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Reflex Biomarker Testing in Metastatic Colorectal Cancer: Implementing BRAF and MSI Assessment

Description: This resource outlines a workflow for reflex biomarker testing in first-line metastatic colorectal cancer (mCRC), focusing on *BRAF* and microsatellite instability (MSI)/mismatch repair (MMR) status to support timely treatment decisions.

Background: The treatment landscape for mCRC has evolved significantly with the expansion of biomarker-driven precision oncology, and first-line decisions increasingly rely on early molecular profiling to guide therapy. Consistent with this approach, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend testing for *KRAS, NRAS, and BRAF* V600E mutations; HER2 overexpression/amplification; and MMR or MSI status (if not previously done) as rapidly as possible for patients with mCRC.[1] Testing should be performed as part of multigene panel testing, enabling identification of rare and actionable mutations and gene fusions.[1]

Among these recommended biomarkers, *BRAF* mutations represent a distinct molecular subtype occurring in approximately 8–12% of patients with mCRC and are associated with poor prognosis.[2] The *BRAF* V600E mutation is the most clinically relevant variant and is generally mutually exclusive with *RAS* mutations.[2] In addition, approximately 20-30% of *BRAF* V600E-mutant tumors are MSI-high[3], which has important therapeutic implications given the potential responsiveness to immune checkpoint inhibitors.[1]

Recent clinical data in the first-line mCRC setting further support the critical role of early biomarker identification. In the BREAKWATER trial, encorafenib and cetuximab plus fluorouracil-based chemotherapy significantly improved response rates and survival compared with chemotherapy alone in patients with *BRAF* V600E–mutant mCRC.[4] These findings have been incorporated into NCCN Guidelines®, which now recommend this combination as the preferred first-line treatment for this population[1], emphasizing the need for timely and comprehensive biomarker testing to inform treatment selection.

However, despite clear guideline recommendations, biomarker testing is not consistently performed at mCRC diagnosis, potentially delaying optimal therapy and impacting patient outcomes. In a real-world analysis of the Flatiron Health electronic health record database, which included more than 25,000 adult patients with mCRC who received at least one line of therapy, only slightly more than half of patients had documented testing for all four key biomarkers (*KRAS, NRAS, BRAF*, and MSI/MMR).[5] This incomplete testing highlights a key opportunity to standardize biomarker testing practices and improve access to actionable molecular data.

In response to this gap, reflex molecular testing – initiated automatically at pathologic diagnosis without a separate oncologist order – offers a practical, widely applicable strategy. It has been associated with reduced time from biopsy to molecular results, facilitating more timely treatment decisions.[6,7] Increasing awareness and adoption of this approach may help ensure consistent access

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to guideline-recommended biomarker information. Accordingly, the following section outlines a structured process for implementing standardized reflex testing workflows for key biomarkers such as *BRAF* and MSI/MMR in clinical practice.

PQI Process:

- Secure multidisciplinary agreement and define scope
    - Convene stakeholders (Gastrointestinal [GI]/Medical Oncology, Pathology, GI surgery, Radiology, Nursing, Pharmacy) to align on the adoption of reflex testing as standard practice
    - Define eligibility criteria that trigger reflex testing (e.g., all newly diagnosed mCRC)
- Develop an institutional reflex testing protocol
    - Create an institution-specific reflex testing protocol (standing algorithm)
    - Specify the biomarker(s) to be reflexed and the testing methodology (e.g., *KRAS, NRAS, and BRAF* mutations; MSI/MMR)
- Define specimen and laboratory considerations
    - Consistent with NCCN Guidelines®, biomarker testing can be performed on formalin-fixed paraffin-embedded tissue or cytology material (preferred), or blood-based circulating tumor DNA (ctDNA)[1]
    - In select clinical scenarios – such as insufficient tissue or anticipated delays in tissue-based testing (e.g., sites with longer turnaround times) – ctDNA testing (liquid biopsy) may be considered
        - For institutions without in-house molecular testing capabilities, Medicare's 14-day tissue retention requirement may delay results for post-surgical inpatients, supporting consideration of ctDNA testing in this setting
    - Document required specimen type(s) (primary vs. metastatic site, per institutional practice), minimum tumor content requirements, and alternative approaches when tissue is limited
- Integrate reflex testing into clinical workflows
    - Operationalize the order pathway within the electronic health record (EHR) and laboratory workflow
    - Build a reflex order set/standing order that allows pathology to initiate molecular testing automatically upon an eligible diagnosis, without requiring a separate oncologist order
    - Define which team initiates the reflex action (e.g., diagnosing pathologist vs molecular laboratory following case sign-out) and specify timing within the diagnostic workflow
- Assign roles and responsibilities
    - Establish clear roles and responsibilities across the testing pathway
    - Assign responsibility for:
        - Tissue stewardship and adequacy assessment, including coordination between pathology and the molecular laboratory, particularly when tissue is limited
        - Result routing and visibility, including where results are displayed in the EHR and which clinicians receive automated notifications
- Maintain and reassess the protocol
    - Periodically evaluate the protocol to ensure it complies with current local and international guidelines, evolving evidence, and reimbursement requirements

Patient-Centered Activities:

- Biomarker testing education: Explain that molecular testing is performed to identify tumor biomarkers that may help guide treatment selection in mCRC

- Shared Decision-Making: Reinforce that molecular test results represent one component of a broader clinical assessment used to guide individualized treatment decisions, including consideration of targeted therapies, immunotherapy, and clinical trial opportunities

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