Biomarker Testing and Targeted Therapy for Cancer Treatment

This document explains the significance of biomarker testing in the management of cancer and how this crucial information shapes treatment decisions to achieve optimal outcomes.

We kindly request that you review this document as part of your preparation before completing the survey questionnaire.

Tremendous progress has been made in treating colorectal cancer over the last 15 years. In the past, all individuals with colorectal cancer received the same standard therapy. However, we now **recognize that each person's colorectal cancer is unique**, **requiring tailored treatment options**. Biomarker testing unlocks precise genetic and molecular details, empowering healthcare providers/oncologists to tailor a personalized treatment plan for you.

Biomarker Testing for Cancer Treatment

What is biomarker testing?

A biomarker is an indicator of disease or abnormal function that can be measured in your blood, tissue, or bodily fluid. In cancer, biomarkers may be used to help choose the best treatment for you.[1]

These biomarkers can be specific proteins, genes, or gene mutations.[1] Biomarkers are often referred to by a 3 or 4 letter abbreviation. Examples of routinely tested biomarkers for colorectal cancer include EGFR, BRAF, KRAS/NRAS, MSI/dMMR, and CEA.[2]

Some other biomarkers such as ctDNA, PTEN loss, PIK3CA, TMB, NTRK, c-MET, VEGF, and HER2 are only available through clinical trials or special testing which is not publicly funded. These biomarkers are not yet routinely tested for, as there are currently no approved standard targeted treatment options that would be impacted by their results. In particular, current clinical trials are exploring the role of HER2- and NTRK-targeted treatments in metastatic colorectal cancer, though this remains experimental.[3]

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[1] National Cancer Institute (2021) Biomarker Testing for Cancer Treatment.

[2] Cancer Support Community (2018) Precision Medicine Plain Language Lexicon.

[3] Puccini A, Seeber A, Berger MD. Biomarkers in Metastatic Colorectal Cancer: Status Quo and Future Perspective. Cancers (Basel). 2022 Oct 3;14(19):4828. doi: 10.3390/cancers14194828. PMID: 36230751

Biomarker testing can be done to look for mutations in a cancer (called somatic mutations). Somatic mutations cause most cancers and can't be passed on to family members.[4] This is different from genetic testing, which looks for mutations in your genes that are inherited from your parents and can be passed on to children.[4] There are several genetic conditions that can increase the risk of developing colorectal cancer in the family members, such as Lynch syndrome, familial adenomatous polyposis (FAP), Cowden syndrome, and others. Lynch syndrome can be suspected based on a specific pattern of mutations in the MSI/MMR testing, in which case your Oncologist may refer you to the familial genetics program for assessment of your family member's risk of cancer.[5] Genetic testing is not otherwise covered in this resource.

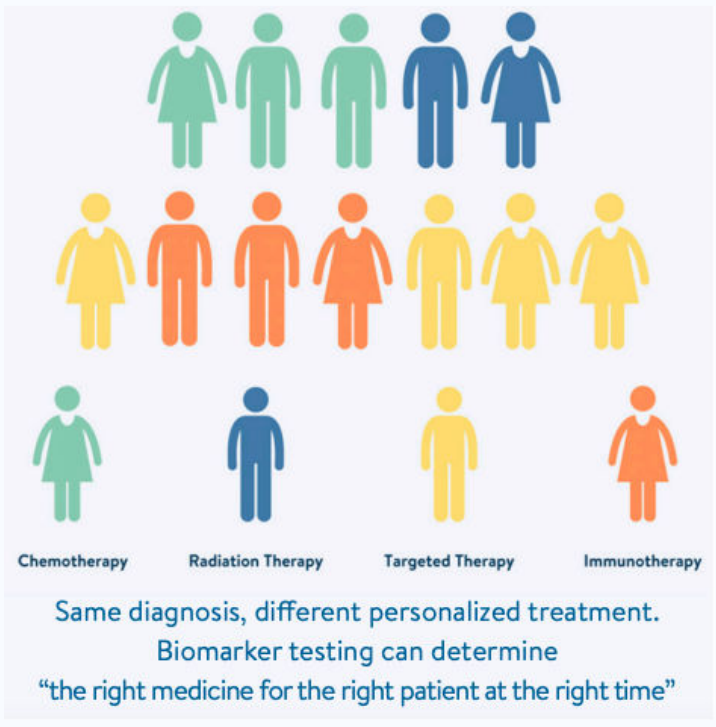

Fig. 1 Source: Colorectal Cancer Canada

How is biomarker testing performed?

