

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	<i>KRAS</i>	<i>NRAS</i>	<i>BRAF</i>
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	<p>Majority of oncogenic mutations: codons 12 and 13 (>90%)</p> <p>Most of the remaining activating mutations: codons 61 and 146^a</p>	<p>Majority of activating mutations: codon 61^a</p> <p>Mutually exclusive with <i>KRAS</i> mutations in individuals with CRC</p> <p>Associated with relative resistance to anti-EGFR therapy</p>	<p>Majority of activating mutations: codon 600</p> <p>Mutually exclusive with <i>KRAS</i> mutations in individuals with CRC</p>
Sensitivity/Specificity	<p>Clinical sensitivity: activating <i>KRAS</i> mutations found in ~40% of CRCs</p> <p>Analytic sensitivity/specificity: 100%</p>	<p>Clinical sensitivity: oncogenic <i>NRAS</i> mutation found in ~3% of CRCs</p> <p>Analytic sensitivity/specificity: 100%</p>	<p>Clinical sensitivity: activating <i>BRAF</i> mutation found in ~10% of CRCs</p> <p>Analytic sensitivity/specificity: 100%</p>
Results	<p>Positive</p> <ul style="list-style-type: none"> Oncogenic <i>KRAS</i> mutation detected Lack of response to therapy with antibodies targeted to EGFR is predicted <p>Negative</p> <ul style="list-style-type: none"> No oncogenic <i>KRAS</i> mutation detected Follow-up <i>BRAF</i> testing is advised prior to initiation of anti-EGFR therapy 	<p>Positive</p> <ul style="list-style-type: none"> Oncogenic <i>NRAS</i> mutation detected Predictive of relative resistance to anti-EGFR therapy <p>Negative</p> <ul style="list-style-type: none"> No oncogenic <i>NRAS</i> mutation detected 	<p>Positive</p> <ul style="list-style-type: none"> Oncogenic <i>BRAF</i> mutation detected Available data suggest resistance to anti-EGFR therapy Appears to be associated with a worse prognosis <p>Negative</p> <ul style="list-style-type: none"> No oncogenic <i>BRAF</i> mutation detected

^aGuidelines recommended extended *RAS* testing, which includes codons 12, 13, 59, 61, 117, and 146. (National Comprehensive Cancer Network, 2021¹).

Featured ARUP Testing

[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

Gene	<i>KRAS</i>	<i>NRAS</i>	<i>BRAF</i>
Limitations	Limit of detection	Limit of detection	Limit of detection
	<ul style="list-style-type: none"> Pyrosequencing: 10% mutant alleles NGS: 5% mutant alleles 	<ul style="list-style-type: none"> Pyrosequencing: 10% mutant alleles NGS: 5% mutant alleles 	<ul style="list-style-type: none"> Pyrosequencing: 10% mutant alleles NGS: 5% mutant alleles
	Pyrosequencing: oncogenic mutations outside of codons 12, 13, 61 will not be detected	Pyrosequencing: oncogenic mutations outside of codons 12, 13, 61 will not be detected	Pyrosequencing: oncogenic mutations outside of codon 600 will not be detected
	A substantial portion of individuals with wild-type <i>KRAS</i> still fail to respond to anti-EGFR agents, implicating downstream mutations	Presence or absence of mutations does not guarantee a response or lack of response to anti-EGFR therapy	

^aGuidelines recommended extended *RAS* testing, which includes codons 12, 13, 59, 61, 117, and 146. (National Comprehensive Cancer Network, 2021¹).

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 (Colon) Cancer

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 Content Review March 2021 | Last Update August 2023