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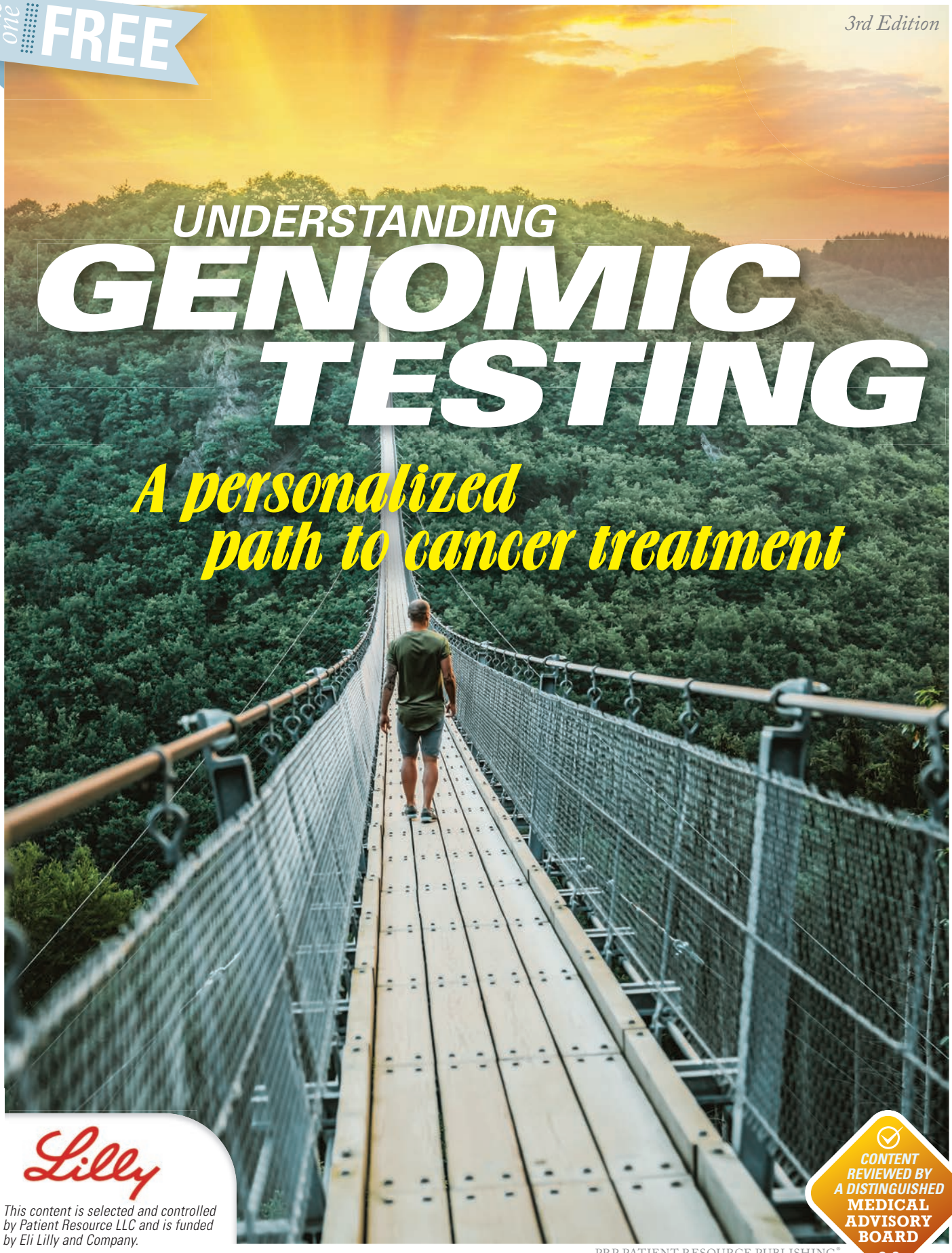
# UNDERSTANDING GENOMIC TESTING

## A personalized path to cancer treatment



Lilly

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3rd Edition

# UNDERSTANDING GENOMIC TESTING

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Facing cancer is hard enough.
Getting resources and medication shouldn't be.

