BRAF mutations have been detected in 8-15% of patients with colorectal cancer. BRAF mutations are pathogenic and testing for these mutations are critical in determining drug sensitivity to tyrosine kinase inhibitors. Some patients with V600E mutations have been shown to be resistant to anti-EGFR therapies such as cetuximab or panitumumab. However, a number of other BRAF inhibitors are in various phases of clinical trials and patients with BRAF mutations have demonstrated a response to these types of targeted therapies when taken in combination with other treatments. BRAF mutations are identified by published guidelines as targetable abnormalities.

Epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor. EGFR mutations have been reported in a number of different cancers, including colorectal cancer. EGFR mutations reported in cases of metastatic colorectal cancer have been suggested to be resistant to EGFR targeted therapies. Testing for EGFR mutations can be useful for screening patients who would benefit from targeted cancer therapies.

HRAS is highly homologous with KRAS and NRAS; all are members of the most frequently mutated family of oncogenes. HRAS mutations have been detected in colorectal cancers. Screening for HRAS mutations can be useful in determining a patients sensitivity to tyrosine kinase inhibitors.

KIT mutations have been detected in colorectal cancers. These mutations increase the phosphorylation of signal transduction proteins. The result is the activation of a cascade of intracellular proteins that promote cell survival and proliferation. Testing for KIT mutations may be useful in determining a patients sensitivity to tyrosine kinase inhibitors.

KRAS mutations have been detected in about 36-40% of colorectal cancers. Patients with mutant KRAS have been shown to be resistant to anti-EGFR antibody therapies such as cetuximab and panitumumab. Testing for KRAS mutations is recommended by published guidelines and can be useful in determining a colorectal cancer patients sensitivity to tyrosine kinase inhibitors.

MET mutations have been detected in numerous solid tumor cancers, including colorectal cancer. MET mutations play a role in the pathogenesis of various cancers. Multiple antibodies against MET and small molecule MET-inhibitors are currently in clinical trials for the treatment of various cancer types.

MSI analysis and/or MMR IHC may be considered for all new colorectal cancer diagnoses to detect patients at increased risk of carrying germline mutations associated with Lynch Syndrome (HNPCC). Testing is recommended by published guidelines for tumors of patients ≤70 years of age or meeting other criteria of the Bethesda Guidelines. MSI is also detected in sporadic colorectal cancer and its presence may imply better prognosis.

MLH1 promoter methylation analysis is useful to distinguish sporadic from inherited colorectal and endometrial cancers in tumors that are MLH1-deficient by IHC staining and/or have high levels of microsatellite instability (MSI-H). The majority of MSI in sporadic cases of these tumors is caused by MLH1 promoter hypermethylation, while hypermethylation is rare in inherited cases. MLH1 promoter methylation analysis results should be considered with other clinical risk factors in determination of likelihood of HNPCC/Lynch Syndrome.

NOTCH1 mutations have been identified in multiple solid tumors and testing for these mutations may be useful in determining sensitivity to targeted therapies. A number of NOTCH1 drug inhibitors are currently in development to target tumors such as colorectal cancers.
NRAS  NRAS is highly homologous with KRAS; both are members of the most frequently mutated family of oncogenes. NRAS mutations have been detected in about 1-6% of colorectal cancers. Colorectal cancer patients with mutated NRAS have been shown to have reduced sensitivity to EGFR monoclonal antibodies. Testing is recommended by published guidelines and can be useful in determining a patient's sensitivity to tyrosine kinase inhibitors.

PDGFRA  Platelet-derived growth factor receptor alpha (PDGFRα) gene is a member of the subfamily of type III receptor tyrosine kinases and has been detected in patients with solid tumors. Testing for PDGFRA mutations in colorectal cancer may be useful in determining sensitivity to tyrosine kinase inhibitors.

PIK3CA  PIK3CA mutations have been identified in about 10-30% of patients with colorectal cancer. PIK3CA mutations are gain of function mutations that increase cancer activity. Early stage clinical trials have shown that colorectal cancer patients with PIK3CA mutations may be more sensitive to PI3K inhibitors. Testing for PIK3CA mutations may be useful in identifying colorectal cancer patients who may benefit from PI3K inhibitors or other kinase therapies.

PTEN  PTEN is one of the most commonly mutated tumor suppressors in solid tumor cancers and have been detected in about 5-14% of patients with colorectal cancers. Clinical trials are currently being conducted on patients with PTEN mutations. Testing for PTEN mutations may be useful in identifying patients that are sensitive to PI3K/AKT inhibitors as well as FRAP/mTOR inhibitors.

SMO  SMO is crucial in the Hedgehog pathway and is very important in oncogenesis. SMO mutations have been detected in colorectal cancers. Testing for SMO mutations can be useful as a prognostic or therapeutic indicator. For example, irtraconazole targets SMO and patients with SMO mutations could potentially respond to this type of therapy. Clinical trials are currently being conducted on SMO mutated patients with solid tumor cancers.

TP53  TP53 mutations are detected in a variety of cancers and are generally associated with a poor prognosis. Testing for TP53 mutations can be useful in the prognostic assessment of patients with colorectal cancer.

MET FISH  MET gene amplification, as detected by FISH, is one mechanism of MET overexpression and is a known mechanism of EGFR-TKI resistance. Clinical trials have demonstrated activity of MET inhibitors against numerous solid tumors. MET amplification is a targetable abnormality that may be useful in determining a patient's sensitivity to targeted therapies.

PTEN FISH  This gene is commonly deleted in tumors and resides in the targetable PI3K/AKT/mTOR pathway. PTEN-deficient tumors may respond to PI3K kinase and mTOR inhibitors.

*Please see our website [neogenomics.com](http://neogenomics.com) for a complete test description and printable specimen requirements. References on file.*