FAQs

Topic: **Molecular Biomarkers for the Evaluation of Colorectal Cancer**[1]

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Why is this evidence-based guideline needed?
Molecular diagnostics is a rapidly evolving field of medicine. This pivotal guideline addresses testing a wide range of molecular biomarkers in patients with early and advanced colorectal cancer (CRC) to help establish standard molecular biomarker testing, guide targeted therapy decisions, and advance personalized care for patients with colorectal cancer, which is the second leading cause of cancer-related death in the U.S. for women and men combined. Results from biomarker testing guide clinicians and oncologists with complex targeted therapy decisions, thereby advancing personalized care for patients with colorectal cancer with the goal of improving outcomes.

How was the guideline developed and by whom?
The collaborating organizations of American Society for Clinical Pathology (ASCP), College of American Pathologists (CAP), Association of Molecular Pathology (AMP) and the Association for Clinical Oncology (ASCO), recognized the need to create this guideline and make biomarker testing recommendations for new discoveries in the field to benefit CRC patients, and convened a panel of experts to develop the guideline and publish in their respective journals. In addition, inclusion in the process of patient advocates, and a public open comment period allowed for refinement of issues specific to practicing pathologists, laboratorians, and clinicians. This guideline follows well-established, evidence-based methods used for development, as well as planning for regular updates, such that new advances in the molecular testing for clinical management of CRC can be integrated in the future in a timely manner.

How many recommendations are included?
Twenty-one guideline statements were established (eight recommendations, 10 expert consensus opinions, and three "no recommendation") based on evidence from a comprehensive literature review, which included over 4,000 articles. The guideline supports mutational testing for genetic molecular biomarkers that predict response to a specific therapy or treatment regimen, known as predictive biomarkers. Additional recommendations are intended to streamline molecular testing processes and contribute to improving patient outcomes.

What biomarkers does the guideline address?
Monoclonal antibody therapies that target the epidermal growth factor receptor (EGFR) bind the EGFR extracellular domain, blocking EGFR signaling pathways. Anti-EGFR monoclonal antibodies have been the main targeted therapies for CRC that require knowledge of the mutational status of genes in the EGFR pathway as predictive biomarkers of response to these therapies.

Initial clinical trial data demonstrated that patients with CRC carrying activating mutations of *KRAS* affecting exon 2 codons 12 and 13 did not benefit from anti-EGFR monoclonal antibody therapy. Subsequent studies described other mutations in genes of the EGFR signaling pathways involving other exons of *KRAS* and in *NRAS*, *BRAF*, *PIK3CA*, and *PTEN* that may affect response of CRC to anti-EGFR monoclonal antibody therapies. Guidelines addressing the molecular testing of EGFR pathway genes beyond *KRAS* have not been established and are needed in clinical practice.

The DNA mismatch repair (MMR) status of CRC may have predictive value in some clinical settings. While testing of CRC for MMR has been recommended for all patients with CRC as a workup test to evaluate for possible Lynch syndrome, guidelines for the use of MMR as a predictive biomarker of response to therapy have not been reported.

Recent molecular biomarker data have shown the importance of microsatellite instability (MSI) testing, a marker of deficient mismatch repair (dMMR), for the selection of patients for immunotherapy. Alterations of a number of critical genes in CRC development and progression such as dMMR and *BRAF* activating mutations have been shown to affect prognosis, as measured by several metrics of tumor progression or survival.

How does the guideline inform laboratory practice for biomarker testing?
The postgenome era and the emphasis on precision genomic-based medicine are providing enormous amounts of new data and many promising new molecular cancer biomarkers that may emerge as molecular diagnostic tools that can be used to enhance successful treatment of patients with CRC and other cancers. Laboratories and regulatory agencies are faced with challenges to rapidly and efficiently provide new test results for the management of patients with cancer.

Laboratory testing of molecular biomarkers involves the selection of assays, type of specimens to be tested, timing of ordering of tests, and turnaround time for testing results. Recent years have shown that a plethora of technical approaches can effectively be used as long as test specificity and sensitivity meet the clinical needs. While earlier testing approaches were focused on one or a few testing targets, the current need for multiple molecular markers from potentially minute tumor samples is leading to greater use of gene panels such as targeted next-generation sequencing (NGS) cancer panels, which can assay from a few to hundreds of genes and amplicons with known mutational hotspots in cancer. Laboratory approaches to operationalize CRC molecular testing are presented.

How will the guideline be enforced? What happens if a laboratory doesn't follow the guideline?
As with any clinical evidence-based guideline, following this guideline is not mandatory. These recommendations may be added to future versions of your laboratory's accreditation requirements; however, they are not currently required by any regulatory accrediting agency unless as previously defined in CLIA. It is encouraged however, that laboratories adopt these high-level evidence-based recommendations.

REFERENCE

1. 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