**Lilly Oncology Support Center™:**
**1-866-472-8663,** Monday–Friday, 8 AM–10 PM ET;
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# Lilly Oncology Support Center

## Resources and programs to help support eligible Patients during treatment

Lilly is dedicated to developing cancer treatments, but we're more than just our medicines. That's why we created the **Lilly Oncology Support Center**, a comprehensive Patient Support Program focusing on two important areas for Patients and their loved ones:

- Financial and coverage issues for eligible Patients (whether they're uninsured, underinsured, or insured), including financial assistance, help with benefits verification, Prior Authorization support, Specialty Pharmacy coordination, access, reimbursement, and more.
- Ongoing personalized care (for some products) from a dedicated staff, including emotional support and other services.

The **Lilly Oncology Support Center** provides a range of personalized services to help qualified Patients get the individual support they need—whether it's financial, emotional, or otherwise. Here's an overview of what's offered:

### Savings Card Program

- Supports eligible Patients with copay and coinsurance costs for prescribed Lilly Oncology products*
- No income eligibility requirement

*This offer is invalid for Patients whose prescription claims are eligible to be reimbursed, in whole or in part, by any governmental program.

### Insurance Support

- Eligibility Determination
- Benefits Investigation
- Prior Authorization Assistance
- Appeals Information
- Specialty Pharmacy Coordination

*Note: These services are provided through coordination with a Patient's physician's office.*

### Resources

*For Patients:*

- Information about potential sources of assistance, including medication provided at no cost to qualifying Patients

*For Healthcare Professionals:*

- Coding and Billing Information
- Payment Methodologies and Allowables
- Payer Policy Information
- Pricing Information

## **Lilly Oncology Support Center**: Helping people living with cancer stay focused on treatment, not how to pay for it

The **Lilly Oncology Support Center** is committed to helping qualified Patients when they're prescribed a Lilly Oncology product. The aim is to help Patients understand their coverage options, locate the appropriate pharmacy, and identify the lowest possible out-of-pocket cost.

Whether it's benefits verification, Prior Authorization, paying for medicine, or Specialty Pharmacy coordination, the **Lilly Oncology Support Center** is available to help. We can also provide support beyond financial assistance for certain products, and we can help Patients connect with non-Lilly resources, such as therapeutic support groups for specific types of cancer.

For more information, call **1-866-472-8663**, Monday–Friday, 8 AM–10 PM ET, or visit **LillyOncologySupportCenter.com**



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# How genomic testing is improving and personalizing cancer care

***Genomic testing is revolutionizing*** cancer treatment by allowing doctors to treat some patients according to the unique characteristics of their cancer. This is known as precision medicine, and it offers a more patient-focused approach to cancer care. Not all doctors currently use genomic testing for every cancer type, but this specialized testing is expected to play a bigger role in diagnosing, treating and monitoring cancer now and in the future.

Use the information in this guide to learn about genomic testing and how it applies to your cancer care. This knowledge will empower you to engage in shared decision-making with your doctor.

## DECODING GENOMIC TESTING

The discovery that cancer begins at the cellular level has paved the way for the use and application of genomic testing (see *Biology Basics*, page 6). Scientists now understand that cancer is a disease of our genes, which are pieces of DNA in our cells. DNA refers to the molecules inside cells that carry genetic information that is passed from one generation to the next through offspring. Almost every cell in the body contains a complete copy of the genome, which contains all the information needed for a person to develop and grow.

Cancer forms when genes begin to change, or mutate, within the structure of normal cells. The foundation of genomic testing is built on finding those mutations. It is important to understand that just as every person has a specific mix of genes that is unique to them, cancers are driven by a mixture of specific mutations. Understanding the types of mutations your tumor has will help you make informed decisions with your doctor about your treatment options.

Genomic testing is a broad term that refers to looking at a cancer's biomarkers from a biopsied tumor tissue or a blood sample. Also known as molecular testing or tumor profiling, it is performed in a laboratory in an attempt to detect biomarkers, which are substances such as genes or molecules that can be measured in the blood, plasma, urine, cerebrospinal fluid or other body fluids or tissues (see *Genomic Testing*, page 8). They are produced by cancer cells or other cells of the body in response to cancer.

