

# ONCOLOGY: Molecular Biomarkers of Colorectal Cancer

**Samples to Test:** Metastatic or recurrent tumor is preferable if available and adequate\*; primary tumor is an acceptable alternative. **Sample Types to Test:** Formalin fixed paraffin embedded tissue (FFPE) or other type of specimens (e.g., cytology). \* *Lynch syndrome screening is recommended for all primary colorectal cancers.*

Biomarker	Specific Alterations/ Alternative Names	Indications	Result Interpretation/ Significance	Assay Techniques
<b>KRAS</b>	Mutations in codons 12, 13 of exon 2; codons 59, 61 of exon 3; codons 117, 146 of exon 4	Consideration of anti-EGFR therapy Should be performed in all patients with metastatic CRC	Patients with these mutations should not be treated with panitumumab and cetuximab  Significant PFS advantage for adding anti-EGFR therapy for <i>KRAS</i> WT tumors compared to chemotherapy alone	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays
<b>NRAS</b>	Mutations in codons 12, 13 of exon 2; codons 59, 61 of exon 3; codons 117, 146 of exon 4	Consideration of anti-EGFR therapy Should be performed in all patients with metastatic CRC	Patients with these mutations should not be treated with panitumumab and cetuximab	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays
<b>BRAF</b>	<i>BRAF</i> V600; V600E, V600K	Prognostic stratification	Poorer PFS and OS compared to <i>BRAF</i> WT patients	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays
		Consideration of anti-EGFR therapy	Unlikely response to panitumumab and cetuximab unless given with a <i>BRAF</i> inhibitor (2)	
		In MMRd tumors with <i>MLH1</i> loss	Presence of mutation strongly favors sporadic tumor; the presence of <i>BRAF</i> mutations does not exclude the risk of Lynch Syndrome	
<b>NTRK</b>	Fusions	Therapy selection	Predicts response to larotrectinib (2)	NGS, pyrosequencing, FISH, IHC, PCR-base assays
<b>MSI/ MMR</b>	Loss of <i>MLH1</i> , <i>PMS2</i> , <i>MSH2</i> , <i>MSH6</i> expression and/or MSI-high status	Lynch syndrome screening	Consideration of genetic counseling and germline testing (in the absence of <i>BRAF</i> mutation or <i>MLH1</i> promoter methylation)	IHC, PCR-based assays
	MSI-high	Therapy selection (stage II patients)	Improved prognosis and no benefit from 5-FU adjuvant therapy  Consideration of immune checkpoint inhibitor therapy	
<b>MLH1 promoter methylation</b>	Methylation of <i>MLH1</i> promoter	<i>MLH1</i> loss by IHC	Presence of <i>MLH1</i> promoter methylation in a setting of <i>MLH1</i> loss suggests sporadic origin	Methylation assays

**Abbreviations:** CRC - colorectal cancer; NGS - next generation sequencing; PFS - progression free survival; OS - overall survival; WT - wild type (non-mutant); MMRd - mismatch repair deficient; MSI - microsatellite instability; IHC - immunohistochemistry

**Note:** Insufficient evidence to recommend *PIK3CA* mutational analysis for therapy selection outside of clinical trial. Insufficient evidence to recommend *PTEN* testing (IHC or FISH) for therapy selection outside of clinical trial.

**Where to Test:** Testing should be performed in the laboratories that are certified under Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity (molecular pathology) testing.

#### References:

1. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Colon Cancer. Version 4.2020 – June 15, 2019; NCCN.org. accessed 9/8/2020



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