FIGHT
COLORECTAL CANCER

BIOMARKERS

Your Guide to Biomarkers and Biomarker Testing

BIOMARKERS

This resource is designed to inform you about colorectal cancer (CRC) biomarkers and biomarker testing. In this publication, we provide a thorough explanation of what biomarkers are, an overview of the importance of biomarker testing, and information about biomarkers that are relevant to colorectal cancer patients.

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FIGHT CRC

ABOUT FIGHT COLORECTAL CANCER

We FIGHT to cure colorectal cancer and serve as relentless champions of hope for all affected by this disease through informed patient support, impactful policy change, and breakthrough research endeavors.

MEDICAL DISCLAIMER

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COVER:
Kimberly Bush-Klinefelter
Caregiver & Research Advocate

BIOMARKERS AND BIOMARKER TESTING

Biomarker is a broad term used across disease states and medical practices. Biomarkers describe measurable characteristics that let us know how the body is functioning.

In terms of understanding why biomarkers are so important in cancer care, it might help to think of them as a roadmap. If you're planning a road trip to somewhere you've never been before, you probably wouldn't start your drive without a map to help guide the way. Maybe you know the general direction, but the specifics to guide your trip are all on the map. Biomarkers work like that map. While you know that you'll receive some type of cancer treatment (see page 5), the specific "turns" to take with your treatment plan can be guided by your biomarkers. Biomarkers can help you and your doctor get to a treatment plan more efficiently, just as a map can help you get to your destination more efficiently. Having the right map, or knowing your cancer biomarkers, can help you feel at ease, and even more than that, empowered!

As you read through these pages, try not to get overwhelmed! There is a lot of information in this booklet that can help you feel comfortable talking about biomarkers with your care team.

TO KEEP IT SIMPLE, USE THIS AS YOUR MAIN TAKEAWAY:

Knowing your biomarkers can help your doctors identify YOUR best treatment options and help you make well-informed decisions about how your cancer will be treated. Knowing your biomarkers will allow you to be your own best advocate.

If you or a loved one have been diagnosed with colorectal cancer (CRC), you likely want to start treatment as soon as possible. However, it's important that you take some time to learn all you can about your cancer before making treatment decisions.

Treating cancer today is different than it was in the past. In the past, oncologists would give the same treatment to everyone. For example, if you had breast cancer, you'd get the standard breast cancer chemotherapy regimen used for all people with breast cancer; lung cancer, you'd get the standard treatment for all people with lung cancer; and so on.

We now understand that two people with the same cancer location (colon, rectal, lung, or breast, for example) may actually have different cancer types at the cellular level.

Thanks to ongoing research efforts, doctors are now able to categorize cancer by some genomic changes, also known as changes in the DNA. This has altered the approach to treatment. Scientists have learned that some cancer types respond better to certain treatments and respond more poorly to others. Your colon or rectal tumor might not respond to the same treatment that other colorectal cancer patients receive, depending on the genomic changes (the biomarkers) in your tumor.

Choosing your course of treatment based on the specific genomic changes of your cancer (what we refer to as biomarkers) will help your team deliver specific care that will be the most beneficial with the least amount of side effects. It will empower you to be an informed partner with your physician in your cancer care.

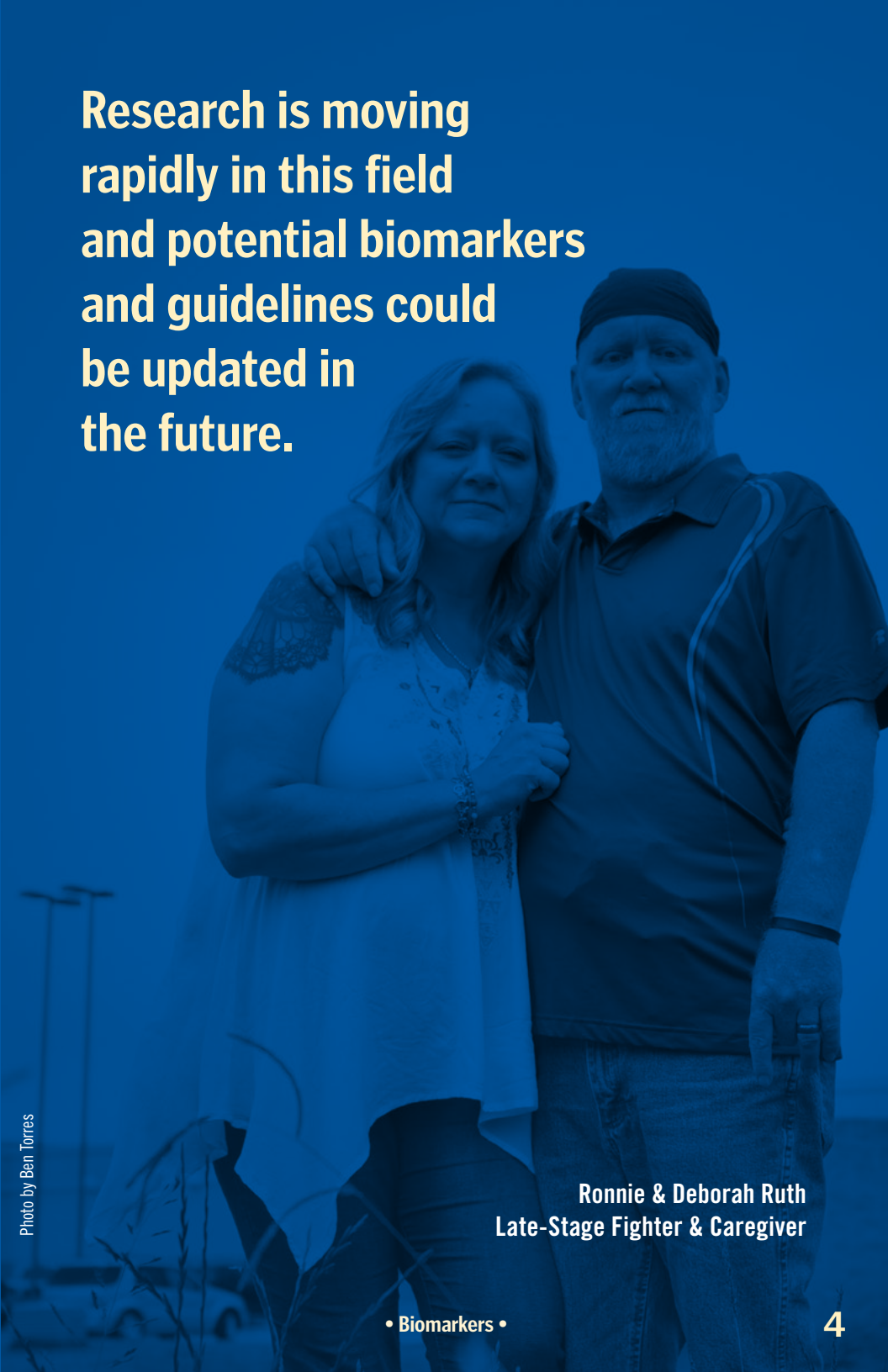
This individualized approach is called **personalized medicine.**

