# Molecular Biomarkers for the Evaluation of Colorectal Cancer Guideline

Statements and Strength of Recommendations

## Summary of Recommendations

| Guideline Statement | | Strength of Recommendation |
|---|---|---|
| 1. | Patients with colorectal carcinoma being considered for anti-EGFR therapy must receive *RAS* mutational testing. Mutational analysis should include *KRAS* and *NRAS* codons 12, 13 of exon 2; 59 and 61 of exon 3; and 117 and 146 of exon 4 ("expanded" or "extended" *RAS*). | Recommendation |
| 2a. | *BRAF* p.V600 (*BRAF* c.1799 [p.V600]) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal carcinoma for prognostic stratification. | Recommendation |
| 2b. | *BRAF* p.V600 mutational analysis should be performed in deficient MMR tumors with loss of *MLH1* to evaluate for Lynch Syndrome risk. Presence of a *BRAF* mutation strongly favors a sporadic pathogenesis. The absence of *BRAF* mutation does not exclude risk of Lynch syndrome. | Recommendation |
| 3. | Clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification. | Recommendation |
| 4. | There is insufficient evidence to recommend *BRAF* c.1799 (p.V600) mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors. | No Recommendation |
| 5. | There is insufficient evidence to recommend *PIK3CA* mutational analysis of colorectal carcinoma tissue for therapy selection outside of a clinical trial.<br>*Note:* Retrospective studies have suggested improved survival with postoperative aspirin use in patients whose colorectal carcinoma harbors a *PIK3CA* mutation. | No Recommendation |
| 6. | There is insufficient evidence to recommend PTEN analysis [expression by immunohistochemistry (IHC) or deletion by fluorescence in situ hybridization (FISH)] in colorectal carcinoma tissue for patients who are being considered for therapy selection outside of a clinical trial. | No Recommendation |
| 7. | Metastatic or recurrent colorectal carcinoma tissues are the preferred specimens for treatment predictive marker testing and should be used if such specimens are available and adequate. In their absence, primary tumor tissue is an acceptable alternative and should be used. | Expert Consensus Opinion |


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## Summary of Recommendations continued

| Guideline Statement | | Strength of Recommendation |
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| 8. | Formalin-fixed, paraffin-embedded tissue is an acceptable specimen for molecular biomarker mutational testing in colorectal carcinoma. Use of other specimens (eg, cytology specimens) will require additional adequate validation, as would any changes in tissue-processing protocols. | Expert Consensus Opinion |
| 9. | Laboratories must use validated colorectal carcinoma molecular biomarker testing methods with sufficient performance characteristics for the intended clinical use. Colorectal carcinoma molecular biomarker validation should follow accepted standards for clinical molecular diagnostics tests. | Strong Recommendation |
| 10. | Performance of molecular biomarker testing for colorectal carcinoma must be validated in accordance with best laboratory practices. | Strong Recommendation |
| 11. | Laboratories must validate the performance of IHC testing for colorectal carcinoma molecular biomarkers (currently IHC testing for MLH1, MSH2, MSH6, and PMS2) in accordance with best laboratory practices. | Strong Recommendation |
| 12. | Laboratories must provide clinically appropriate turnaround times and optimal utilization of tissue specimens by using appropriate techniques (eg, multiplexed assays) for clinically relevant molecular and immunohistochemical biomarkers of colorectal cancer. | Expert Consensus Opinion |
| 13. | Molecular and IHC biomarker testing in colorectal carcinoma should be initiated in a timely fashion based on the clinical scenario and in accordance with institutionally accepted practices.<br>*Note:* Test ordering can occur on a case-by-case basis or by policies established by the medical staff. | Expert Consensus Opinion |
| 14. | Laboratories should establish policies to ensure efficient allocation and utilization of tissue for molecular testing, particularly in small specimens. | Expert Consensus Opinion |
| 15. | Members of the patient's medical team, including pathologists, may initiate colorectal carcinoma molecular biomarker test orders in accordance with institutionally accepted practices. | Expert Consensus Opinion |
| 16. | Laboratories that require send out of tests for treatment predictive biomarkers should process and send colorectal carcinoma specimens to reference molecular laboratories in a timely manner.<br>*Note:* It is suggested that a benchmark of 90% of specimens should be sent out within three working days. | Expert Consensus Opinion |
| 17. | Pathologists must evaluate candidate specimens for biomarker testing to ensure specimen adequacy taking into account tissue quality, quantity, and malignant tumor cell fraction. Specimen adequacy findings should be documented in the patient report. | Expert Consensus Opinion |
| 18. | Laboratories should use colorectal carcinoma molecular biomarker testing methods that are able to detect mutations in specimens with at least 5% mutant allele frequency, taking into account the analytical sensitivity of the assay (limit of detection or LOD) and tumor enrichment (eg, microdissection).<br>*Note:* It is recommended that the operational minimal neoplastic carcinoma cell content tested should be set at least two times the assay's LOD. | Expert Consensus Opinion |


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## Summary of Recommendations continued

| Guideline Statement | | Strength of Recommendation |
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| 19. | Colorectal carcinoma molecular biomarker results should be made available as promptly as feasible in order to inform therapeutic decision-making, both prognostic and predictive.<br>*Note:* It is suggested that a benchmark of 90% of reports available within 10 working days from date of procedure for specimen acquisition. | Expert Consensus Opinion |
| 20. | Colorectal carcinoma molecular biomarker testing reports should include a results and interpretation section readily understandable by oncologists and pathologists. Appropriate Human Genome Variation Society (HGVS) and Human Genome Organisation (HUGO) nomenclature must be used in conjunction with any historical genetic designations. | Expert Consensus Opinion |
| 21. | Laboratories must incorporate colorectal carcinoma molecular biomarker testing methods into their overall laboratory quality improvement program, establishing appropriate quality improvement monitors as needed to ensure consistent performance in all steps of the testing and reporting process. In particular, laboratories performing colorectal carcinoma molecular biomarker testing must participate in formal proficiency testing programs, if available, or an alternative proficiency assurance activity. | Strong Recommendation |

Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. *Arch Pathol Lab Med*. 2017;141(5):625-657. doi: 10.5858/arpa.2016-0554-CP