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) who may respond 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
- 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

- Simultaneously evaluates mutations in 48 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

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*, extended *KRAS*, and *PIK3CA*

Solid Tumor Mutation Panel by Next Generation Sequencing 2007991

- Simultaneously evaluates mutations in 48 genes, including *BRAF, KRAS, NRAS,* and *PIK3CA*
- Predicts prognosis and therapeutic response in patients with solid tumor cancers

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

PTEN by Immunohistochemistry 2004115
PTEN with Interpretation by Immunohistochemistry 2007031

- Detects loss of PTEN expression in tumor tissue
- Possibly associated with relative resistance to anti-EGFR therapy

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, PIK3CA, PTEN*

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

Limitations

- Limit of detection
  - Pyrosequencing and MassARRAY – 10% mutant alleles
  - 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