VOCABULARY

- **Personalized medicine** is a way of medically treating each person individually.

  This includes taking steps to identify patients more likely to benefit from a certain treatment over another and to identify patients who may be at a higher risk of side effects from certain treatments.

Research is moving rapidly in this field and potential biomarkers and guidelines could be updated in the future.



Ronnie & Deborah Ruth
Late-Stage Fighter & Caregiver

Photo by Ben Torres

COMMON TREATMENT OPTIONS FOR METASTATIC COLORECTAL CANCER (mCRC)

CANCER CARE SHOULD INCLUDE A **multi-disciplinary** approach.

A multi-disciplinary approach to treatment means there are many different medical professionals working together to create a treatment plan. This could include a surgeon, radiologist, oncologist, social worker, and others. Effective teamwork requires collaboration and communication when it comes to comprehensive, high-quality care; therefore, it's important to ensure all your providers communicate with one another and help you understand your treatment options.

Metastatic CRC (mCRC) is also known as "late-stage" CRC

For a more detailed description about treatment options, download *Your Guide in the Fight* at ***FightCRC.org/Guide***

SHARED DECISION-MAKING

Shared decision-making occurs when you and your doctors share the responsibility of making treatment and medical care decisions. Today, there are more treatment options available to choose from, and your preferences and values are important when it comes to selecting the right one for you. For shared decision-making, you will be involved in discussions about treatment options. Your doctor will talk to you about the pros and cons of each option, and you will work with your doctors to agree on an approach.

If at any time you have questions or are confused by a treatment option, don't hesitate to ask! Being as informed as possible can be helpful during this process.

Photo by Ben Torres

TREATMENT TYPE / APPROACH AND DESCRIPTION FOR mCRC

There are many treatment approaches for colorectal cancer. Below are the most common types you may discuss with your doctors.

Chemotherapy · Chemotherapy is used to stop or limit the growth of rapidly-dividing cancer cells. It can be taken by mouth (oral chemotherapy) or injected into a vein (intravenous chemotherapy) to reach cancer cells throughout the body.

Targeted Therapy · Targeted therapies include drugs that block the growth of cancer by interfering with the molecules involved in tumor growth and spreading. They attack cancer cells by locating the specific genomic change or changes that are making the cancer grow. This type of treatment could lead to less damage to normal cells because they target specific genes or proteins that are altered within the cancer cells. This is often used in combination with chemotherapy.

Surgery · Colon cancer patients may receive surgery before or after chemotherapy. Rectal cancer patients may receive radiation and chemotherapy before surgery. For stage III and IV patients, surgery alone is not enough, and the medical team will recommend additional treatments.

Radiotherapy/Radiation · Radiation therapy uses high-energy x-rays or other types of radiation to kill cancer cells or keep them from growing. There are several types of radiation therapy.

Immunotherapy · Immunotherapy uses parts of a person's immune system to fight disease. The goal is to boost a patient's immune reaction to the cancer cells, allowing them to fight the disease more effectively. It has not been shown to be effective for all CRC patients and is still being studied.

Clinical Trials · Clinical trials are a treatment approach. They test new treatments like drug therapy, surgery, radiation, and immunotherapy for CRC and other cancers, or they may include multiple treatment types in combination. The goal is to discover new, beneficial ways to treat cancer. There are also clinical trials that test new ways to stop cancer from recurring or reduce the side effects of cancer treatment.

FIGHT CRC TRIAL FINDER
POWERED BY PATIENTS

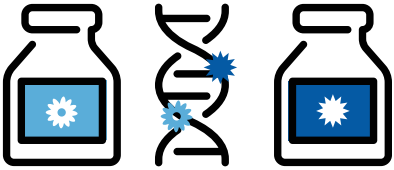
MORE AT: ***FightCRC.org/ClinicalTrials***

ALL ABOUT BIOMARKERS

WHAT ARE BIOMARKERS?

