Knowing your biomarker profile can help you and your care team to better understand the characteristics of your tumour and to personalize your treatment plan.

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An exciting scientific development in recent years has been the identification of biomarkers – molecules found in your tumour or other tissues that can reveal whether a process in your body is normal or pathogenic (causing disease). If you have been diagnosed with stage IV colorectal cancer, it is crucial to know your tumour’s biomarker profile so that your care team can develop a personalized treatment plan for you.

What is a biomarker?

One of the most exciting scientific developments of the past few decades has been the identification of biomarkers – molecules found in your tumour or other tissues that can reveal whether a process in your body is normal or pathogenic (causing disease).

Biomarkers, short for biological markers or molecular markers, include DNA, proteins, and genetic mutations found in blood, tissue, or other body fluids. Biomarker testing is sometimes called tumour testing, molecular testing, and genomic testing.

Several biomarkers are used for the evaluation of stage IV colorectal cancer. These offer value in several ways:

- Diagnostic biomarkers detect the disease
• Prognostic biomarkers are associated with understanding the prognosis i.e. a clinical outcome regardless of the treatment received
• Predictive biomarkers can predict the benefit or lack of benefit of a treatment

When is biomarker testing done?

Your tumour biomarker status should be determined as soon as you are diagnosed with stage IV colorectal cancer. Testing will assist in developing the most appropriate personalized treatment plan. At present, it is believed that tumour molecular profiling does not offer value in the earlier stages of colorectal cancer (non-metastatic) unless there is a recurrence of the disease.

If you had surgery, a sample of your tumour was likely taken then and sent to the pathology department for analysis. If biomarker tests have not been performed, ask your surgeon or oncology team about how to get your tumour tested. If no sample was taken, ask your doctor about your options for testing.

“I was young when I was diagnosed. I wanted to know if I had an inherited type of rectal cancer, so I asked about biomarker testing. I was relieved to learn I did not have any inherited form but I’m glad I asked.”

Marie Taurasi
Stage III Rectal Cancer Survivor

What will the tests show?

Biomarker testing will reveal whether your tumour has mutations that may affect how it responds to drug treatments. These tests may also be used to help detect the growth, reduction or recurrence of your cancer. Finally, knowing the location, type, stage and genetic profile and of your tumour will help your oncologist or surgeon recommend a personalized treatment plan for you.

Companion diagnostics
Genetic tests can tell whether or not a certain therapy is likely to work for that patient. Knowing this outcome in advance helps to reduce unnecessary treatment side effects, raised hopes and costs. Now that more is known about the role of biomarkers in predicting a patient’s response to therapy, new classes of anti-cancer drugs are often developed together with a ‘companion diagnostic’. This is a test for a predictive biomarker that enables cancers to be classified into responders and non-responder groups for that specific drug treatment.

Companion diagnostics are so named because these tests are specifically developed for use as a companion to a particular drug. In addition to helping identify the right patient, companion diagnostics may also help avoid adverse drug reactions by allowing doctors to identify patients who are at increased risk for serious side effects from certain medicines. They also give doctors the opportunity to adjust drug therapy in order to achieve better clinical results. Companion diagnostics will permit delivering the right drug to the right patient at the right time by evaluating a particular feature of a person’s disease that is a target for that precise and targeted medicine.

**Which biomarkers should be tested and what information will they give us?**

There are several classes of biomarker tests used in determining treatment choices for stage IV (and some stage III) colorectal cancer patients.

**1. Mutations affecting responsiveness to anti-cancer drugs.**

Certain genes are present on the surface of tumours. These ‘oncogenes’ include RAS and BRAF, which are found in colorectal cancer. Mutations in these genes prevent many standard therapies for advanced colorectal cancer from working. Therapies such as Erbitux® or Vectibix® belong to a class of medications that inhibit biological structures that are important for cancer cell growth: epidermal growth factor receptors (EGFR). These drugs are rendered ineffective by proteins produced by the mutated genes.

a) RAS mutations
RAS is a family of genes that makes proteins involved in cell signaling pathways that control cell growth and cell death. Members of the RAS gene family that are present in colorectal cancer include KRAS and NRAS.

