

Spotlight on Health

Colorectal Cancer Tumor Mutation Testing

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States.¹ It can be inherited, familial, or sporadic. Sporadic CRC, the most common form, results from an accumulation of mutations, over time, that result in a growth advantage for the cells carrying them. This newsletter focuses on how identifying mutations that are often present in sporadic CRC can help improve treatment and patient care.

Driver Mutations

Sporadic CRC is caused by an accumulation of inherited and somatic mutations.² Some of these give cells a selective advantage by allowing them to grow better or faster; these are called driver mutations. They play an important role in the development of cancer. Estimates for the number of driver mutations in individual cancers vary from 5 to as many as 20.²

Driver Mutations in Colorectal Cancer

Driver mutations in CRC commonly occur in the mitogen-activated protein kinase (MAPK) pathway.³ This pathway leads to a number of downstream events, including cell division. Activation of the pathway occurs when signaling molecules bind to the epidermal growth factor receptor (EGFR).

Activation of the MAPK pathway can also be blocked. This is the basis of anti-EGFR antibody therapies for metastatic CRC. In this case, binding of an antibody to the EGFR blocks activation of the pathway. However, driver mutations in the *KRAS*, *NRAS*, and *BRAF* genes, located downstream in the pathway, can cause resistance to anti-EGFR antibody therapies by causing continuous activation of the pathway. This is true of many *KRAS* mutations in exons 2, 3, and 4.^{4,5} (Exons are the segments of genes that code for proteins.) It is also likely true for mutations in exons 2, 3, and 4 of the related gene *NRAS*,^{5,6} as well as for the most common *BRAF* mutation.^{3,6}

Recommendations for Tumor Mutation Testing

The American Society of Clinical Oncology (ASCO) recommends that all metastatic CRC patients who are candidates for anti-EGFR antibody therapy should undergo tumor testing. They should be tested for mutations in exons 2, 3, and 4 of both the *KRAS* and *NRAS* genes.⁵ In addition to testing for these mutations, the National Comprehensive Cancer Network (NCCN) recommends testing for *BRAF* mutations in tumors from patients with suspected metastatic CRC.^{6,7} Anti-EGFR antibody therapies do not play a role in the management of stage I to III CRC. So the NCCN recommends tumor testing when stage IV CRC is diagnosed.⁷



Why Choose a Multi-Gene Test?

Some tumors have more than 1 mutation, and interactions may occur between them. A benefit of next-generation sequencing technology is that it is more efficient at analyzing multiple mutations in multiple genes at the same time. For some patients, comprehensive mutation analysis may lead to more informed clinical decisions.

How Were the Genes in the Panel Chosen?

Genes included in the IBM Watson® Genomics from Quest Diagnostics® Core panel were selected based on their role as a key target of, or predictive marker for, an anti-cancer therapy. Some mutations may be a target of an FDA-approved drug. Others may be the target of a therapy currently in development or a clinical trial. All the genes are considered clinically “actionable”. Knowledge that a patient has a mutation in the gene can be used to help determine the optimum treatment for the patient.

How the Laboratory Can Help

Quest Diagnostics offers the IBM Watson® Genomics from Quest Diagnostics® Core solid tumor profile. It uses next-generation sequencing and includes 50 “actionable” genes that are frequently altered in solid tumors, including *KRAS*, *NRAS*, and *BRAF*. A patient-specific report is generated in collaboration with IBM Watson. The report includes

- Mutation(s) identified and their role in cancer, including information on
 - Mutation prevalence
 - Mutation effect
 - Applicable guidelines
 - Therapeutic implications
 - Prognostic implications
- Information about drugs known to target the mutations
 - FDA-approved drugs for patient’s mutation(s) in patient’s tumor type
 - FDA-approved drugs for patient’s mutation(s) in other tumor types
- Any relevant clinical trials the physician and patient may want to consider

Quest Diagnostics also offers the Colorectal Cancer Mutation Panel (*KRAS*, *PIK3CA*, *BRAF*, *NRAS*). This test uses polymerase chain reaction and sequencing to detect actionable mutations associated with CRC in the *KRAS*, *PIK3CA*, *BRAF*, and *NRAS* genes.

References

1. American Cancer Society. Cancer facts & figures 2016. cancer.org/research/cancerfactsstatistics/cancerfactsfigures2016. Accessed January 10, 2017.
2. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. *Nature*. 2009;458:719-724.
3. Graham DM, Coyle VM, Kennedy RD, Wilson RH. Molecular subtypes and personalized therapy in metastatic colorectal cancer. *Curr Colorectal Cancer Rep*. 2016;12:141-150.
4. Semrad TJ, Kim EJ. Molecular testing to optimize therapeutic decision making in advanced colorectal cancer. *J Gastrointest Oncol*. 2016;7(Suppl 1): S11-20.
5. Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS Gene Mutation testing in metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. *J Clin Oncol*. 2016;34:179-185.
6. National comprehensive cancer network clinical practice guidelines in oncology (NCCN Guidelines®). Colon cancer version 1.2017. nccn.org/. Updated November 23, 2016. Accessed January 10, 2017.
7. National comprehensive cancer network clinical practice guidelines in oncology (NCCN Guidelines®). Rectal cancer version 1.2017. nccn.org/. Updated November 23, 2016. Accessed January 10, 2017.