Biomarker is short for biological marker. Biomarker testing is sometimes called tumor testing, molecular testing, and genomic testing. Cancer biomarkers are biological, chemical, or biophysical entities that are present in tumor tissues or body fluids. They can give valuable information about the characteristics of a tumor. They can also give information about the tumor's future behavior (how it may grow or react to treatment) as well as give an idea as to whether cancer is still present or not in a person after treatment ends.

Most biomarkers are proteins which are coded for by tumor cell DNA. Their presence shows that there are genomic abnormalities (changes) that distinguish tumor cells from healthy cells. Also, their presence can provide clues to what drives the cancer cells to grow and spread. These abnormal proteins can be found in cancer cells or in the cell membranes of those cells. They can be



detected by tests done directly on tumor tissue or on body fluids, most commonly blood. By understanding an individual tumor's biomarkers, doctors can predict how the tumor may grow and spread in addition to whether or not the tumor may respond to specific treatments.

Your colon or rectal tumor might not respond to the same treatment that other colorectal cancer patients receive depending on the biomarkers within your tumor. Therefore, addressing your course of treatment by learning the specific genomic changes of your cancer—your colorectal cancer biomarkers—will help your team deliver care that will be the most beneficial with the least amount of side effects.

Specific colorectal cancer biomarkers to be aware of are described on pages 11-17.

QUESTIONS THAT BIOMARKERS ANSWER

Biomarkers are used for a variety of purposes. They answer a number of questions that help guide treatment and other issues related to cancer.

1 How aggressive does this cancer behave? ***Prognostic biomarkers*** are used to learn about the estimated course of cancer if it goes without treatment. This type of biomarker helps identify how well functioning a cell is, or if it is not functioning.

2 Is this the best drug to treat my cancer? ***Predictive biomarkers*** are used to identify the best available treatment because they may predict whether or not the body will respond to a specific treatment. This is the type of biomarker that is discussed when it comes to treatment decision-making.

3 **Will my cancer come back?**
Recurrence biomarkers are used to monitor if the cancer is coming back after it has been treated.

4 **What type of cancer is this?**
Diagnostic biomarkers help identify the cancer type.

5 **What is the correct dose of drugs to treat an individual patient?**
Pharmacodynamic biomarkers help with dosing decisions.

In this magazine, we focus on biomarkers that address the top 3 questions.

WHEN SHOULD BIOMARKER TESTING HAPPEN?

BEFORE TREATMENT

Biomarker testing should happen as close to your diagnosis as possible, before selecting a treatment plan. If you begin receiving a treatment before knowing your tumor type, this may exclude you from future treatment options, including some clinical trials. Take the time to talk to your doctor about tumor testing before making treatment decisions.

If you've already started treatment prior to tumor testing, it is recommended that you still receive the testing (it could affect your current treatment plan). The hospital where you had surgery most likely retained some of your tumor tissue. Contact your surgeon and connect them with your oncology team to learn more about how to get your sample sent to a pathologist for testing. If your tumor tissue was not saved, ask your doctor about the best way to move forward with biomarker testing.

Photo by Ben Torres

RONNIE & DEBORAH RUTH
Late-Stage Fighter & Caregiver

RELENTLESS **CHAMPIONS** ***OF*** **HOPE** ***IN THE*** **FIGHT AGAINST** ***COLORECTAL CANCER***

F!GHT
COLORECTAL CANCER

Photo by Ben Torres

BIOMARKER TESTING

BIOMARKER TESTS ARE PERFORMED on tumor biopsies to identify gene mutations, also known as biomarkers.

After the biopsy is collected, it will be analyzed by a pathologist. A pathologist is a scientist who inspects laboratory samples of body tissue while studying the causes and effects of diseases. The pathologist will provide a report back to your doctor on what was discovered about your tumor.

To learn more about hereditary CRC, download our Genetics Mini Magazine at ***FightCRC.org/GeneticsMiniMag***

LIQUID BIOPSY	TUMOR BIOPSY
A sample of blood that pathologists use to look for DNA from tumor cells or tumor cells in the blood. Pathologists are looking for circulating tumor DNA (ctDNA) and/or circulating tumor cells (CTCs).	A sample of cells or tissues from the tumor to be examined by a pathologist. There are incisional biopsies where only a sample of tissue is removed, and excisional biopsies, where the entire tumor is removed.

GENETIC TESTING VS. BIOMARKER (GENOMIC) TESTING

A LOT OF TESTS GET ORDERED DURING THE COURSE OF A CANCER diagnosis and treatment, and it can be overwhelming to keep them straight.

GENOMIC (SOMATIC) MUTATIONS	GENETIC (GERMLINE) MUTATIONS
BIOMARKERS, which may be called genomic or somatic mutations, are not inherited. These are the mutations within a person's tumor that are not inherited. These are the mutations that are seen in the tumor, not in your inherited DNA. For this type of testing, experts look at mutations in the cancer cells to help with treatment decisions. This process is often referred to as somatic testing.	Genetic (germline) mutations identify if you have a genetic link to developing cancer. Testing is usually done with a blood test that looks at your inherited DNA. The risk of developing CRC may be higher for those with a first-degree relative (parents, siblings) diagnosed with CRC, those who have two or more relatives diagnosed with CRC, and those with relatives diagnosed with CRC at a young age. Before genetic testing, talk to a genetic counselor to learn more.
SOMATIC TESTING	**GERMLINE TESTING**
Somatic testing aims to identify mutations within a person's tumor. These are not inherited traits. These mutations arise during a person's lifetime sporadically or in response to an external exposure. **Somatic testing is done to see what gene mutations have accumulated in cancer cells. This is the most common type of testing for biomarkers. Next-generation sequencing (NGS) is becoming more widely used as the method for somatic mutation analysis in cancer. Learn more about NGS on page 16.**	Germline testing aims to identify traits within a persons genes or genetic makeup. These are traits that are inherited from a parent and are found in every cell of your body. **THERE ARE 3 TYPES OF GERMLINE TESTS** 1. **SINGLE SITE** looks at a specific mutation in a specific gene 2. **SINGLE GENE** looks at many locations along one or a few specific genes to find a mutation 3. **MULTI-GENE PANEL** used to evaluate many genes in a single test

