered."	0	25	0	6
ESOPH-1, ESOPH-10, ESOPH-19 External Request: Submission from Foundation Medicine (06/22/20) to amend the algorithm to recommend tumor mutational burden (TMB) when metastatic disease is documented/suspected as determined by a validated and/or FDA-approved assay to inform the use of pembrolizumab.	Based on a review of the data and discussion, the panel did not add TMB-H to the pages proposed in the submission. However, the panel supported revising the Principles of Pathologic Review and Biomarker Testing (ESOPH-B 5 of 6) as follows: Under, Next-Generation Sequencing (NGS) revised to "…Pembrolizumab is based on testing for MSI by PCR/ MMR by IHC or PD-L1 expression by CPS *and high tumor mutation burden (TMB) by NGS*. The FDA granted… In these scenarios, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory may be used for the identification of HER2 amplification, MSI, MMR mutations, *TMB*, and NTRK gene fusions…"	0	25	0	6
ESOPH-10 External Request Submission from Guardant Health (08/26/20) requesting change to, "Perform **HER2 by IHC, FISH, or plasma or tissue NGS**; MSI by PCR**/, or plasma or tissue NGS**; MMR by IHC; and PD-L1 testing **by IHC** (if not done previously) if metastatic squamous cell carcinoma is suspected."	Based on a review of the data and discussion, the panel did not use the language proposed in the submission. However, the panel supported adding the following sub-bullet to the recommendation noted in the submission: "If sufficient tissue is available after the above testing has been completed, NGS may be considered."	0	25	0	6

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ESOPH-10, ESOPH-19 External Request Submission from Foundation Medicine (08/26/20) requesting that for patients with confirmed unresectable locally advanced, locally recurrent, or metastatic disease, add the following: "Recommend comprehensive genomic profiling via a validated NGS assay for the identification of MSI, TMB, MMR mutations, HER2 (ERBB2) alterations, and NTRK gene fusions as opposed to sequential testing of single biomarkers or use of limited molecular diagnostic panels (≤50 genes)."	Based on a review of the data and discussion, the panel did not add the proposed language to the requested pages. However, the panel supported adding the following recommendation to the guidelines: "If sufficient tissue is available after the above testing has been completed, next generation sequencing (NGS) may be considered."	0	25	0	6
ESOPH-B page 3 External Request Submission from Daiichi-Sankyo/Astra Zeneca 06/04/20) under "Assessment of Overexpression or Amplification of HER2 in Gastric/Esophageal and Esophagogastric Junction Cancers," • Consider changing first sentence to "For patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the **stomach/**esophagus or EGJ ~~for whom trastuzumab therapy is being considered~~, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) methods is recommended."	Based on a review of the data and discussion, the panel consensus was not to make changes to the current recommendations	0	25	0	6

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ESOPH-B (3 of 6) External Request Submission from Guardant Health (08/26/20) under "Assessment of Overexpression or Amplification of HER2 in Gastric/Esophageal and Esophagogastric Junction Cancers," Consider revising to: "... Next-generation sequencing (NGS), **whether it be through plasma ("liquid biopsy") or tissue**, offers the opportunity to assess numerous mutations simultaneously, along with other molecular events such as amplification, deletions, tumor mutation burden, and microsatellite instability status. **Comparable outcomes for HER2 amplifications detected by NGS performed on plasma (as in "liquid biopsy") have been reported.** ~~When limited diagnostic tissue is available for testing and the patient is unable to undergo additional procedures,~~ NGS can be considered instead of sequential testing for single biomarkers**, especially by means of a test that has been specifically validated in esophageal and EGJ cancers**.	Based on a review of the data and discussion, the panel did not use the language proposed in the submission. However, the panel supported adding the following language: "…and microsatellite instability status. ~~When limited diagnostic tissue is available for testing and the patient is unable to undergo additional procedures,~~ NGS can be considered instead of sequential testing for single biomarkers *when limited diagnostic tissue is available or when the patient is unable to undergo a traditional biopsy*. It should…"	0	25	0	6
ESOPH-B (3 of 6) External Request Submission from Foundation Medicine (08/26/20) under "Assessment of Overexpression or Amplification of HER2 in Gastric/Esophageal and Esophagogastric Junction Cancer, remove the last sentence, "It should be noted that NGS has several inherent limitations and thus, whenever possible, the use of gold standard IHC/ISH should be performed" **(Also for ESOPH-B 5)**	Based on a review of the data and discussion, the panel consensus was not to make changes to the current recommendations.	0	25	0	6

