KEY POINTS

- To understand why people with metastatic colorectal cancer (mCRC) respond differently to different treatments, it is important to learn more about a tumor, including its biomarkers.

- Evidence suggests that certain targeted treatments, known as anti-epidermal growth factor receptor (EGFR) monoclonal antibody therapies, work well in patients with RAS wild-type mCRC by binding to receptors that regulate the growth, survival and increase of cells.

- In mCRC, RAS genes have been identified as a key biomarker that can help predict how well an individual is likely to respond to particular treatments, making it essential that a RAS biomarker test is performed at the time of diagnosis, or before starting first-line therapy.

- Merck, in separate collaborations with Sysmex Inostics and Biocartis respectively, have introduced two novel liquid biopsy RAS biomarker tests that can enable precision medicine for patients with mCRC.

- The results of a RAS biomarker test help to inform discussions between physicians and their patients around personalized treatment options, ultimately leading to selection of treatment that may improve patients’ long-term outcomes.

WHAT ARE BIOMARKERS? WHAT DO THEY MEAN FOR PATIENTS WITH mCRC?

Biomarkers are measurable indicators of the presence or severity of a condition and used to monitor and predict the disease course of patients so that appropriate treatment can be planned.

Biomarkers play an increasingly important role in helping physicians tailor care and treatment for their patients.

The latest research demonstrates that identification of biomarkers in certain tumor types can help physicians ensure that the most appropriate treatment according to the individual patient and/or their cancer is selected at the time of diagnosis.

Biomarkers have played a central role in the clinical management of mCRC since 2008, when it was discovered that KRAS mutations contribute to tumor development. Since then, further studies have substantiated the role of the RAS gene family in predicting treatment efficacy.

Now, physicians can test tumors for biomarkers within the ‘RAS’ gene (specifically testing for mutations in exons 2, 3 and 4 of KRAS and NRAS). This biomarker test can be used to help select the most appropriate therapy for each individual mCRC patient.
WHAT IS THE ROLE OF RAS AND HOW CAN MUTATIONS IN RAS AFFECT THE FUNCTIONING OF CANCER CELLS?

RAS genes play an important role in the EGFR signaling pathway – a complex signaling cascade that is involved in the development and progression of cancer. When a fault in the RAS gene occurs it leads to it being permanently switched on. This results in signals being sent to cells to grow and divide uncontrollably, creating a tumor.\(^8\)

WHAT IS THE LIQUID BIOPSY RAS BIOMARKER TEST?

Once a patient is diagnosed with mCRC, a sample of cancer cells taken from the patient’s tumor is sent for analysis to determine whether the tumor is RAS wild-type or RAS mutant.\(^9\)

The liquid biopsy RAS biomarker test is a method for determining the RAS mutation status of a tumor, using a simple blood sample. This new test only requires a small blood sample (10 ml), rather than a tissue biopsy, to determine the mutation status of tumors and results can be made available more rapidly than with conventional testing, helping to guide faster treatment decisions and treatment initiation.\(^10,11\) The liquid biopsy RAS biomarker test has a similar performance to tissue-based testing.\(^11\)

About half of mCRC tumors will have RAS wild-type genes and about half will have RAS mutant genes.\(^11,12\)
**WHO SHOULD BE TESTED?**

Patients who have been diagnosed with mCRC, where the primary tumor has spread to other areas of the body, such as the lungs and/or liver.

In cases where the tumor is difficult to reach, or the patient cannot tolerate an invasive procedure, the liquid biopsy RAS biomarker test still offers these patients the opportunity for a personalized treatment approach.

**WHAT IS THE PROCESS?**

1. A blood sample (7-10ml) is taken
2. The tumor DNA is isolated in the lab
3. Highly sensitive PCR-based technologies identify the RAS status of the tumor
4. The physician and patient discuss treatment options based on results
5. Patient starts treatment

**WHEN SHOULD TESTING TAKE PLACE?**

Patients should receive a RAS biomarker test around the time of diagnosis with mCRC; tumor DNA fragments are found at relatively high concentrations in the circulation of most patients with metastatic disease.13

Knowing the RAS mutation status is critical to selecting the most appropriate first-line therapy1 and to improving the chances for successful treatment.

**WHAT DOES RAS BIOMARKER TESTING MEAN FOR PATIENTS?**

RAS biomarker testing at the time of diagnosis can help physicians ensure that the most appropriate treatment is selected from the outset. This can ultimately help to improve patients’ long-term outcomes while avoiding unnecessary treatment and toxicity.1-5

The liquid biopsy RAS biomarker test can help expand the delivery of precision medicine to more patients with mCRC.
predictive biomarkers in metastatic colorectal cancer

CT, computerized tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.


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