TISSUE BIOPSY

[4] National Cancer Institute (2021) Biomarker Testing for Cancer Treatment

[5] Mouade El Bali, Joaira Bakkach, Mohcine Bennani Mechita, "Colorectal Cancer: From Genetic Landscape to Targeted Therapy", Journal of Oncology, vol. 2021, Article ID 9918116, 17 pages, 2021. https://doi.org/10.1155/2021/9918116

Biomarker testing is performed on a sample of your cancer cells called tissue biopsy. It can be done on both primary (site of origin of cancer - colon in this case) tumors and metastatic tumors. An example of a metastatic

tumor is a liver lesion that has spread from the colon. Currently, for colorectal cancer, biomarker testing is performed as tissue biopsy either from primary tumor or metastatic site.[2]

LIQUID BIOPSY

Liquid Biopsy is a new technique to perform the biomarker testing on the blood sample containing parts of cancer cells (like DNA). This is currently not publicly funded in Canada but may be offered to you in the clinical trial setting.[6]

Why are biomarkers tests used in oncology?

Biomarker testing can help identify a specific mutation in a cancer cell, reveal the "drivers" that can cause cancer to grow in different ways, or predict how well your body responds to certain types of treatment. It can also be used to determine:

- Risk (also called susceptibility): to help assess how likely you or your family member are likely to develop cancer or determine whether you should undergo more intensive screening.
- Diagnosis: to help detect or confirm a disease or condition.
- Prognosis: to forecast how your cancer will progress in the absence of therapy.
- Prediction: to help assess whether you will respond to treatment.
- Response: to help predict your response — both beneficial or harmful — to a certain treatment.
- Monitoring: to help determine how you are doing over time, either on or off treatment.
- Safety: to help measure the likelihood, presence, or extent of side effects before or after undertaking a treatment.

In the figure below, you can check how biomarker testing can be used in different moments of the patient pathway **(Figure 2).**

[6] National Cancer Institute (2021) Biomarker Testing for Cancer Treatment.

USES OF BIOMARKERS IN CANCER CARE					
Diagnosis	**After Cancer Diagnosis**				**Post-Treatment**
Diagnostic	**Prognostic**	**Predicting treatment response**	**Safety**	**Monitoring treatment response**	**Monitoring for recurrence**
Do I have cancer? What type of cancer do I have?	What is the expected course of my cancer?	Will my cancer respond to this treatment?	Am I likely to experience side effects?	How is my cancer responding to this treatment?	Will my cancer come back? Do I have an increased risk of recurrence?

Fig. 2 Use of biomarkers in cancer care.[7] Adapted from Research Advocacy Network "Precision Medicine in Oncology"

Knowing your cancer's biomarkers can help you and your healthcare team make fully informed decisions about how your cancer will be treated. You can ask your healthcare team about biomarker testing at any decision point before new treatment begins, including upon diagnosis, recurrence, or progression.[8]

Keep in mind that even when a cancer biomarker is present, there is no guarantee that a targeted therapy will work against your cancer. One reason for this is that the molecular makeup of cancer can change over time. This means that the target molecule of the biomarker can change. The tumor can also find ways to grow and spread without that molecule.[9] If a drug stops working or your cancer returns, that may mean that your tumor cells have become resistant to a treatment. At that point, another biomarker test may be needed to understand how your tumor has changed. This could identify new biomarkers that may be targeted for treatment.[9]

The biomarkers that are tested for in a patient with colorectal cancer depends on their cancer stage (Figure 3).

All cancer stages (I-IV) undergo automatic MSI/dMMR testing on their tissue sample (pathology). Please check with your Oncologist to verify which stage your cancer falls int. Patients with stage II-IV cancer will have CEA levels drawn from their blood when requested by their Oncologist. Patients with stage IV (metastatic) cancer will have BRAF, KRAS, NRAS testing automatically completed on their tissue sample. In the figure below, you can find key colorectal cancer biomarkers and their testing recommendations depending on the cancer stage (Figure 4).[10,11]

Colorectal Cancer Stages

[7] Research Advocacy Network (2021) Precision Medicine in Oncology.
[8] Lungevity (2021) Biomarker Conversation Starter.
[9] Cholangiocarcinoma Foundation (2020) For Cancer Patients, Biomarkers Matter.
[10] Colorectal Cancer Canada (2024) Biomarkers.
[11] Global Colon Cancer Association (2024) Colorectal cancer biomarkers overview.