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ESOPH-B (4 of 6) External Request Submission from Guardant Health (08/26/20) request for MSI/MMR Testing section: Consider change to: "….The testing is performed on formalin-fixed, paraffin-embedded (FFPE) tissue and results are interpreted as MSI-high (MSI-H) or mismatch repair-deficient (dMMR) in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines**. MSI may be determined by plasma or tissue NGS using a well validated test.** MMR or MSI testing should be performed only in CLIA-approved laboratories. Patients with MSI-H or dMMR tumors should be referred to a genetics counselor for further assessment."	Based on a review of the data and discussion, the panel consensus was not to make changes to the current recommendations.	0	25	0	6

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ESOPH-B (5 of 6) Internal Request Panel Member request to consider adding TMB-H as a criterion for offering pembrolizumab External Request Submission from Merck and Co (06/17/20) requesting the inclusion of pembrolizumab as a treatment option for patients with advanced tumor mutational burden-high (TMB-H) esophageal squamous cell carcinoma, esophageal adenocarcinoma and EGJ adenocarcinoma who have progressed following prior treatment and have no satisfactory alternative treatment to pages ESOPH-B (4 and 5 of 6). External Request Submission from Foundation Medicine (06/22/20) to add a section for TMB in "Principles of Pathologic Review and Biomarker Testing" (page ESOPH-B 4 of 6) that includes a recommendation for TMB measurement and reporting to follow recommendations as outlined in Merino DM, et al. *J Immunother Cancer* 2020;8:e00147. External Request Submission from Foundation Medicine (06/22/20). Add pembrolizumab as a treatment option for patients with unresectable or metastatic tumors with tissue tumor mutational burden-high (tTMB-H) ≥10 mutations/megabase, as determined by an FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options.	Based on the review of the data in the noted reference, the panel consensus was to revise the pembrolizumab recommendation under the Next-Generation Sequencing section as follows: "…Pembrolizumab is based on testing for MSI by PCR/ MMR by IHC or PD-L1 expression by CPS *and high tumor mutation burden (TMB) by NGS*…. In these scenarios, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory may be used for the identification of HER2 amplification, MSI, *MMR mutations, TMB,* and *NTRK* gene fusions…." See submission for references.	25	0	0	6

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ESOPH-B (5 of 6) External Request: Submission from Guardant Health (01/30/20) requesting: • that Plasma-based comprehensive genomic profiling (CGP) should be recommended in patients with newly diagnosed metastatic or unresectable recurrent stage III/IV Esophageal/Esophagogastric Cancers, when patients have not been tested for MSI/dMMR or when primary gastric tissue has been tested on tissue but negative for *ERBB2* (HER2) amplification.	Based on the review of the data, the panel consensus was to revise the recommendations under "Liquid Biopsy" as follows: "…Therefore, for patients who *have metastatic or advanced esophageal/esophagogastric cancers and* are unable to undergo a traditional biopsy, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered…"	25	0	0	6
• that Guardant360 should be named in the guidelines	Based on a review of the data and discussion, the panel consensus was not to make changes to the current recommendations	0	25	0	6
• to include a statement such as the following: "**Well validated plasma-based comprehensive genomic profiling tests should be used. In addition to clinical validation, assays with substantial published outcomes studies demonstrating clinical utility are recommended.**	Based on a review of the data and discussion, the panel consensus was not to make changes to the current recommendations	0	25	0	6