40-50% of colorectal cancers have a KRAS or NRAS mutation. A mutation in either KRAS or NRAS genes means that the patient will be unlikely to respond to standard therapies that inhibit epidermal growth factor receptors (EGFR).

The approximately 50-60% of colorectal cancer patients whose tumours do NOT have mutations in either RAS or KRAS (called ‘RAS wild-type’) may respond well to these treatments.

‘Extended RAS testing’ examines several variants of mutation within the KRAS and NRAS genes and is recommended for patients with stage IV cancer.

“When my cancer recurred in my pelvis after 7 years in remission, oncology research had progressed considerably since my original diagnosis in 2010. Access to genetic panels helped me to access anti-EGFR therapy (Panitumumab) along with FOLFOX as a first-line therapy. That combination shrank my tumour by 80%, making for a far safer operation. All mCRC patients deserve that chance.”

Robin McGee
Stage IV Rectal Cancer Patient

b) BRAF mutations
The BRAF gene provides instructions for making a protein that helps transmit chemical signals from outside the cell to the cell’s nucleus. This protein is part of a signaling pathway which regulates the growth and division of cells, the process by which cells mature to carry out specific functions, cell movement, and the self-destruction of cells.

BRAF testing is recommended for stage IV patients at the time of diagnosis. BRAF testing is typically done at the same time as RAS testing. Approximately 5-10% of colorectal cancers show BRAF mutations. The presence of a BRAF mutation is associated with a poorer prognosis. However, it may also identify patients who may benefit from BRAF-inhibitor targeted therapies.

c) PIK3CA mutation testing
PI3 kinase (PIK3CA) genes control multiple functions that influence the growth and survival of cells. Although one in five colorectal cancer patients has a PIK3CA mutation, testing for this gene is not standard practice in Canada. Drugs that inhibit PIK3CA have been approved for treatment of other types of cancer, but they have not demonstrated activity in colorectal cancer.

For some patients there may be value in knowing their PIK3CA status, however. Recent studies suggest that patients with this mutation may benefit from aspirin therapy after surgical resection to help decrease the risk of recurrent cancer.

d) HER 2
HER2 is a protein involved in normal cell growth and well known as a target for treatment in breast cancer. Approximately 4% of colon cancers also over-express (make too much of) the HER2 protein, and this over-expression contributes to cancer cell growth and survival. HER2 targeted therapies can dramatically improve outcomes for HER2-positive colon cancers and all colorectal cancers should be tested for HER2. There are several medications available that may target HER2 and are currently under investigation for activity in HER2-positive colorectal cancers.

e) TRK
TRK fusions are chromosomal abnormalities that occur when one of the NTRK genes (NTRK1, NTRK2, NTRK3) becomes abnormally connected to another, unrelated gene (e.g. ETV6, LMNA, TPM3). This abnormality results in uncontrolled TRK signaling that can lead to cancer. TRK fusions occur rarely but can arise in colon cancer. TRK fusions can be identified through various diagnostic tests, including targeted next-generation sequencing (NGS), immunohistochemistry (IHC), polymerase chain reaction (PCR), and fluorescent in situ hybridization (FISH). A Health Canada-approved therapy is available to treat a gene fusion cancer: larotrectinib (Vitrakvi®). TRK gene fusions are very rare in colorectal cancers, estimated to be found in < 1-2% of cases.

2. Testing for defects in DNA repair mechanisms: MSI-H/dMMR testing

The term dMMR stands for ‘deficient mismatch repair’ and refers to a condition within a cell where damage to DNA is not repaired, resulting in a higher level of mutations. Genes that regulate DNA repair (called Mismatch Repair genes) work like genetic ‘spell checkers’ by correcting errors in DNA as cells divide, similar to how ‘spell checkers’ correct typos on a computer. When MMR genes stop functioning at their highest potential, areas of DNA could start to become unstable due to the errors. This condition results in ‘microsatellite instability’, or MSI. A tumour is designated as MSI-H when there are high levels of instability.