COLORECTAL CANCER BIOMARKERS

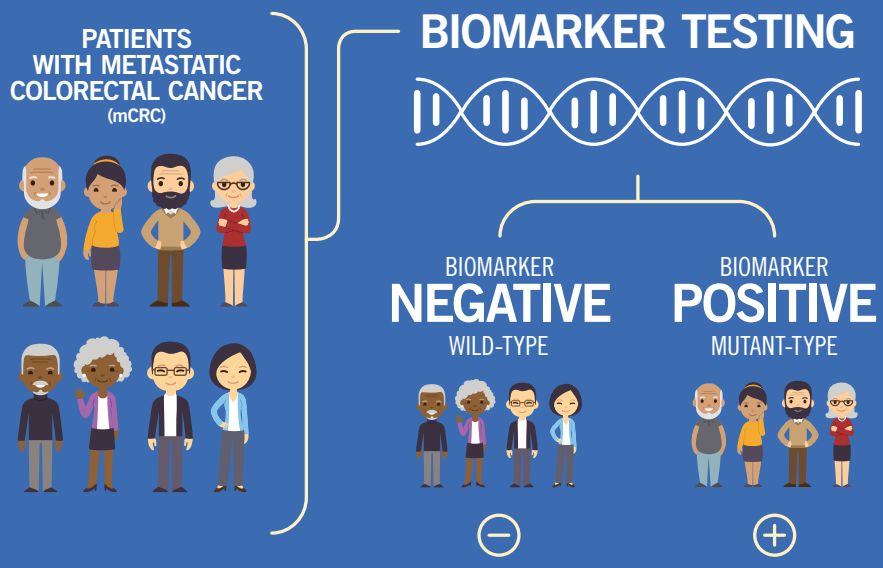
IT'S IMPORTANT TO KNOW YOUR BIOMARKERS BECAUSE THEY MAY HAVE CLINICAL IMPLICATIONS FOR YOU – MEANING THEY MAY IMPACT THE TREATMENT YOU RECEIVE.

QUESTIONS TO ASK YOUR DOCTOR:

1. **How will these biomarker test results affect my treatment plan?**
2. **What do these results mean for my prognosis?**

The next few pages review the most common biomarkers for CRC as of March 2020. These include genetic biomarkers, biomarkers found in proteins, biomarkers found in DNA abnormalities, and others.

LEARN MORE IN *YOUR GUIDE IN THE FIGHT* AT *FightCRC.org/Guide*



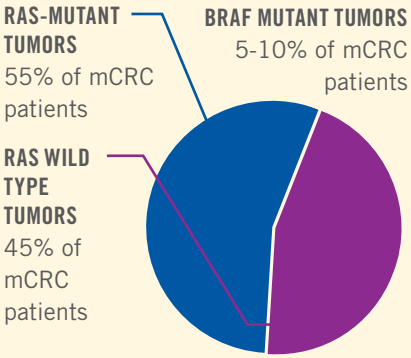
GENETIC BIOMARKERS

RAS

The **RAS** genes include the **KRAS** and **NRAS** biomarkers. KRAS and NRAS are genes that play an important role in instructing colorectal cancer cells to grow and divide as part of the epidermal growth factor receptor (EGFR) process.

- If a biomarker test indicates a KRAS or NRAS mutation, EGFR-inhibitors (drugs that target EGFR) may NOT be beneficial.
- Patients who are KRAS wild-type or NRAS wild-type (meaning, without mutations) may respond well to certain treatment plans that include EGFR-inhibitors.

Testing Recommendations:
KRAS and NRAS testing is typically recommended for stage IV patients and stage III recurrence.



EGFRs ARE LOCATED ON A CELL'S SURFACE. They receive signals that let them know when It's time for the cells to grow and divide.

For more about EFGRs, download our Skin Toxicity Mini Magazine at ***FIGHTCRC.ORG/SKINTOX***

BRAF

BRAF is a gene that signals cells to divide. Approximately 1% of patients with metastatic CRC have a tumor with a BRAF mutation other than **BRAF V600e**. The prognosis of the mCRC patients with tumors that harbor a BRAF mutation other than the specific V600e mutation is better than that of the average person with metastatic CRC. Patients with a BRAF mutation may not respond to EGFR-inhibitor drugs, such as cetuximab (Erbitux) and panitumumab (Vectibix).

- If a BRAF mutation is detected, there may be a poorer prognosis with the use of standard chemotherapy regimens, therefore clinical trials may be a good option. On the other hand, patients with a BRAF wild-type (meaning, there is no mutation) tumor generally have better survival than those with the BRAF mutation. Additionally, research is showing that emerging subgroups of the BRAF mutation can affect prognosis.
- The presence of a **BRAF V600e** mutation suggests a particularly aggressive cancer that requires aggressive treatment. It is present in approximately 15% of patients with early-stage CRC and 6% of those with metastatic CRC. Approximately 20% of patients with BRAF V600E–mutated metastatic CRC also have microsatellite instability. Just like any other patients with microsatellite instability, these patients can respond to checkpoint inhibitors such as nivolumab and

pembrolizumab. Additionally, vemurafenib is a drug that was included as a therapeutic option to treat BRAF V600e CRC in the 2018 version of the National Comprehensive Cancer Network's Clinical Practice Guidelines.

