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 PDGFRA
- 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
  - Can indicate responsiveness to BRAF inhibitors in melanomas

**CRC**

**BRAF Codon 600 Mutation Detection by Pyrosequencing 2002498**
- Use to detect activating BRAF mutations at codon 600
  - 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

**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
  - Melanoma – BRAF, NRAS, KIT
  - 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