Stages	Description
Stage I (localized)	• The tumor has grown into a superficial part of the bowel wall
Stage II (localized)	• The tumor has grown into a deeper part of or through the bowel wall, possibly invading other nearby organs
Stage III (locally advanced)	• The cancer has spread to nearby lymph nodes, but has not spread to other parts of the body
Stage IV (metastatic)	• The cancer has spread to other parts of the body (e.g. liver, lungs, peritoneum)

Fig. 3 Source: Colorectal Cancer Canada

Biomarkers	Description	Testing Recommendation
MSI-H/dMMR	• Known as Microsatellite Instability – high (MSI-H)/mismatch repair deficient (dMMR) • dMMR status that is given to patients when the genes that fix DNA errors as it is dividing (the mismatch repair genes), are unable to do their job. • MSI/dMMR mutation is found in 15% of colorectal cancer patients.	• Colorectal cancer patients with any stage of cancer.
Carcinoembryonic antigen (CEA)	• Carcinoembryonic antigen (CEA) is a protein that is found on the surface of colorectal cancer cells. • Elevated CEA levels may indicate a cancer recurrence • CEA tests may be used to find out if cancer treatment is working, or to find out if cancer has come back after treatment (recurrence).	• CEA tests may be used to find out if cancer treatment is working, or to find out if cancer has come back after treatment (recurrence).
KRAS/NRAS/BRAF	• NRAS/KRAS/BRAF are part of genes that are involved in controlling cell growth and cell division. • Mutations in KRAS/NRAS/BRAF can lead to uncontrolled cell growth, leading to tumor formation/cancer. • KRAS is abnormal/mutated in 35-45%, NRAS in 5% and BRAF in 10% of colorectal cancer patients.	• Colorectal cancer patients with stage IV cancer. • Patients being considered for EGFR inhibitor treatment.

Fig. 4 Source: Colorectal Cancer Canada

Other biomarker testing can be completed in the setting of a clinical trial, or through private testing. In stage IV colorectal cancer that has progressed after initial treatments, extra biomarker testing through different private companies such as Foundation Medicine® can be considered.[12]

There is an out-of-pocket expense to this (approximately $2500), and the likelihood of this test to identify an actionable biomarker that has an approved targeted treatment in Canada is very low.[12] Patients may consider whether pursuing extra biomarker testing is right for them and discuss this with their healthcare provider.

[12] D., McKinnon, M., Mukhtar, L., Awan, A., Lo, B., & Wheatley-Price, P. (2021). The Impact of Foundation Medicine Testing on Cancer Patients: A Single Academic Centre Experience. Frontiers in oncology, 11, 687730. https://doi.org/10.3389/fonc.2021.687730

What happens after I get tested?

Once the biomarker testing is done on a tissue sample, a lab report is generated that will show if any biomarkers were identified in your cancer cells that may be helpful in selecting the right treatment approach for you.

The test results can approximately take up to 2 weeks to be received by your healthcare team. Your medical oncologist will then discuss the test results and potential next steps including the decision regarding the choice of cancer treatments based on the results of the tissue biomarker testing.

Targeted Therapy for Cancer

Upon receipt of the biomarker testing results, your oncologist will discuss the report with you and may subsequently propose personalized targeted therapy options based on the specific outcomes of the biomarker testing.

What is targeted therapy?

Targeted therapy is a type of treatment that attacks specific cells (with specific biomarkers) in the body to stop or slow their growth. This treatment is based on the characteristics of an individual's own cells.[13]

Unlike chemotherapy or radiotherapy, targeted therapies can halt cancer growth and destroy specific cancer cells with less harm to normal cells.

They do so by blocking the action of certain enzymes, proteins or other molecules involved in the growth and spread of cancer cells. They are only likely to work on cancer cells that have specific biomarkers.[14]

What are different types of targeted therapies and how do they work?

Targeted therapies "target" specific cancer cells in various ways.[15] They can:

- Block or turn off signals that tell cancer cells to grow and divide. Example: a tyrosine kinase inhibitor (TKI) drug or 'growth blocker' (Figure 5)
- Block cancers from growing blood vessels. Example: an antiangiogenic drug (Figure 6)
- Prevent cancer cells from living longer. Example: monoclonal antibodies (Figure 7)

[13] LUNGevity Foundation (2021) Targeted Therapy Brochure.

