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# ABSTRACTS

## Advanced Colorectal Cancer

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**Using Biomarkers to Manage Therapy in Advanced Colorectal Cancer**

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Over the past several years, the use of biomarkers such as KRAS has become standard in the care of colorectal cancer (CRC) patients, and the promise of personalized medicine has led to the incorporation of biomarker studies in nearly every clinical trial. However, the requirement of positive EGFR staining prior to insurance approval of cetuximab (when initially approved) serves as a cautionary historical footnote of how adoption of biomarkers prior to sufficient data being available can lead the field down a wrong path. Numerous "promising" predictive biomarkers for cytotoxic chemotherapy agents have failed to be confirmed in large studies. Weighing the level of evidence which makes a biomarker suitable for widespread clinical use is complex.

Testing for KRAS codon 12/13 mutations has become standard of care and the FDA-approved package inserts for both cetuximab and panitumumab have been changed accordingly. It is important to recall that KRAS mutations are a negative predictive test: i.e., patients with a KRAS codon 12/13 mutation do not benefit, and may even be harmed, by treatment with an EGFR-targeting monoclonal antibody (mAb). However, not all patients with wildtype KRAS derive benefit from these agents, and in fact the clinical activity of EGFR-targeting mAb's is modest even in the KRAS WT population. Additionally, EGFR-targeting mAb's have no benefit in the adjuvant setting regardless of KRAS status, and large first-line studies such as the COIN and NORDIC VII trials where cetuximab was combined with oxaliplatin/5-FU regimens were negative. Additionally, it is unclear whether we should be "lumpers" or "splitters" when it comes to KRAS mutations. For instance, there is one report indicating that patients with codon 13 mutations actually benefit from cetuximab (De Roock, 2010), and it is not clear whether all codon 12 mutations behave the same. Thus, much work remains in our efforts to understand the patient population who will benefit from EGFR-targeting mAb's.

BRAF testing serves as another cautionary tale, since nearly every retrospective study showed no benefit to EGFR-targeting mAb's in BRAF MT patients, yet the prospective studies indicate that while BRAF is a poor prognostic factor, such patients should not necessarily be eliminated from consideration of cetuximab (Van Cutsem, 2011). The role of epiregulin and amphiregulin is still being examined. As for the other targeted agent in widespread use, bevacizumab, a predictive test is desperately needed.

With cytotoxic agents, the track record of biomarkers has been fairly poor due to a lack of consistency across studies. Expression and polymorphisms in thymidylate synthase (5-FU), topoisomerase (irinotecan), methylenetetrahydrofolate reductase (5-FU), and ERCC (oxaliplatin) appeared promising in small studies but have not been consistently confirmed in larger studies such as FOCUS (Braun, 2008; Richman, 2011). Even predictive tests for toxicity such as dihydropyrimidine dehydrogenase (DPD) deficiency (5-FU) and UDP-glucuronosyltransferase (UGT) 1A1 (irinotecan) have not shown consistent results despite the FDA-approval of UGT1A1 testing (McLeod, 2010). Deficient mismatch repair (dMMR) proteins have been consistently associated with better prognosis, but the relationship between dMMR and adjuvant 5-FU treatment, for instance, has not been as clear (Hutchins, 2011).

In conclusion, while biomarkers have shown promise and testing for KRAS codon 12/13 mutations has become standard of care, there is insufficient data to recommend routine testing of numerous other biomarkers for cytotoxic and targeted therapies. In order to advance the field, large biomarker datasets will be needed, requiring national and international collaboration and support from patients, physicians, pharmaceutical companies, and funding agencies.

**References**


Braun MS, Richman SD, Quirke P, et al, Predictive Biomarkers of Chemotherapy Efficacy in Colorectal Cancer: Results From the UK MRC FOCUS Trial. *JCO* 2008:26(16):2690-2698.

De Roock W, Jonker DJ, De Nicolantonio F, et al, Association of KRAS p.G13D Mutation With Outcome in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer Treated With Cetuximab. *JAMA* 2010:304(16):1812-1820.

Hutchins G, Southward K, Handley K, et al, Value of Mismatch Repair, KRAS, and BRAF Mutations in Predicting Recurrence and Benefits From Chemotherapy in Colorectal Cancer. *JCO* 2011:29(10):1261-1270.

McLeod HL, Sargent DJ, Marsh S, et al, Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: results from North American Gastrointestinal Intergroup Trial N9741. **JCO** 2010:28(20):3227-3233.

Richman S, Barret JH, and Seymour MT, Failure to Validate Toxicity and Outcome Biomarkers From the FFCD 2000-05 Trial in the MRC CR08 FOCUS Trial. JCO 2001:29(12):e354-355.

Van Cutsem E, Kohne CH, Lang I, et al, Cetuximab Plus Irinotecan, Fluorouracil, and Leucovorin As First-Line Treatment for Metastatic Colorectal Cancer: Updated Analysis of Overall Survival According to Tumor KRAS and BRAF Mutation Status. **JCO** 2011:29(15):2011-2019.