- Current research is exploring combinations of immunotherapy and targeted therapy in patients with BRAF-mutated microsatellite-stable CRC.
- Metastatic CRC (mCRC) patients with BRAF wild-type (without mutation) tumors generally have better survival than those with the BRAF mutation.
- Treatment options which might be considered for BRAF V600E positive patients, including dabrafenib plus trametinib and cetuximab or panitumumab as well as encorafenib plus cetuximab or panitumumab and binimetinib

Testing Recommendations:
BRAF testing is typically recommended for stage IV patients, although it is sometimes done for patients with stage III cancer. This test can be done at the same time as KRAS and NRAS testing.

NTRK

TRK fusions are genetic abnormalities that occur when one of the NTRK genes (NTRK1, NTRK2, NTRK3) become connected (FUSED) to another gene that is not related (e.g. ETV6, LMNA, TPM3). This connection leads to TRK signaling that is uncontrolled and could lead to cancer. TRK fusions are rare; however, when they are present there could be an option for a clinical trial for treatments targeting TRK inhibition. Additionally, new drugs which target NTRK fusion-positive metastatic CRC have recently been approved, including entrectinib and larotrectinib. These have been approved for metastatic solid tumors who have either progressed following prior therapies or as initial therapy when there are no acceptable standard therapies.

PIK3CA

PI3 kinase (PIK3CA) are genes needed for multiple cell functions, including cell growth (proliferation) and survival. Testing for this mutation is not standard of care per guidelines as of September 2018.

- Studies suggest that patients with PIK3CA mutation may benefit from aspirin therapy after surgical resection. Studies suggest that aspirin therapy can help decrease the risk of recurrent CRC in patients who have the PIK3CA mutation
- Make sure to talk to your doctor about the use of aspirin before you start, as it might not be a good fit for everyone.

Testing Recommendations:
Currently there are no recommendations for routine testing, however PIK3CA testing may be suggested for stage I, II, and III patients.

PROTEINS

CARCINOEMBRYONIC ANTIGEN (CEA)

CEA is a protein that is commonly elevated in CRC patients. Higher levels of CEA may indicate that cancer is growing, while lower levels may indicate that treatment is working.

Testing Recommendations: CEA testing is recommended for stages II, III, and IV colorectal cancer, and is done with a blood test.

For follow-up care and monitoring a patient 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. For many patients, monitoring the levels of CEA can let doctors know if cancer is growing.

15-20%

PIK3CA mutations are present in 15-20% of colorectal cancers

Photo by Brian Threlkeld

TARA Principali
Stage II survivor

DNA ABNORMALITIES

MICROSATELLITE INSTABILITY HIGH (MSI-HIGH OR MSI-H)

MSI-H happens when genes that regulate DNA (called Mismatch Repair Genes) don't work correctly. Mismatch Repair Genes (MMR) 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.

An MSI biomarker test looks for changes in the DNA sequence between normal tissue and tumor tissue, and can identify whether or not there is a high amount of instability, which is called MSI-High. This is found in about 15% of colon tumors. It is often in tumors associated with the hereditary syndrome, Lynch syndrome*, though many MSI-High tumors are sporadic (not due to a hereditary syndrome). Patients who test MSI positive are considered to have an MSI-High tumor.

An additional test (immunohistochemistry test) is often used to make the distinction between hereditary and non-hereditary MSI-High. If it is hereditary (meaning the patient has Lynch syndrome) there is a risk that their family members could also have it, therefore have an increased chance of developing colorectal or other tumors. If Lynch syndrome is the cause of an MSI-High tumor in a patient, their immediate family members should talk to their doctors about testing for Lynch syndrome*.

Many patients with MSI-H tumors have had a positive response to immunotherapy treatments (specifically immune-checkpoint therapies). Therefore, knowing your MSI status is extremely important prior to selecting a treatment.

15%

MSI is detected in about 15% of all colorectal cancers

Testing Recommendations:
MSI testing is recommended for ALL colorectal cancer patients. Talk to your surgeon or oncologist about MSI testing.

"It is important that all newly-identified colorectal tumors be tested for Mismatch Repair. This not only helps identify patients who might have a familial tendency to develop colorectal (and other) cancers, but will be useful in selecting effective therapies if necessary. For patients who need treatment beyond surgery, testing for RAS and BRAF biomarkers should also be requested to help determine the best course of treatment."

- Jan A. Nowak, MD, PhD
Clinical Chief of Molecular Pathology
Roswell Park Comprehensive Cancer Center

*To learn more about hereditary colorectal cancer, download our Genetics Mini Magazine at ***FightCRC.org/GeneticsMiniMag***

HER2 AMPLIFICATION

CRC BIOMARKERS IN RESEARCH

HER2 AMPLIFICATION

HER2 (or human epidermal growth factor receptor 2) is currently being studied in colorectal cancers. In approximately 5% of KRAS non-mutated (wild-type) cancers, HER2 is amplified. Combination therapies including trastuzumab and lapatinib have been tested with these patients in phase II studies, resulting in a 35% overall response rate and a median time to progression of about five and a half months. This suggests that anti-HER2 therapy may be effective in this group of mCRC patients. There is also evidence that HER2 amplification may cause resistance to a class of drugs called EGFR inhibitors such as cetuximab and panitumumab. Currently, there are no recommendations for routine testing for HER2 in CRC.