[14] Cancer Support Community. Precision Medicine Plain Language Lexicon.

[15] Canadian Cancer Society (2024) Targeted therapy for colorectal cancer.

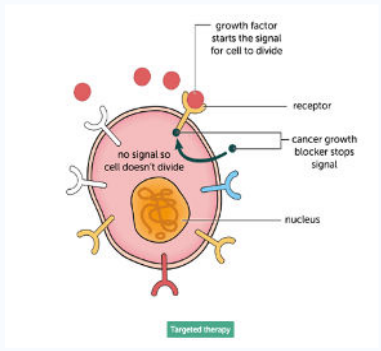

Fig. 5 "TKI" (Growth Blocker)[16]

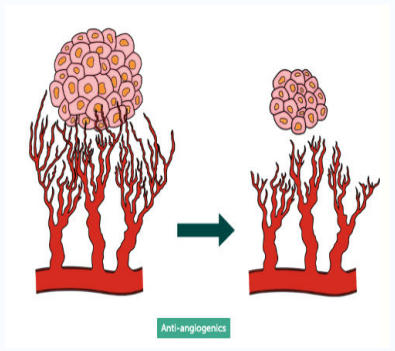

Fig. 6 "Anti-angiogenic"[16]

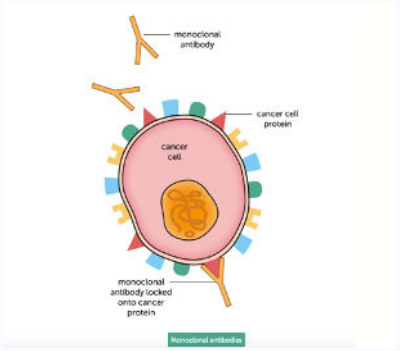

Fig. 7 "Monoclonal antibody"[16]

What can I expect while taking targeted therapy?

Since targeted therapies act on specific cancer cells, you may experience specific side effects from these treatments which may be different than traditional treatment options such as chemotherapy and radiotherapy.[15]

Side effects will vary depending on where your cancer is located, what biomarkers are identified on your cancer cells and specific treatment offered to you. Once a treatment is chosen, specific drug information including side effects would be discussed separately by your Oncologist.

Targeted therapy for colorectal cancer most commonly has the following side effects: fatigue, headache, skin problems, fever, bleeding, blood clots, mouth sores, loss of appetite, diarrhea, and low white blood cell counts.[15]

Targeted therapy is an important modality of cancer treatment. As researchers learn more about specific changes in cancer cells, they will develop additional treatment options. Currently only a few cancer types are routinely treated with targeted therapies alone. Many people may also need other forms of cancer treatment such as surgery, chemotherapy, radiotherapy or sometimes hormone therapy.[17]

When considering targeted therapy, it is important to know its limitations including:

- A targeted treatment will not work if your cancer does not have the specific biomarker to target[15]
- Some targeted treatments are only indicated for certain stages of cancer (e.g. stage IV)
- Even if you have the specific biomarker, it is possible the cancer will not respond to the therapy
- The response to the treatment may not last over time

[16] Cancer.org from American Cancer Society (2021) How Targeted Therapies Are Used to Treat Cancer.

[17] Cancer.net from ASCO (2021) What is targeted therapy?

If a targeted therapy stops working or your cancer returns, that may mean that your tumor cells have become resistant to a treatment. Resistance can happen when the target — the biomarker — changes, and your cancer finds another way to grow.[18]

Additionally, clinical trials with targeted therapies can offer an important treatment option to people affected by colorectal cancer. Advances in targeted therapies are based on information learned from patients enrolled in clinical trials.[18] You can speak to your Oncologist about clinical trials.

[18] LUNGevity Foundation (2021) Targeted Therapy Brochure.

Glossary

Biomarker Testing and Targeted Therapy for Cancer Treatment

Biomarker

A biomarker is a sign of disease or abnormal function that can be measured in your blood, tissue, or bodily fluid. In cancer, biomarkers are often used to help choose the best treatment for you. These biomarkers can be proteins, genes, or gene mutations. Biomarkers are often referred to by a 3 or 4 letter abbreviation. Examples of biomarkers are MSI-H/dMMR, NRAS, KRAS, NTRK and BRAF in colorectal cancer.

