NRAS Mutations in Melanoma and Colorectal Cancer

Indications for Ordering

NRAS mutation detection
• Screen individuals with melanoma who may respond to therapy targeted at downstream genes in the MAPK signaling pathway
• Screen individuals with colorectal cancer (CRC) for prediction of response to anti-EGFR therapies

Test Description
Polymerase chain reaction/pyrosequencing
• Single gene assay for detection of mutations in NRAS

Tests to Consider

Primary test
NRAS Mutation Detection, Pyrosequencing 2003123
• Detects activating NRAS mutations (codons 12, 13, 61) associated with relative resistance to anti-EGFR therapy in CRC
• Predicts response to anti-EGFR and MAPK pathway therapies in a variety of malignancies (eg, melanoma and CRC)

Related tests

Melanoma
Solid Tumor Mutation Panel by Next Generation Sequencing 2007991
• Aids in therapeutic decisions for solid tumor cancers
• Simultaneously evaluates mutations in 44 genes, including BRAF, NRAS, KIT
• Predicts prognosis and therapeutic response in patients with solid tumor cancers

KIT Mutations, Melanoma 2002695
• Detects activating mutations in KIT and PDGFR
• Predicts response to tyrosine kinase inhibitor (TKI) therapy
• Insurance providers may require documentation of drug-sensitive activating mutation for TKI reimbursement

BRAF Codon 600 Mutation Detection by Pyrosequencing 2002498
• Use to detect activating BRAF mutations at codon 600
  o Can indicate resistance to anti-EGFR therapy in CRC
• Also used within the Lynch syndrome reflex testing pathway (for CRC specimens only)

BRAF V600E Mutation Detection in Circulating Cell-Free DNA by Digital Droplet PCR 2013921
• Determines BRAF V600E mutation status in patients with solid tumors to select candidates for targeted therapy with kinase inhibitors (BRAF and/or MEK)
• Monitors response to therapy and disease progression in patients carrying BRAF V600E mutation

CRC
Colon Cancer Gene Panel, Somatic 2011616
• Use for individuals with metastatic CRC to guide treatment with anti-EGFR monoclonal antibodies
• Detects mutations in BRAF, KRAS, NRAS, and PIK3CA

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KRAS Mutation Detection with Reflex to BRAF Codon 600 Mutation Detection 2001932
• Determine eligibility for anti-EGFR (cetuximab and panitumumab) therapy in patients with metastatic CRC

KRAS Mutation Detection 0040248
• Detects activating KRAS mutations (codons 12, 13, 61) associated with anti-EGFR therapy resistance
Disease Overview

Treatment issues
• Metastatic melanoma and CRC are associated with a poor prognosis and poor response to traditional chemo- or radiotherapy
• Targeted therapy may play a role in disseminated disease
• Genetic mutations guide utilization of targeted therapy
  o Melanoma – BRAF, NRAS, KIT
  o CRC – BRAF, KRAS, NRAS

Genetics

Gene – NRAS

Structure/function – GTPase-encoding gene in the RAS/RAF/MAPK pathway

Mutations
• Majority of activating mutations – codon 61
• Mutually exclusive with KRAS mutations in individuals with CRC
• Associated with relative resistance to anti-EGFR therapy

Test Interpretation

Sensitivity/specificity
• Clinical sensitivity – oncogenic NRAS mutation found in a small percentage of melanomas and ~3% of CRCs
• Analytical sensitivity/specificity – 100%

Results
• Positive
  o Oncogenic NRAS mutation detected
  o Predictive of relative resistance to anti-EGFR therapy in CRC
  o Possibly predictive of response to therapy targeted at downstream genes in the MAPK signaling pathway in melanoma
• Negative
  o No oncogenic NRAS mutation detected

Limitations
• Limit of detection
  o Pyrosequencing and MassARRAY – 10% mutant alleles
  o NGS – 5% mutant alleles
• Pyrosequencing and MassARRAY – oncogenic mutations outside of codons 12, 13, and 61 will not be detected
• Presence or absence of mutations does not guarantee a response or lack of response to anti-EGFR therapies or therapies targeted at downstream genes in the MAPK signaling pathway