Guideline Page and Request	Panel Discussion/References	Institution Vote			
		YES	NO	ABSTAIN	ABSENT
COL-3 <u>External request:</u> Submission from Natera requesting that the presence of post-surgical tumor-informed ctDNA be added as a high-risk factor for recurrence in T3N0, T4N0, and T1-3N1. Proposed modification of footnote in COL-3: "High-risk factors for recurrence (exclusive of those cancers that are MSI-H: poorly differentiated/undifferentiated histology, lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, or positive margins. *Presence of postsurgical tumor-informed ctDNA is associated with a high risk of recurrence*. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy."	Based on a review of data and discussion, the panel consensus did not support these changes. This is an area of investigation. The trial information will be considered for the Discussion section. • See Submission for references.	0	29	0	2
COL-4 <u>External request:</u> Submission from Guardant Health, requesting the following changes: 1. Plasma-based comprehensive genomic profiling (CGP) should be recommended in patients with newly diagnosed metastatic or unresectable recurrent stage III/IV CRC, when patients have not been comprehensively tested and tissue is infeasible. 2. Guardant360 should be named in the guidelines. There are currently 150 publications utilizing Guardant360. No other liquid biopsy assay has been validated by literally dozens of external clinical validity studies. In addition, seven clinical outcomes studies for Guardant360 in advanced CRC and two studies with pan-cancer outcomes for Guardant360-detected MSI-High and NTRK1 fusions have been published.	Based on a review of data and discussion, the panel consensus did not support these changes. The Panel felt the current wording in the Guidelines was sufficient. • See Submission for references.	0	29	0	2

Guideline Page and Request	Panel Discussion/References	Institution Vote			
		YES	NO	ABSTAIN	ABSENT
COL-4/REC-7 External request: Submission from Foundation Medicine requesting the following changes: Amend the algorithm to recommend tumor mutational burden (TMB) as determined by a validated and/or FDA-approved assay to inform the use of pembrolizumab and add a footnote referencing Merino DM, et al. J Immunother Cancer 2020;8:e000147.	Based on a review of data and discussion, the panel consensus did not support these changes. Data for colorectal cancer are limited and this is an area of investigation. The trial information will be considered for the Discussion section. • See Submission for references.	0	29	0	2
COL-5 External request: Submission from Society of Interventional Oncology requesting the following changes: 1. mFOLFOX + bevacizumab + DEBIRI may be considered as first line therapy for patients with liver-limited metastases. 2. Consider modifying footnote to indicate while resection is preferred over locally ablative procedures, for unresectable patients, the preferred therapy is image-guided ablation, assuming it is technically feasible.	Based on a review of data and discussion, the panel consensus did not support these changes. The Panel felt the current wording in the Guidelines was sufficient. • See Submission for references.	0	29	0	2
COL-8 External request: Submission from Natera requesting tumor-informed ctDNA assay be added as a component of postsurgical surveillance in stage II, III colon cancer as an additional bullet. Proposed bullet: Longitudinally tumor-informed ctDNA assay every 3 months for 2 years, then every 6 months for a total of 5 years. Additionally, we recommend changing “Serial CEA elevation or documented recurrence” to “Serial CEA elevation, detection of tumor-informed ctDNA by serial analysis, or documented recurrence.” In COL-9, recommend changing “Serial CEA elevation” to “Serial CEA elevation or detection of tumor-informed ctDNA by serial analysis”	Based on a review of data and discussion, the panel consensus did not support these changes. This is an area of investigation. The trial information will be considered for the Discussion section. • See Submission for references.	0	29	0	2

Guideline Page and Request	Panel Discussion/References	Institution Vote			
		YES	NO	ABSTAIN	ABSENT
COL-8 External request: Submission from Natera requesting changing "Serial CEA elevation" to "Serial CEA elevation or detection of tumor-informed ctDNA by serial analysis"	Based on a review of data and discussion, the panel consensus did not support these changes. This is an area of investigation. The trial information will be considered for the Discussion section. • See Submission for references.	0	29	0	2
COL-A External request: Submission from Society of Interventional Oncology requesting the following changes: 1. Consider updating the last bullet point under "Monitoring", which currently states "PET/CT is not indicated. For monitoring of patients having undergone locoregional therapies, including thermal ablation or radioembolization, PET/CT may be beneficial.	Based on a review of data and discussion, the panel consensus supported the addition the following bullet: PET/CT can be considered for assessment of response and liver recurrence after image-guided liver-directed therapies (ie, ablation, radioembolization) • See Submission for references.	29	0	0	2
COL-B 2 of 8 External request: Submission from HalioDx requesting the evaluation of immune response as a recommendation for risk assessment of early colon cancer patients, indicating the relation of immune response with outcome in early stage colon cancer, and that this evaluation should be performed via a validated test such as Immunoscore.	Based on a review of data and discussion, the panel consensus did not support these changes. This is an area of investigation. Additional data needed. • See Submission for references.	0	29	0	2

