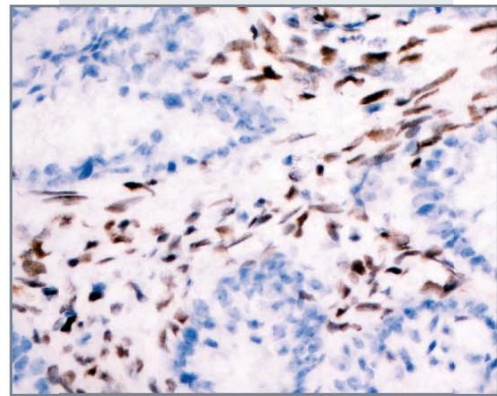
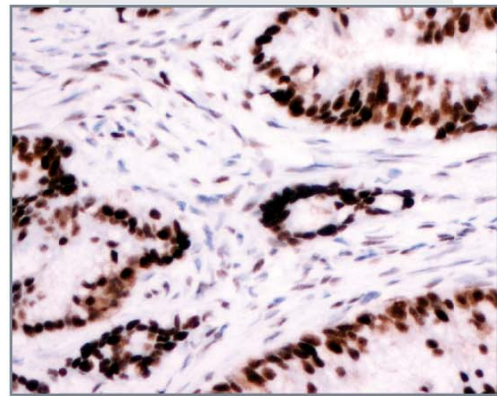


H&E



MLH1



MSH2

Colorectal adenocarcinoma showing selective loss of MLH1 MMR, with retention of MSH2, in tumor cell population.

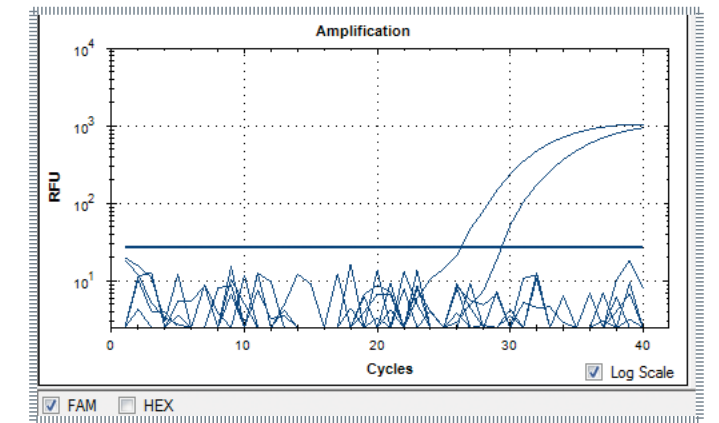
Tissue-based markers are now available that can provide the GI oncologist with tools to help predict responsiveness to selected therapies and to assess the clinical outcome in patients with colorectal adenocarcinoma.

Microsatellite Instability, Mismatch Repair Genes, and Colonic Neoplasia

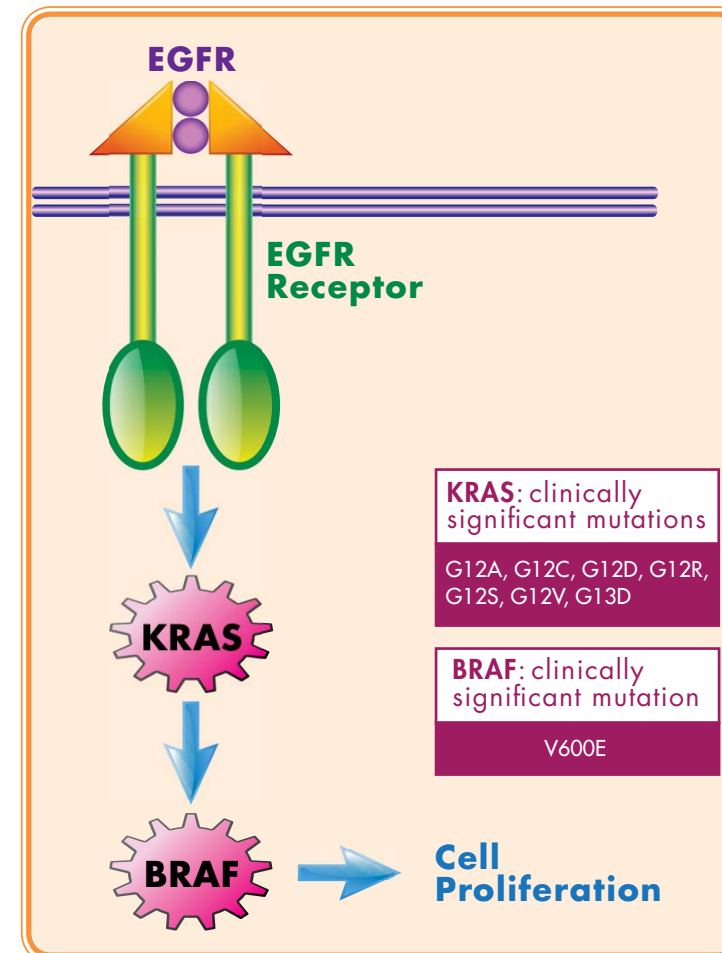
Microsatellite instability (MSI) due to defective mismatch repair genes has been reported in the vast majority of tumors from patients with Lynch syndrome (hereditary non-polyposis colorectal cancer (HNPCC) syndrome). In addition, an important subset of sporadic colorectal adenocarcinomas also display MSI. Several studies have demonstrated that colorectal adenocarcinomas demonstrating microsatellite instability (MSI) exhibit loss of expression of one or more of the mismatch repair (MMR) enzymes MLH1, MSH2, PMS2 and MSH6, which can be assessed by IHC (dMMR). IHC can therefore be a surrogate technique for the identification of MSI tumors. Tumors retaining MMR expression by IHC are referred to as pMMR. Thus, IHC is a highly accurate and cost-effective method for identifying patients with microsatellite unstable tumors who should be investigated for Lynch syndrome; in addition, in the context of sporadic colorectal adenocarcinomas identification of MSI tumors can help identify patients who have more favorable outcomes and may not respond to standard fluorouracil-based chemotherapy regimens. We recommend MSI testing by IHC over PCR especially in the setting of Lynch syndrome evaluation, as IHC identifies the involved gene in a given patient for potential sequencing studies.

KRAS and BRAF Mutation Analysis

KRAS and BRAF are key components of the RAS-RAF-MAPK signal transduction pathway, which is normally activated when EGFR is activated by its ligand, EGF. Colon cancers that have activating mutations in KRAS are resistant to anti-EGFR-targeted therapies such as cetuximab. Determination of KRAS mutational status in all cases of metastatic colorectal adenocarcinomas has been recommended in NCCN guidelines. BRAF is downstream of KRAS in the signaling cascade, and some studies show that mutated BRAF may also be predictive of anti-EGFR therapy responsiveness. The KRAS and BRAF mutation assays performed at PhenoPath Laboratories use a very sensitive and specific real-time PCR method on genomic DNA isolated from macrodissected tumor cells, and these PCR assays cover the most clinically relevant activating mutations in KRAS and BRAF.



KRAS
Real time PCR tracing of mutation positive case



EGFR is a receptor tyrosine kinase that conveys extracellular growth signals to the cell nucleus by activating downstream signal transduction proteins. KRAS and BRAF are key signal transduction proteins in this pathway. Activating mutations of KRAS and BRAF render this pathway refractory to EGFR antibody blockade. Patients with any of the 7 listed KRAS activating mutations in codons 12 and 13 therefore should NOT be treated with drugs such as cetuximab.