COMMON TERMS

Wild-Type – no mutation in the biomarker DNA sequence

Mutation – an alteration in the biomarker DNA sequence

First-Line treatment – the initial (first) treatment for a cancer patient that is accepted by the medical community as the best option

Recurrence – the return of cancer after a period of remission (or, after you've been declared no evidence of disease (NED))

Stage III – cancer that has spread to lymph nodes

Metastatic / Stage IV - cancer that spread beyond its original location in the colon or rectum and formed one or more tumors in other areas of the body, like the liver and/or lungs

Next Generation (Gen) Sequencing (NGS) a technology that allows for multiple genes to be tested at the same time, at a fairly low cost

Pathologist a doctor with training to identify diseases by looking at their cells. They use microscopes to study tissues and cells.

PATHWAYS

YOU MAY HEAR YOUR TREATMENT team refer to pathways or signaling pathways when talking about biomarkers or your treatment plan. These are a type of biomarker that determine the behavior of cancer cells. The PD-1/PD-L1 and Wnt pathways are commonly discussed in colorectal cancer research and are targets for some treatments.

PD-1 / PD-L1 PATHWAY

PD-L1 is an immunosuppressive driver, meaning that it stops the immune system from functioning at its optimal level. Some cells within the body, called T-cells, have receptors on them which make sure that abnormal or mutated cells don't multiply. Think of these T-cells as security guards and PD-L1 as a disguise on abnormal cells. With the presence of PD-L1, the T-cell receptors are unable to see that the mutated cells are mutated due to the PD-L1 "disguise," therefore the mutated cells get through the security guards and are able to multiply, becoming cancer.

Nearly half of all cancers have the PD-L1 biomarker. Therefore, many researchers are using the presence of PD-L1 as a pathway to fight cancer.

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TUMOR MUTATIONAL BURDEN (TMB)

TMB is a biomarker made up of the total number of mutations per coding area of a tumor genome. Some researchers are now using it to identify which patients would benefit from the checkpoint inhibitor therapy (like ones that target PD-1/PD-L1). A high level of TMB may indicate that you would benefit from this type of treatment

WNT PATHWAY

The Wnt pathway is a complex pathway responsible for stability and is often highly mutated in colorectal cancer patients. When not functioning properly, the pathway could lead to mutations in adenomatous polyposis coli (APC) genes in the body, which are found in most of all sporadic colorectal cancer in addition to familial adenomatous polyposis (FAP - a heritable syndrome. To learn more, download our Genetics Mini Magazine). Targeting the Wnt pathway, especially through the use of combination therapies, is something researchers a re studying for more effective treatment plans.

BIOMARKER RESEARCH IS MOVING QUICKLY AND AGGRESSIVELY!

We don't know everything about cancer biology, and not all biomarkers are clearly understood... yet!

PATIENT STORIES

"IT IS SUPER IMPORTANT to have tumor testing done so that you know right from the get go what type of CRC you have and what options are out there for you. I am microsatellite stable (MSS), with a left sided tumor and no mutations, so I am just praying first line chemo keeps working for me until they find a cure. My doctor said she will retest if my body stops responding to this chemo."

– Jessica Dilts-Cash
Stage IV survivor

"I GOT THREE DIFFERENT OPINIONS from doctors before I decided on treatment. I also was very hands-on with choosing my treatment. I asked questions and did my homework. I asked about biomarkers; I made sure my tumor was tested. Because I asked, I made a better choice about treatment. I had more control than I thought."

– Rachel Durst-Streaker
Stage III survivor

"MY HUSBAND WAS diagnosed with stage III colon cancer at age 41 in 2013 during a time when he was training for a marathon. It wasn't until he had undergone multiple rounds of treatment that biomarker testing was recommended. The testing was offered as a way to help his doctor understand why he wasn't responding to the treatment in the way he expected. After learning that his tumor was KRAS mutant, it was clear that the regimen he was on, which included an EGFR-inhibitor, was not going to work for him. My husband quickly transitioned to a clinical trial. In hindsight, I wish that we had been offered the testing earlier – or had known about it to ask the doctor about it before treatment. It would have saved my husband a lot of distress due to the side effects he experienced from a treatment that was never going to work for him."

– Dana Georges
Caregiver & Advocate

QUESTIONS & ANSWERS

HERE ARE COMMON QUESTIONS patients ask us about biomarkers. To talk with someone about your biomarker questions, call our Resource Line at 1-877-427-2111. *Note: The line only provides information and resources, not medical advice.*

Q: As a stage I or II CRC patient, what are the current recommendations for biomarker testing as it relates to my treatment decision-making?

A: Currently, only MSI testing is recommended. However, it is strongly recommended that all CRC patients learn about their family health history of colon and rectal cancers. Depending on the history, patients will be referred to genetic counseling to learn if they are at a higher risk for developing other cancers or if their family members are also at a higher risk.

Q: When should I talk to my doctor about biomarkers?

A: Talk with your healthcare team about tumor biomarker tests immediately after your diagnosis. If you are already on treatment and are unsure whether or not you have received biomarker testing, ask your treatment team.

Q: What will my results look like?

A: Your test results will show whether your tumor has a mutation (positive test results) or if it is wild-type (negative test results; no mutation detected). Your doctor will review your test results with you and discuss how they will affect your treatment decisions. If you would like a copy of your test results, be sure to request them. Finally, if you have questions for your treatment team, be sure to ask!

Q: Will I need another biopsy to test my tumor?