The MSI screening test looks for changes in the DNA sequence between normal tissue and tumour tissue and can identify whether or not there is high amount of instability (also known as MSI-H). Similarly, an MMR test looks for the presence or absence of the mismatch repair proteins within the tumour. The results between the two types of tests are strongly correlated.
MSI-H or dMMR is found in about 15% of colon tumours (approximately one-quarter of which are associated with an inherited condition) and only rarely in rectal tumours. Only a small subgroup (about 4%) of patients with metastatic colorectal cancer has MSI-H or dMMR tumours.

“MSI/MMR genetic testing of my tumour was an integral part of my diagnosis. It helped to guide me to what the best treatment options were for me and by exposing this previously unknown cancer risk in my family. It proved to be the catalyst in helping others in my family become more proactive with their health, which has led to many saved lives.”

Roslyn Fitzpatrick  
Stage III Colon Cancer Survivor

Immune checkpoint inhibitors, better known as immunotherapies, are showing promise in treating MSI-H tumours:

- Pembrolizumab (Keytruda®)
- Nivolumab (Opdivo®)

Knowing your tumour MSI status is extremely important prior to selecting a treatment. MSI or MMR testing is recommended especially for colorectal cancer patients suspected to have a hereditary syndrome.

**How immune checkpoint inhibitors work**

Immune checkpoint inhibitor drugs work by allowing the body’s immune response to do its job of attacking and killing abnormal cells, to stop them from multiplying and causing cancer.

This immune response involves T cells, which are activated when they recognize an abnormal or mutated cell. PD-1 is a checkpoint protein on the surface of T cells which normally acts as a type of “off switch” to help keep the T cells from attacking other cells in the body. It does this when it attaches to PD-L1, a protein on some normal (and cancer) cells. When PD-1 binds to PD-L1, it basically tells the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1, which helps them hide from an immune attack.

Monoclonal antibodies that target either PD-1 or PD-L1 can block this binding and boost the immune response against cancer cells. These drugs have shown a great deal of promise in treating certain cancers.
In the diagram above, before immunotherapy (top), the tumor cell’s PD-1 ligand, or PD-L1, molecule (red) binds to a type of white blood cell called a T cell in a way that enables the tumor cell to evade destruction by the immune system. During immunotherapy (bottom), an anti-PD-1 inhibitor drug (bright green) blocks PD-L1 binding, enabling the T cell to target the tumor cell for destruction.


3. CEA Testing

Carcinoembryonic antigen (CEA) is a protein normally found in very low levels in the blood of adults and its level may be increased in colorectal cancer. This is also known as a tumour marker. Your doctor may order this test if cancer is suspected, to find out if the cancer treatment is working, or to see whether there has been a recurrence after treatment.

Testing for CEA is done with a blood sample. Once active treatment is completed, CEA tests are recommended every 3-6 months during the first and second year, and every 6 months during years three, four and five after treatment ends.

4. Right vs. Left Sided Colon Cancer

There are quite significant differences in the biology of colorectal tumours depending on which side of the colon the cancer originates. (Tumours initiated in the transverse colon are quite rare.) Recent research has shown that the sidedness of a tumour has implications for prognosis and treatment.
Tumours originating in the left or right side of the colorectum have significantly different characteristics and require different approaches to treatment.

For example, tumours originating on the right side of the colon (cecum and ascending colon) tend to have a worse prognosis and are more prevalent in women. There are more KRAS and BRAF mutations and higher levels of microsatellite instability (MSI-H). Right sided colon cancers are associated with a poorer prognosis. They are typically treated with bevacizumab combined with conventional chemotherapy.

Primary tumours on the left side of the body (in the descending colon, sigmoid colon and rectum) are seen more often in men and have a better prognosis. These cancers tend NOT to show mutations in the KRAS gene, have elevated levels of epidermal growth factor ligands amphiregulin (AREG) and epiregulin (EREG), and contain HER2 receptors. Treatment of these tumours is quite different. They may be treated with bevacizumab or anti-EGFR antibodies (such as cetuximab or panitumumab) combined with conventional chemotherapy.