Guideline Page and Request	Panel Discussion/References	Institution Vote			
		YES	NO	ABSTAIN	ABSENT
COL-B 4 of 8 <u>External request:</u> Submission from HalioDx requesting the addition of immune response testing via a validated test such as Immunoscore indicating that i) Stage II patients with a high immune response (Immunoscore-High tumors) have a good prognosis regardless MMR/MSI status and might be spared chemotherapy ii) immune response assessment in Stage III patients refines prognosis in both low-risk (T1-3/N1) and high-risk (T4/N2) groups and iii) immune response assessment may help guide the chemotherapy duration for Stage III patients.	Based on a review of data and discussion, the panel consensus did not support these changes. This is an area of investigation. Additional data needed. • See Submission for references.	0	29	0	2
COL-B 4 of 8 <u>External request:</u> Submission from Guardant Health requesting the following changes: 1. The *comprehensive genomic profiling* ~~testing~~ can be performed on formalin-fixed paraffin-embedded tissue. *or circulating tumor DNA (sometimes referred to as "liquid biopsy") using a well validated plasma-based next-generation sequencing assay such as Guardant360 or other similarly well validated test (irrespective of panel size as long as evidence thresholds have been surpassed).* The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the KRAS, NRAS, and BRAF mutations are similar in both specimen types. 2. Testing for MSI may be accomplished by polymerase chain reaction (PCR) or a validated *tissue or plasma* NGS panel, the latter especially in patients with metastatic disease who require *comprehensive genomic profiling* ~~genotyping~~ of RAS and BRAF.	Based on a review of data and discussion, the panel consensus did not support these changes. The Panel felt the current wording in the Guidelines was sufficient. See Submission for references.	0	29	0	2

Guideline Page and Request	Panel Discussion/References	Institution Vote			
		YES	NO	ABSTAIN	ABSENT
COL-B 4 of 8 External request: Submission from Guardant Health requesting the following changes: 1. NGS o*n tissue or plasma* is another methodology for testing for HER2 amplification	Based on a review of data and discussion, the panel consensus did not support these changes. The Panel felt the current wording in the Guidelines was sufficient. • See Submission for references.	0	29	0	2
COL-B/REC-B 5 of 8 External request: Submission from Foundation Medicine requesting the following changes: Include TMB testing through a validated and/or FDA-approved assay (per Merino et al 2020) to inform the use of pembrolizumab.	Based on a review of data and discussion, the panel consensus did not support these changes. Data for colorectal cancer are limited and this is an area of investigation. The trial information will be considered for the Discussion section. • See Submission for references.	0	29	0	2
COL-C 2 of 3 External request: Submission from Society of Interventional Oncology requesting the following changes: Add yttrium-90 radioembolization radiation lobectomy to portal vein embolization and staged liver resection as options to induce future liver remnant hypertrophy when hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume.	Based on a review of data and discussion, the panel consensus supported the modification of the following bullet: When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization, staged liver resection, or *yttrium-90 radioembolization* can be considered. • See Submission for references.	29	0	0	2

Guideline Page and Request	Panel Discussion/References	Institution Vote			
		YES	NO	ABSTAIN	ABSENT
COL-C 2 of 3 External request: Submission from Society of Interventional Oncology requesting the following changes: "Combination of systemic therapy with image-guided thermal ablation leads to improved overall survival for patients who are not resectable," and consider modifying the comment about conformal external beam radiation to: "Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of clinical trial and should not be used indiscriminately in patients whose tumors are potentially surgically resectable or ablatable."	Based on a review of data and discussion, the panel consensus did not support these changes. The Panel felt the current wording in the Guidelines was sufficient. • See Submission for references.	0	29	0	2
COL-D/REC-F External request: Submission from Society of Interventional Oncology requesting the following changes: Consider the addition of a footnote or other statement to appear within the algorithms, addressing the consideration of locoregional therapies for highly selected patients who have developed chemotherapy-resistant/-refractory disease with predominant hepatic metastases.	Based on a review of data and discussion, the panel consensus did not support these changes. The Panel felt the current wording in the Guidelines (COL-C, COL-D) was sufficient. See Submission for references.	0	29	0	2
COL-D/REC-F 1 of 13 External request: Submission from Merck & Co. requesting pembrolizumab as a first-line therapy option for patients with MSI-H/dMMR unresectable or metastatic colon and rectal cancers be changed from category 2A to category 1 based on the FDA approved indication of pembrolizumab in MSI-H/dMMR colorectal cancer. We also request the removal of the associated footnote "Patients should be followed closely for 10 weeks to assess for response."	Based on a review of data and discussion, the panel consensus did not support these changes. The Panel felt the current wording in the Guidelines was sufficient. The panel consensus did support the notation of preferred for pembrolizumab for patients with dMMR/MSI-H mCRC. See Submission for references.	0	29	0	2