A: No. When you had surgery, some of your tumor tissue was removed and stored at the hospital. Your doctor can arrange for your tissue to be sent to a lab. Results will go to your doctor. The tissue sample tested can be from your original cancer in your colon or rectum, or from a metastatic tumor that has spread.

Q: Why haven't I heard about this before?

A: Biomarker (tumor) testing is becoming more common, especially in clinical trials. It is a new step in the treatment process that is still on a journey of reaching all oncologists and providers.

Q: Can I be BRAF and *KRAS* positive?

A: It would be extremely rare. If you have a BRAF-mutant tumor you will not be KRAS mutant, and vice versa.

Q: What are the downsides of biomarker testing?

A: There are multiple biomarkers that have been scientifically shown to be meaningful in colorectal cancer. While more and more biomarkers are being studied, not all are shown to have clinical relevance or benefit the patient's treatment decision-making.

Q: I've had genetic testing. Does this mean I've had biomarker testing?

A: Genetic testing is a type of biomarker testing, but does not ensure that you have received all the biomarker tests necessary to make an informed treatment decision. (See: Genetic vs Genomic testing on page 10.)

Q: I've been told I have Lynch syndrome. Does this mean I've had biomarker testing?

A: This means that you have received MSI testing. To learn if you have received testing for additional biomarkers you will need to check with your doctor.

RIGHT VS LEFT

RESEARCH SUGGESTS

there may be a difference in tumor biology depending on the side of the colon that cancer originates (right versus left).

Patients with right-sided tumors may not have the same results and success rates if EGFR-inhibitor therapy is used as the first-line of treatment as compared to patients with left-sided tumors. Additionally, in July 2018 the American College of Surgeons announced evidence that increasing the number of lymph nodes removed during surgery on right-sided colon cancers may lead to improved survival rates.

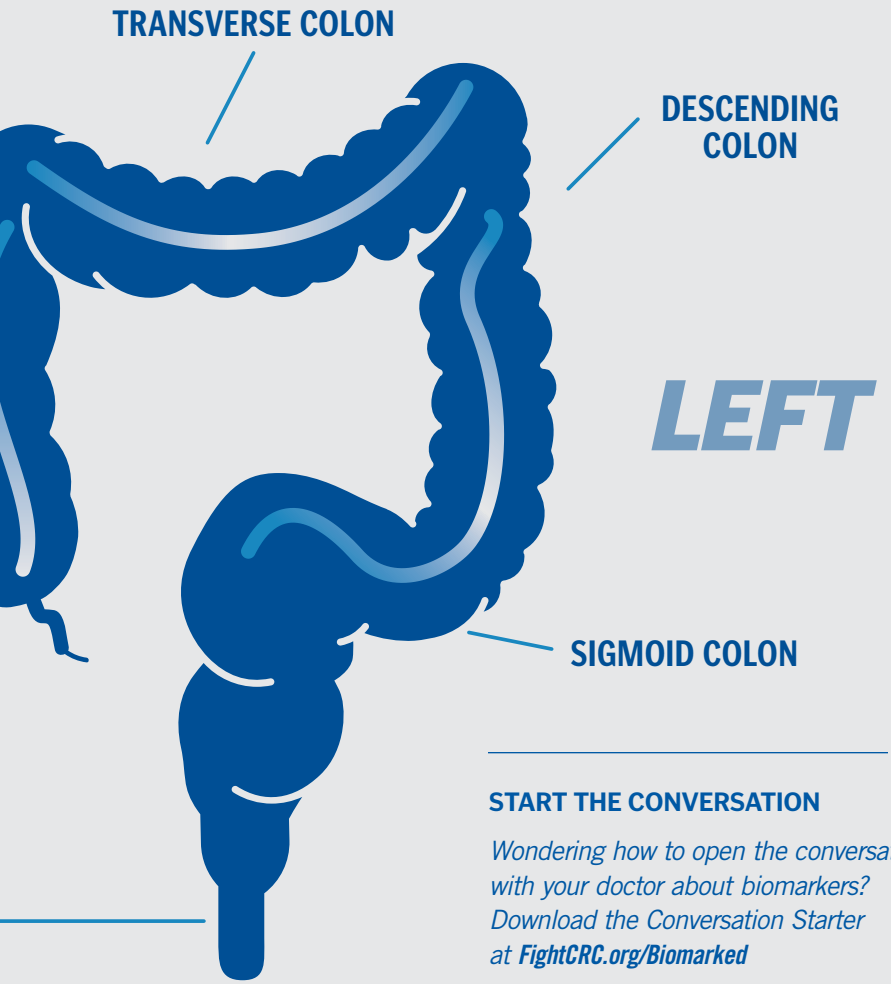
Ask your doctor about whether or not your treatment plan will be different based on the "sidedness" of your tumor.

Q: Will I get to see my test results?

A: Your doctor will likely explain he results of your biomarker test with you when they come in. If they don't, just ask! Additionally, if you'd like to keep a copy of the report for your records, don't hesitate to ask for one. Make sure you clearly understand the results so that you can participate in shared decision-making for your treatment plan.

Q: Is there financial assistance for biomarker testing?

A: Some people may avoid testing due to perceived financial burden. Luckily, many labs offer patient assistance for out-of-pocket costs, and insurance companies may cover costs as well. Talk to your social worker and call your insurance provider to learn more.



START THE CONVERSATION

Wondering how to open the conversation with your doctor about biomarkers? Download the Conversation Starter at ***FightCRC.org/Biomarked***

Q: Who makes the guidelines?