Anti-HER2 agents such as trastuzumab (Herceptin®), lapatinib (Tykerb®), and other agents are in development and their effectiveness for the treatment of metastatic colorectal cancer are being determined.

This is an emerging field of research, so ask your oncologist whether your treatment plan will be different based on the ‘sidedness of your tumour’.

**Having a thoughtful dialogue with your treating oncologist:**

**Informed consent**
Personalized treatment, based in part on your biomarker profile, offers a more targeted approach to managing your stage IV colorectal cancer. Because of the range of options now available, it is more important than ever that you and your oncologist or surgeon share decisions about your treatment plan.

This means that you are both responsible for understanding the alternatives available, the reasons behind each one, and the upsides and downsides of each of the choices before you.

To prepare yourself for this role, you need to have full information and maintain an open dialogue with your treating physician. Informed consent can only be given once you are confident that you have all the facts you need to make a decision and that any concerns have been fully addressed. Also bear in mind that your preferences and values are important when selecting the right choice for you.

As a partner in this process, it is important to find out as much as possible about the alternatives being offered and to engage with your treating physician to make sure you both have full information. Your doctor will inform you about the pros and cons of each option, and you will work with your physician to agree on an approach.

Don’t feel embarrassed if you don’t understand something. Don’t worry that you are wasting the physician’s time. They are there to work with you to arrive at an approach that is best for you.

Your biomarker status is important information to have. If you have not already had these tests, you must advocate to ensure they are done. The results of the tests will help you to make an informed decision.

Here are some sample questions to ask your doctor about biomarker testing:

- How will the test results affect my treatment plan?
- What does this mean for my prognosis?
- Are there any downsides to biomarker testing?
- May I see the results of my biomarker testing?
- Will the tests reveal any information about my hereditary status?

Once you receive the answers to your questions, you will be able to provide informed consent. Informed consent is permission granted by a patient to a doctor for a treatment or test with the knowledge of the possible consequences, risks and benefits.

Your oncologist or surgeon can identify your best treatment options by knowing your biomarker status and, in turn, you will be able to make well informed decisions about how your cancer will be treated.

A Bit About Next Generation Sequencing

Second generation sequencing technologies, commonly referred to as Next Generation Sequencing (NGS), have been developed in an effort to enable the routine genomic study of every tumour. NGS allows for rapid and
accurate sequencing of many genes at once utilizing the genetic material in the patient’s tumour, either DNA or RNA

With these larger panel tests entering the market in oncology, patients may access a test that can be administered at the time they are being worked up for diagnosis where they can test hundreds of different biomarkers. These tests are becoming more readily available and testing smaller samples for a wide array of markers in one panel.

**Genomic Profiling (NGS) Guiding Treatment Decision Making in Oncology**

A Canadian guideline on the use of NGS in oncology was published in April 2019. It was developed by a steering committee of pathologists, geneticists, oncologists, and genetic counsellors from across Canada. It provides guidance for oncologists on the use of NGS for the identification of cancer mutations. A number of targeted therapies have been approved in Canada for use in patients harbouring specific mutations in their cancer. By correctly identifying patients who might respond to those agents, oncologists can both treat those who could derive benefit and spare those who are unlikely to benefit from unnecessary toxicities. Moreover, NGS can be used to identify patients who could be susceptible to drug toxicities.

For patients who experience disease progression, NGS can then be useful in the detection of resistance genes that might cause treatment failure to guide selection of subsequent treatments. For example: KRAS, NRAS and BRAF mutations are associated with resistance to therapy targeting epidermal growth factor receptor (EGFR). Patients may also proceed to a clinical trial based on the identification of a driver mutation from the results of NGS testing once standard of care therapies have been exhausted.

Would you like additional information, please call us, we are eager to help.

1 833 79 CCRAN (22726)
A well-supported patient is a well-coping patient.
Together, anything is possible!