Biomarker testing

(also referred to as Comprehensive biomarker testing, Gene-based cancer testing, Genetic testing of the cancer, Cancer marker testing, Next generation sequencing, Genomic profiling, Mutation biomarker testing, Genomic testing, Molecular profiling, Tumor marker testing, Mutation testing, Molecular testing)

Biomarker testing helps your doctor match the right drugs to the specific subtype of cancer you have. In biomarker testing, a sample of your cancer is collected from your blood, bodily fluids, or tissue taken during surgery or biopsy.

Your sample is sent to a lab. The test looks for biomarkers in your cancer sample. The test results can be used to help guide your treatment options. Biomarkers tell your doctor about the subtype of the cancer in your body (Cancer Support Community, Precision Medicine Plain Language Lexicon).

Cells

In biology, the smallest unit that can live on its own and that makes up all living organisms and the tissues of the body. A cell has three main parts: the cell membrane, the nucleus, and the cytoplasm.

The cell membrane surrounds the cell and controls the substances that go into and out of the cell. The nucleus is a structure inside the cell that contains the nucleolus and most of the cell's DNA. It is also where most RNA is made. The cytoplasm is the fluid inside the cell. It contains other tiny cell parts that have specific functions, including the Golgi complex, the mitochondria, and the endoplasmic reticulum.

The cytoplasm is where most chemical reactions take place and where most proteins are made. The human body has more than 30 trillion cells (National Cancer Institute, Dictionary of Cancer Terms).

Chemotherapy

A treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Chemotherapy may be given by mouth, injection, or infusion, or on the skin, depending on the type and stage of the cancer being treated.

It may be given alone or in combination with other therapies (National Cancer Institute, Dictionary of Cancer Terms).

Clinical trials

A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study (National Cancer Institute, Dictionary of Cancer Terms).

Diagnostic test

A type of test used to help diagnose a disease or condition (National Cancer Institute, Dictionary of Cancer Terms).

Enzymes

A protein that speeds up chemical reactions in the body (National Cancer Institute, Dictionary of Cancer Terms).

Genetic testing

The process of analyzing human cells or tissue to look for changes in inherited genes, chromosomes, or proteins that may be a sign of a disease or condition, such as cancer. These changes may also be a sign that a person has an increased risk of developing a specific disease or condition. Genetic testing may be done on tumor tissue to help diagnose cancer, plan treatment, or find out how well treatment is working (National Cancer Institute, Dictionary of Cancer Terms).

Hormone therapy

Treatment that adds, blocks, or removes hormones. For certain conditions (such as diabetes or menopause), hormones are given to adjust low hormone levels. Hormones can also cause certain cancers (such as prostate and breast cancer) to grow. To slow or stop the growth of cancer, synthetic hormones or other drugs may be given to block the body's natural hormones, or surgery is used to remove the gland that makes a certain hormone. Also called endocrine therapy, hormonal therapy, and hormone treatment (National Cancer Institute, Dictionary of Cancer Terms).

Molecule

The smallest particle of a substance that has all of the physical and chemical properties of that substance. Molecules are made up of one or more atoms. If they contain more than one atom, the atoms can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms (National Cancer Institute, Dictionary of Cancer Terms).

Precision medicine

A form of medicine that uses information about a person's own genes or proteins to prevent, diagnose, or treat disease. In cancer, precision medicine uses specific information about a person's tumor to help make

a diagnosis, plan treatment, find out how well treatment is working, or make a prognosis (National Cancer Institute, Dictionary of Cancer Terms).

Protein

A molecule made up of amino acids. Proteins are needed for the body to function properly. They are the basis of body structures, such as skin and hair, and of other substances such as enzymes, cytokines, and antibodies (National Cancer Institute, Dictionary of Cancer Terms).

Radiotherapy

The use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy or brachytherapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy (National Cancer Institute, Dictionary of Cancer Terms).

Targeted Therapy

Targeted therapy drugs keep cancer from growing and spreading with less harm to cells that are not cancer. They may have fewer side effects than other treatments because they are better able to attack your cancer cells and leave healthy cells alone. These drugs "target" specific cancer subtypes. They are only likely to work in those specific subtypes. (Cancer Support Community, Precision Medicine Plain Language Lexicon).

Side effect

A problem that occurs when treatment affects healthy tissues or organs. Some common side effects of cancer treatment are nausea, vomiting, fatigue, pain, decreased blood cell counts, hair loss, and mouth sores.