Guideline Page and Request	Panel Discussion/References	Institution Vote			
		YES	NO	ABSTAIN	ABSENT
COL-D/REC-F 1 of 13 External request: Submission from Bristol Myers Squibb requesting the consideration of clinical data that was presented as a poster presentation at the 2020 American Society for Clinical Oncology (ASCO) Annual Meeting for nivolumab in combination with ipilimumab as first-line treatment in microsatellite instability-high/DNA mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer. Internal request: Consider adding nivolumab monotherapy as a first-line treatment option in MSI-H/dMMR metastatic colorectal cancer.	Based on a review of data and discussion, the panel consensus supported the addition of nivolumab alone, or in combination with ipilimumab, as first-line treatment options for patients with dMMR/MSI-H mCRC. Nivolumab ± ipilimumab was also added as a treatment option on COL-6. Consideration for nivolumab ± ipilimumab was also added to COL-5, REC-8, REC-9. • See Submission for references.	29	0	0	2
COL-D/REC-F 2 through 6 of 13 External request: Submission from Taiho Oncology requesting the inclusion of trifluridine and tipiracil in combination with bevacizumab for patients with metastatic colorectal cancer.	Based on a review of data and discussion, the panel consensus supported the addition of bevacizumab in combination with trifluridine + tipiracil as a subsequent therapy option for patients with mCRC. • See Submission for references.	29	0	0	2
COL-D/REC-D 2 through 6 of 13 External request: Submission from Foundation Medicine requesting the addition of pembrolizumab as a treatment option for patients with unresectable or metastatic with tissue tumor mutational burden-high (TMB-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 a review of data and discussion, the panel consensus did not support these changes. Data for colorectal cancer are limited. The trial information will be considered for the Discussion section. • See Submission for references.	0	29	0	2

Guideline Page and Request	Panel Discussion/References	Institution Vote			
		YES	NO	ABSTAIN	ABSENT
COL-D/REC-F 2 through 6 of 13 External request: Submission from Daiichi-Sankyo/AstraZeneca requesting the inclusion of fam-trastuzumab deruxtecan-nxki for patients with HER2-positive and *RAS* and *BRAF* WT metastatic colorectal cancer. Also requested the following for the dosing pages: Add "Fam-trastuzumab deruxtecan-nxki 6.4 mg/kg IV on Day 1, cycled every 21 days" with a footnote: "fam-trastuzumab deruxtecan-nxki is approved for metastatic HER2-positive breast cancer at a different dose of 5.4 mg/kg IV on Day 1, cycled every 21 days"	Based on a review of data and discussion, the panel consensus supported the addition of fam-trastuzumab deruxtecan-nxki as a subsequent therapy option for patients appropriate for intensive therapy with HER2-positive and *RAS* and *BRAF* WT metastatic colorectal cancer. Also included as a first-line treatment option for patients not appropriate for intensive therapy. In addition, the dosing regimen was added. The Panel consensus did not support the addition of a footnote. • See Submission for references.	29	0	0	2
COL-F External request: Submission from HalioDx requesting the addition of immune response testing.	Based on a review of data and discussion, the panel consensus did not support these changes. This is an area of investigation. Additional data needed. • See Submission for references.	0	29	0	2
COL-F External request: Submission from HalioDx requesting the addition of a benefit of 6 months is superior to 3 months of FOLFOX in stage III patients with Immunoscore-High tumors (among both low and high-risk subgroups), whereas no significant benefit is indicated for patients with Immunoscore-Low tumors.	Based on a review of data and discussion, the panel consensus did not support these changes. This is an area of investigation. Additional data needed. • See Submission for references.	0	29	0	2