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EDITORIAL

Guidelines for Colorectal Cancer Testing

Evidence-Based Practice Recommendations

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As the New Year begins, we renew our professional commitment to excellence in laboratory practice and diagnostic collaboration. In this issue, *The Journal of Molecular Diagnostics* features the most recent laboratory practice recommendations developed through collaboration of The Association for Molecular Pathology, the American Society for Clinical Oncology, the College of American Pathologists, and the American Society for Clinical Pathology.[1–4] This report and the accompanying supplemental material describe a joint, multisociety effort to systematically evaluate the available published evidence from clinical studies of colorectal cancer to determine the strength of evidence for the clinical utility of multiple biomarkers. The systematic review outlined five key questions to establish standard approaches to molecular biomarker laboratory testing: i) What biomarkers are useful to select patients with colorectal cancer (CRC) for targeted and conventional therapies? ii) How should tissue specimens be processed for biomarker testing for CRC management? iii) How should biomarker testing for CRC management be performed? iv) How should molecular testing of CRC be implemented and operationalized? and v) Are there emerging genes/biomarkers that should be routinely tested in CRC? Twenty-one practice recommendations were formulated, each with varying degrees of evidentiary support and strength of recommendation, for clinical practice in the diagnosis, prognosis, and treatment stratification of patients with colorectal cancer. The draft recommendations were developed by the multidisciplinary subject matter expert panel with inclusion of patient advocate representatives. These draft recommendations were subsequently available for public comment, additional feedback was gathered, and feedback was considered by the expert panel before the final guideline formulation and recommendation manuscript development. The manuscript was reviewed by experts within each organization, and the composite product was then submitted for peer review and evaluated by external experts who were not part of the original societal review teams. These external reviewers were jointly selected by the Editors in Chief of the participating scholarly journals in which this guideline now appears.

This *tour de force* critical evaluation of molecular testing for colorectal cancer is the culmination of a long process that started with a proposal within our organization, expanded to engage the other professional associations, and culminated with a comprehensive systematic review of published work to identify evidence of effectiveness of diagnostic testing strategies in a multisociety collaborative effort. It is important for readers to recognize that this Guideline differs from a literature review. A systematic review of published evidence is a much more structured process and has a different goal to identify strength for practice recommendations, whereas a literature review is designed to inform the reader with a summary of current literature. Systematic reviews are lengthy and iterative processes to assess with strict defined criteria, the quality of studies and data produced that merit inclusion as supporting proposed practice recommendations. Many excellent scientific articles may have been excluded, not because the conclusions were unclear or the study design was faulty, rather there may have been insufficient detail describing the biomarker evaluation criteria to determine meaningful assessment of the evidence presented.

The output is a comprehensive overview proposing 21 recommendations for effective laboratory testing of patients with colorectal cancer. This was a huge,

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Table 1 Summary of Recommendations, Strength of Evidence, and Objectives Fulfilled

Grades for strength of recommendation	Recommendation	Objective	Diagnostic sector
Strong recommendation	9. Laboratories must use validated colorectal carcinoma molecular biomarker testing methods with sufficient performance characteristics for the intended clinical use. Colorectal carcinoma molecular biomarker testing validation should follow accepted standards for clinical molecular diagnostics tests.	1	Laboratory
	10. Performance of molecular biomarker testing for colorectal carcinoma must be validated in accordance with best laboratory practices.	4	Laboratory
	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.	1	Laboratory
	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 assure 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.	3	Laboratory
Recommendation	1. Colorectal carcinoma patients 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*).	1	Laboratory
	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.	1	Laboratory
	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.	1	Laboratory
	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.	3	Oncologist
Expert consensus	7. Metastatic or recurrent colorectal carcinoma tissues are the preferred specimens for treatment-predictive biomarker 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.	2	Oncologist
	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.	2	Laboratory
	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.	4	Laboratory
	13. Molecular and IHC biomarker testing in colorectal carcinoma should be initiated in a timely manner based on the clinical scenario and in accordance with institutionally accepted practices. Note: Test ordering can occur on a case-by-case basis or by policies established by the medical staff.	3	Oncologist
	14. Laboratories should establish policies to ensure efficient allocation and utilization of tissue for molecular testing, particularly in small specimens.	2	Laboratory
	15. Members of the patient's medical team, including pathologists, may initiate colorectal carcinoma molecular biomarker test orders in accordance with institutionally accepted practices.	3	Oncologist
	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. Note: It is suggested that a benchmark of 90% of specimens should be sent out within 3 working days.	1	Laboratory

(*table continues*)