NRAS Mutation Detection, Pyrosequencing

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Metastatic melanoma is associated with a poor prognosis and poor response to traditional chemotherapy or radiation therapy,[1] as is metastatic CRC.[2] Targeted therapy may play a role in treatment of disseminated disease. Genetic variants guide utilization of targeted therapy for melanoma (*BRAF*, *NRAS*, *KIT*)[3] and CRC (*BRAF*, *KRAS*, *NRAS*). *NRAS* mutation detection screens for individuals with melanoma who may respond to therapy targeted at downstream genes in the MAPK signaling pathway[3] and screens for individuals with CRC who may show relative resistance to anti-EGFR therapies.[2] (For more information, see the Colorectal Cancer - Predictive Testing for Anti-EGFR Therapy Test Fact Sheet).

Featured ARUP Testing

NRAS Mutation Detection by Pyrosequencing 2003123

Method: Polymerase Chain Reaction/Pyrosequencing

- Use to detect activating *NRAS* mutations (codons 12, 13, 61) associated with relative resistance to anti-EGFR therapy in colorectal cancer (CRC).
- Use to predict response to anti-EGFR and MAPK pathway therapies in a variety of malignancies (eg, melanoma and CRC).

Genetics

Gene

NRAS

Structure/Function

GTPase-encoding gene in the RAS/RAF/MAPK pathway

Mutations

- Majority of activating mutations are in exon 2 (codons 12 and 13) and exon 3 (codon 61).[4]
- *NRAS*, *KRAS*, and *BRAF* mutations are mutually exclusive in individuals with CRC.[5]
- *NRAS* mutations rarely overlap with *BRAF* and *KIT* mutations in melanoma.[3]
- Guidelines suggest extended *RAS* testing in CRC, which includes codons 12, 13, 59, 61, 117, and 146.[2]

Test Interpretation

Sensitivity/Specificity

Clinical Sensitivity

Activating *NRAS* mutations are found in 20% of metastatic melanomas[6] and approximately 3% of CRCs.

Analytic Sensitivity/Specificity

100%

Results

Result	Variant(s) Detected	Interpretation
Positive	Oncogenic *NRAS* mutation detected	Predictive of relative resistance to anti-EGFR therapy in CRC[2] Possibly predictive of response to therapy targeted at downstream genes in the MAPK signaling pathway in melanoma[3]
Negative	No oncogenic *NRAS* mutation detected	n/a

Limitations

- Limit of detection: 10% mutant alleles
- Does not cover extended *RAS*; 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.

References

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6. Dummer R, Schadendorf D, Ascierto PA, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18(4):435-445.

Related Information

Melanoma
Colorectal (Colon) Cancer
Colorectal Cancer - Predictive Testing for Anti-EGFR Therapy

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