Colorectal Cancer - Predictive Testing for Anti-EGFR Therapy

Colorectal cancer (CRC) is the third most common cancer diagnosed in men and women in the United States (excluding skin cancers), and is the second most common cause of cancer deaths in both men and women. Two anti-EGFR monoclonal antibodies (cetuximab and panitumumab) are available for treatment of advanced CRC. *KRAS*, *BRAF*, and possibly *NRAS* mutations are associated with resistance to anti-EGFR therapy.

Genetics and Test Information

Gene	*KRAS*	*NRAS*	*BRAF*
Gene Function	GTPase-encoding gene in the RAS/RAF/MAPK pathway	GTPase-encoding gene in the RAS/RAF/MAPK pathway	Kinase-encoding gene in the RAS/RAF/MAPK pathway
Mutations	Majority of oncogenic mutations: codons 12 and 13 (>90%) Most of the remaining activating mutations: codons 61 and 146[a]	Majority of activating mutations: codon 61[a] Mutually exclusive with *KRAS* mutations in individuals with CRC Associated with relative resistance to anti-EGFR therapy	Majority of activating mutations: codon 600 Mutually exclusive with *KRAS* mutations in individuals with CRC
Sensitivity/ Specificity	Clinical sensitivity: activating *KRAS* mutations found in ~40% of CRCs Analytic sensitivity/specificity: 100%	Clinical sensitivity: oncogenic *NRAS* mutation found in ~3% of CRCs Analytic sensitivity/specificity: 100%	Clinical sensitivity: activating *BRAF* mutation found in ~10% of CRCs Analytic sensitivity/specificity: 100%

[a]Guidelines recommended extended RAS testing which includes codons 12, 13, 59, 61, 117, and 146. (National Comprehensive Cancer Network, 2021[1])

Tests to Consider

Solid Tumor Mutation Panel by Next Generation Sequencing 2007991

Method: Massively Parallel Sequencing

- Aids in therapeutic decisions for solid tumor cancers.
- May assist in predicting response to anti-EGFR therapy in CRC.
- Simultaneously evaluates mutations in 44 genes, including *BRAF*, *KRAS*, and *NRAS*; for more detailed information about this test, refer to the Solid Tumor Mutation Panel by Next Generation Sequencing Test Fact Sheet.

KRAS Mutation Detection 0040248

Method: Polymerase Chain Reaction/Pyrosequencing

May assist in predicting response to anti-EGFR therapy in CRC.

NRAS Mutation Detection by Pyrosequencing 2003123

Method: Polymerase Chain Reaction/Pyrosequencing

May assist in predicting response to anti-EGFR therapy in CRC.

BRAF Codon 600 Mutation Detection by Pyrosequencing 2002498

Method: Polymerase Chain Reaction/Pyrosequencing

May assist in predicting response to anti-EGFR therapy in CRC.

See Related Tests

Gene	*KRAS*	*NRAS*	*BRAF*
Results	Positive • Oncogenic *KRAS* mutation detected • Lack of response to therapy with antibodies targeted to EGFR is predicted Negative • No oncogenic *KRAS* mutation detected • Follow-up BRAF testing is advised prior to initiation of anti-EGFR therapy	Positive • Oncogenic *NRAS* mutation detected • Predictive of relative resistance to anti-EGFR therapy Negative • No oncogenic *NRAS* mutation detected	Positive • Oncogenic *BRAF* mutation detected • Available data suggest resistance to anti-EGFR therapy • Appears to be associated with a worse prognosis Negative • No oncogenic *BRAF* mutation detected
Limitations	Limit of detection • Pyrosequencing: 10% mutant alleles • NGS: 5% mutant alleles Pyrosequencing: oncogenic mutations outside of codons 12, 13, 61 will not be detected A substantial portion of individuals with wild type *KRAS* still fail to respond to anti-EGFR agents, implicating downstream mutations	Limit of detection • Pyrosequencing: 10% mutant alleles • NGS: 5% mutant alleles Pyrosequencing: oncogenic mutations outside of codons 12, 13, 61 will not be detected Presence or absence of mutations does not guarantee a response or lack of response to anti-EGFR therapy	Limit of detection • Pyrosequencing: 10% mutant alleles • NGS: 5% mutant alleles Pyrosequencing: oncogenic mutations outside of codon 600 will not be detected

[a]Guidelines recommended extended RAS testing which includes codons 12, 13, 59, 61, 117, and 146. (National Comprehensive Cancer Network, 2021[1])

References

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology, colon cancer, Version 2.2021. [Updated: Jan 2021; Accessed: Feb 2021]

Related Information

Colorectal Cancer
NRAS Mutation Detection, Pyrosequencing

Related Tests

BRAF V600E Mutation Detection in Circulating Cell-Free DNA by Digital Droplet PCR 2013921

Method: Polymerase Chain Reaction

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