

Genzyme provides a comprehensive test menu to assist with the personalized management of patients with colorectal cancer.

KRAS Mutation Analysis Aids in Therapeutic Decision Making

KRAS Mutation Analysis, part of our colorectal cancer portfolio, provides additional guidance in therapeutic treatment decisions for patients with metastatic colorectal cancer.

Individuals respond differently to chemotherapeutic and targeted biologic agents. The evaluation of therapeutic markers, such as KRAS, can help physicians individualize cancer therapy for their patients.

Recent studies have shown that assessing KRAS gene mutational status in tumor tissue can help identify patients who may not benefit from cetuximab (ERBITUX[®]) or panitumumab (Vectibix[®]) treatment.

The Clinical Significance of KRAS Mutations

Mutations in the KRAS Gene

- Are associated with poor prognosis in patients with colorectal cancer.^{1,3,4}
- Have been reported in approximately 30–50% of colorectal carcinoma.^{4,5,6}
- Are associated with resistance to anti-epidermal growth factor receptor (anti-EGFR) therapy.^{1,2,9}
- Are found more frequently in patients who show limited clinical response to targeted therapeutics, such as cetuximab or panitumumab.^{1,2,9}

Clinical Studies Demonstrated a Lack of Response

Response Rate

Clinical studies demonstrated a significant lack of response to anti-EGFR targeted therapies in patients with KRAS mutations in the tumor tissue.

Author	Treatment	Tumors with KRAS Mutations (overall)	Response Rate*		
			# of Patients Treated	Wild Type	KRAS Mutation
Lièvre	cetuximab	32%	114	44%	0%
Di Fiore	cetuximab [†]	37%	59	32%	0%
Finocchiaro	cetuximab	40%	81	27%	6.3%
De Roock	cetuximab [‡]	46%	37	40%	0%
Amado	panitumumab	43%	208	17%	0%
Freeman	panitumumab	36%	59	16%	0%

*Patients with complete or partial response were classified as responders.

†Patients treated with cetuximab plus chemotherapy.

‡Patients treated with cetuximab plus irinotecan or cetuximab in monotherapy.

KRAS Mutation Analysis and Overall Survival

Time to Progression and Overall Survival

Clinical studies demonstrated a statistically significant decrease in time to progression and overall survival in patients with KRAS mutations treated with anti-EGFR targeted therapies compared to patients without KRAS mutations present in the tumor tissue.

Author	Treatment	Median Time to Progression (months)		Overall Survival (months)	
		Mutations	Wild Type	Mutations	Wild Type
Lièvre	cetuximab	2.1	7.4	10.1	14.3
Finocchiaro	cetuximab	3.7	6.3	8.3	10.8
De Roock	cetuximab*	7.0	7.5		
Amado	panitumumab	1.7	2.9		
Di Fiore	cetuximab†	3.0	5.5		

*Patients treated with cetuximab plus irimotecan or cetuximab in monotherapy.

†Patients treated with cetuximab plus chemotherapy.

Method

KRAS Mutation Analysis analyzes codons 12 and 13 of the KRAS gene by single nucleotide primer extension.

Specimen Requirements

■ Fixed Paraffin Block with Corresponding H&E:

- Tissues should be well-fixed in formalin. If an alternative fixative is used, it should be noted on the requisition.
- Store specimen at room temperature (20–23.5°C).
- Use cold pack for transport. Be sure cold pack is not in direct contact with specimen during transport.

■ Unstained Slides:

- Send all slides within 5–7 days of cutting.
- Minimum of 4 slides (w/1 H&E) or 5 slides (w/o H&E).
- Pre-cut slides from paraffin block in 7 micron sections.
- Air dry. Do not oven dry.
- Store specimens at room temperature (20–23.5°C).

CPT Code

- 83890, 83892, 83898, 83904, 83907, 83908, 83912

Please Note: If you submit a sample for both EGFR FISH and EGFR mutation analysis testing, please consult with your sales representative for complete specimen submission details.

REFERENCES

- 1) Lièvre, A. et al., KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol* 2008; 26:374-9.
- 2) Di Fiore, F. et al., Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by cetuximab plus chemotherapy. *Br J Cancer* 2008; 96:1166-9.
- 3) Ince, W. L. et al., Association of k-ras, b-raf, and p53 status with the treatment effect of bevacizumab. *J Natl Cancer Inst* 2005; 97:981-9.
- 4) Oliveira, C. et al., KRAS and BRAF oncogenic mutations in MSS colorectal carcinoma progression. *Oncogene* 2007; 26:158-63.
- 5) Bos, J. L., ras oncogenes in human cancer: a review. *Cancer Res* 1989; 49:4682-9.
- 6) Benhattar, J. et al., Prognostic significance of k-ras mutations in colorectal cancer. *Gastroenterology* 1993; 104:1004-8.

MEETING ABSTRACTS

- 7) Finocchiaro, G. et al., EGFR, HER2, and Kras as predictive factors for cetuximab sensitivity in colorectal cancer. 2007 ASCO Annual Meeting Proceedings Part 1. Vol 25, No. 18S; Abstract # 4021.
- 8) De Roock, W. et al., KRAS mutations preclude tumor shrinkage of colorectal cancers treated with cetuximab. 2007 ASCO Annual Meeting Proceedings Part 1. Vol 25, No. 18S; Abstract # 4132.
- 9) Freeman, D. et al., Association of somatic KRAS gene mutations and clinical outcome in patients (pts) with metastatic colorectal cancer (mCRC) receiving panitumumab monotherapy. *European Journal of Cancer Supplements*. Vol 5, No 4: page 239.
- 10) Amado, R. G. et al., analysis of KRAS mutations in patients with metastatic colorectal cancer receiving panitumumab monotherapy. *European Journal of Cancer Supplements*. Vol 5, No. 6: Page 8.



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