A: In May 2017, four professional groups published evidence-based guidelines for biomarker testing for colorectal cancer. The Guideline, entitled Molecular Biomarkers for the Evaluation of Colorectal Cancer Guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology and American Society of Clinical Oncology provides recommendations for mismatch repair status testing. RAS mutation testing for patients being considered for anti-EGFR therapy, and BRAF testing for colorectal cancer patients, in addition to other recommendations and expert consensus opinions for the implementation of biomarker testing. As research continues to evolve, guidelines and recommendations will also likely change to reflect the most relevant and meaningful research.

RECOMMENDED BIOMARKER TESTING FOR COLORECTAL CANCER

WHEN IS KRAS AND NRAS TESTING RECOMMENDED?	
For stage IV patients at time of diagnosis	For stage III recurrence at time of diagnosis
HOW IS IT DONE?	
Biopsy	
HOW WILL THIS AFFECT ME?	
KRAS/NRAS WILD-TYPE (negative) EGFR-inhibitor drugs may be a good option for treatment	**KRAS/NRAS MUTANT (positive)** EGFR-inhibitor drugs may not be beneficial and are therefore not recommended
WHEN IS BRAF TESTING RECOMMENDED?	
For stage IV patients	Sometimes done in patients with stage III cancer
HOW IS IT DONE?	
Biopsy	
HOW WILL THIS AFFECT ME?	
BRAF WILD-TYPE Patients who test negative for BRAF are recommended EGFR-inhibitor treatments	**BRAF MUTATION** Patients with a BRAF mutation do not respond to EGFR-inhibitor drugs
WHEN IS MSI TESTING RECOMMENDED?	
Recommended for all colorectal cancer patients	
HOW IS IT DONE?	
Biopsy	IHC testing (blood test)
HOW WILL THIS AFFECT ME?	
MSI-H (positive) Patients who test positive for MSI-H may respond well to immunotherapy treatments.	**MSS (negative)** Patients who test negative for MSI have microsatellite stable tumors that do not respond to current immunotherapy, or don't have the same responses to immunotherapy, therefore this type of treatment is not recommended.
CHECK OUT OUR LYNCH SYNDROME RESOURCES AT *FightCRC.org/Lynch*	CHECK OUT THE LATE STAGE MSS-CRC TRIAL FINDER AT *TrialFinder.FightCRC.org*

Recommendations as of March 2017. See page 25 for more information.

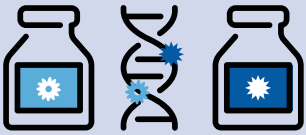
FOR DOCTORS AND PATIENTS WHO NEED HELP FACILITATING BIOMARKER TESTING

LEARN ABOUT YOUR BIOMARKER TESTING OPTIONS: Fight CRC has partnered with Perthera to help facilitate the biomarker testing process. Perthera can help you and your doctor get your tumor tissue sample to a participating lab for testing. When the testing is completed, Perthera will provide you and your doctor with a comprehensive, easy to read report about your tumor. Their A.I. based system will provide a list of ranked therapeutic options, which will include any appropriate clinical trials.

If you have had biomarker testing completed in the last 12 months, Perthera can also analyze these results for appropriate therapeutic options including clinical trials.

FIGHT CRC STAYS UP TO DATE ON THE LATEST INFORMATION. SIGN UP TO GET BREAKING NEWS AT *FIGHTCRC.ORG/SIGNUP*

REVIEW



IN THIS MAGAZINE, we've covered multiple biomarkers and various recommendations for testing. Make sure you talk to your doctor about them as soon as possible – whether that's before treatment begins or years after diagnosis. It's important to know if you've had your biomarkers tested!

In 2017, highly-respected groups of pathologists and oncologists* came together and formed guidelines for biomarker testing for colorectal cancer patients. The recommended testing noted in this magazine reflects the recommendations in these guidelines. The evidence-based guideline for molecular testing for colorectal cancer is a joint publication between the four organizations: American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology.

The complete title of the guideline is: *Molecular Biomarkers for the Evaluation of Colorectal Cancer Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology.*

Research about biomarkers in colorectal cancer is moving rapidly! If you're a CRC patient, or caring for one, make sure to ask your doctors about biomarkers to find out which testing is appropriate for you. If you're a physician, make sure you know the latest on biomarkers for CRC.

Last, if you've asked the questions, gotten the test, and know your biomarkers, make sure to share that information with others. Your entire treatment team and your family members may benefit from the knowledge. Other patients will, too! Your story is powerful and by taking what you know about your cancer and sharing it outwardly with others, you'll inspire other patients to know their tumors and get tested.

To share your biomarkers story, visit ***FightCRC.org/Biomarked***

FOR MORE INFORMATION & SUPPORT

Fight Colorectal Cancer is a trusted, nonprofit advocacy organization dedicated to empowering patients to be their own health advocates.

RESEARCH

At Fight CRC, we fight to make breakthrough research a reality. We fund innovative research grants, convene meetings with national and global experts on the biggest issues in CRC, and we train survivors and caregivers to be a part of the scientific discussions. To get involved in research and stay up to date on the latest scientific breakthroughs, follow ***@FightCRC*** on Twitter, or visit us at ***FightCRC.org/research.***

ADVOCACY

Are you ready to turn your pain into purpose? By sharing your story and raising awareness, you can help change policy around colorectal cancer. That's what the Fight CRC Advocacy Program is all about! We advocate on Capitol Hill. We engage and teach grassroots advocates like you to get involved in your communities. To learn more about how to raise your voice for CRC advocacy, visit ***FightCRC.org/action-center.***

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RESOURCES

To download or request print materials, go to: ***FightCRC.org/Resources***

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SPONSORS

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