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ESOPH-B (5 of 6) External Request Submission from Guardant Health (08/26/20) request to make the following changes under "Liquid Biopsy," • For Fourth sentence in bulleted statement: Please consider expanding this use of a well validated ctDNA assay beyond. "patients who are unable to undergo a traditional biopsy" to give physicians greater autonomy in their choice of testing modality. • Revise to: "… The detection of mutations/alterations in DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. **Excellent outcomes for some alterations, especially MSI and HER2 amplifications, detected by NGS performed on plasma have been reported.** Therefore, ~~for patients who are unable to undergo a traditional biopsy~~, testing using a validated NGS-based comprehensive genomic profiling assay performed **on plasma** in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications". • Consider suggesting that plasma-based CGP be used in the respective guidelines when MSI and ERBB2 (HER2) testing on tissue has not been completed or is uninformative, regardless of the patient's ability to undergo additional invasive biopsy. • to add specific language to suggest using a FDA-approved ctDNA assay that has not only published analytical and clinical validation, but also published outcomes studies based on ctDNA-identified ERBB2 (HER2) and MSI6 in detecting alterations in gastric and esophageal cancers. • to categorize types of testing based on *evidence*, classifying specific tests that meet evidence thresholds (*i.e.*, 2A, 2B), with validation and outcomes studies demonstrating utility. To this end, NCCN may wish to *name* the well validated plasma assay Guardant360 (whose validation studies have outcomes specifically in gastrointestinal cancer) in *delineating what should be covered*, as its panels for breast and prostate cancers have done in mentioning other FDA approved assays, noting the level of evidence for these tests.	Based on a review of the data and discussion, the panel consensus was not to make changes to the current recommendations.	0	25	0	6

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ESOPH-B (5 of 6) External Request Submission from Guardant Health (01/30/20) Requesting that plasma-based comprehensive genomic profiling (CGP) be recommended in the respective guidelines when MSI testing has not been completed or when ERBB2 (HER2) testing on primary gastroesophageal tissue is negative.	Based on a review of the data and discussion, the panel consensus was not to make changes to the current recommendations.	0	25	0	6
ESOPH-F (3 of 16) Submission from Merck & Co (03/12/20) request as follows: • Pembrolizumab as first line treatment option for MSI-H/dMMR GEJ Cancer based on post hoc analysis from KN 062 study and presented by Shitara et al. and Chao et al. • Efficacy data be incorporated in the NCCN Guidelines under Category 1 for second line treatment.	Based on a review of the data and discussion, the panel consensus did not support the inclusion of pembrolizumab as a first-line treatment option for unresectable locally advanced, recurrent, or metastatic disease.	0	25	0	6
ESOPH-F (4 of 16) External Request Submission from Merck & Co (03/20/20). Request that the updated publication by Marabelle et al. be added as a reference to support pembrolizumab as a treatment option for patients with MSI-H esophageal and esophago-gastric junction cancers.	Based on a review of the data and discussion, the panel consensus was to add the noted reference to support pembrolizumab as a second-line or subsequent therapy treatment option for patients with MSI-H esophageal and esophago-gastric junction cancers. Marabelle et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase 2 KEYNOTE-158 study. J Clin Oncol 38:1-10.	25	0	0	6

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ESOPH-F (4 of 16) External Request Submission from Merck & Co (06/17/20) Request the inclusion of pembrolizumab as a treatment option for patients with advanced tumor mutational burden-high (TMB-H) esophageal squamous cell carcinoma, esophageal adenocarcinoma and EGJ adenocarcinoma who have progressed following prior treatment and have no satisfactory alternative treatment. External Request Submission from Foundation Medicine (06/22/20). Add pembrolizumab as a treatment option for patients with unresectable or metastatic tumors with tissue tumor mutational burden-high (tTMB-H) ≥10 mutations/megabase, as determined by an FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options	Based on the review of the data in the noted reference, the panel consensus was to include pembrolizumab for TMB high (≥10 mutations/megabase) tumors (and corresponding dosing) as a second-line or subsequent therapy option for unresectable locally advanced, recurrent, or metastatic disease. This is a category 2A [useful in certain circumstances] recommendation. Reference Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21:1353-1365.	25	0	0	6