Biomarkers are routinely tested for in certain cancers and are increasingly being used for more cancers. This type of testing allows doctors to learn about the tumor's genome. By unlocking the DNA code of the tumor, doctors can better understand the tumor's unique characteristics, such as the cancer's behavior, how aggressive it might be and whether it will metastasize (spread). It also offers the possibility of treating the

TABLE 1

## TYPES OF GENOMIC TESTS

| Test | What the test does | Sample type | Purpose |
|---|---|---|---|
| **Comprehensive biomarker testing** | **Looks for known biomarkers** | Tissue | **Determine treatment** |
| **Cytogenetic testing** | **Looks for changes in chromosomes, including broken, missing, rearranged or extra chromosomes** | Tissue, blood or bone marrow | **Diagnose, plan treatment, determine treatment effectiveness** |
| **Fluorescence in situ hybridization** (FISH) | **Looks at genes or chromosomes in cells and tissues and identifies where a specific gene is located on a chromosome, how many copies of the gene are present and any chromosome abnormalities** | Tissue | **Diagnose, determine prognosis, evaluate remission** |
| **Immunohistochemistry** | **Tests for certain antigens (markers), such as proteins like PD-L1; it may also be used to determine the difference between cancer subtypes** | Tissue | **Diagnose** |
| **Immunophenotyping** | **Tests for and identifies markers on cells** | Blood or bone marrow | **Diagnose and classify blood cancers** |
| **Karyotype** | **Looks for abnormal numbers or structures of chromosomes** | Blood, bone marrow or tissue | **Diagnose and identify the Philadelphia chromosome found in chronic myelogenous leukemia** |
| **Liquid biopsy** (also called circulating tumor DNA or circulating tumor cells) | **Looks for cancer cells or pieces of DNA from a tumor that are circulating in the blood** | Blood | **Detect cancer at an early stage, plan treatment, determine treatment effectiveness, monitor for recurrence** |
| **Microarray** | **Generates a genetic profile for a given tissue sample that reflects the activity of thousands of genes** | Tissue | **Identify cancer subtypes** |
| **Multi-gene panel testing** | **Studies many genes in a sample of tissue to find mutations in certain genes that may increase a person's risk of cancer** | Blood | **Find cancer, plan treatment or determine treatment effectiveness** |
| **Next-generation sequencing** (NGS) | **Tests multiple genes simultaneously** | Tissue | **Diagnose, determine prognosis and plan treatment** |
| **Polymerase chain reaction** (PCR) | **Looks for certain changes in a gene or chromosome** | Blood, saliva, mucus or tissue | **Find and/or help diagnose a cancer** |
| **Reverse transcription PCR** (RT-PCR) | **Amplifies traces of DNA for accurate analysis; looks for activation of certain genes** | Blood, saliva, mucus or tissue | **Diagnose** |

cancer more effectively without damaging healthy cells, as well as sparing people with slow-growing disease the side effects from aggressive treatments. If a biomarker is detected, your doctor may evaluate potential targeted therapy and immunotherapy options (see *Treatment Options*, page 10).

### THE TIMING OF BIOMARKER TESTING

Biomarker testing may be performed at diagnosis, during treatment or if the cancer returns. When a tumor returns, it may have different mutations than before, which may affect treatment options and prompt another round of biomarker testing. The test(s) your doctor chooses may depend on the type of cancer you have and the known mutations associated with it (see Table 1).

In the cases where this testing has a clinical benefit, some of the additional potential uses include the following:

- Staging a cancer
- Determining prognosis (outlook)
- Evaluating whether therapies are available to treat mutations in that specific cancer
- Monitoring treatment effectiveness
- Watching for progression or recurrence
- Predicting how the tumor might behave, such as how fast-growing it is and how likely it is to spread (metastasize)

See Table 2 for more information about how biomarkers are used.

### WHAT YOU NEED TO KNOW

Knowing whether your cancer has any biomarkers may help you take a more active role in treatment planning. This approach to treating cancer is more personalized and precise than traditional treatment strategies. It may be challenging to process all of the new information you receive when you are diagnosed; however, this is a good time to ask about biomarker testing and whether your doctor has already had it done or plans to. Sometimes your doctor will order biomarker testing on a tissue sample collected during a biopsy without you realizing it.

Not all cancer centers offer molecular testing, so it is important to determine whether it has been performed on your blood or tissue samples (see *Have the genomic conversation with your doctor*). If it was, ask your doctor to explain which biomarkers were tested for and the results. If the testing has not been performed, request it to find out whether you may have access to drug therapies that target the cancer.

Testing may be used to find one or multiple types of mutation in tumor cells. With some cancer types, it is recommended you have comprehensive biomarker testing, which looks for all possible mutations in a tumor regardless of whether drugs are available to treat these mutations. Keep in mind that not every tumor has known mutations, and some are identified that do not yet have a specialized treatment.

### LOOKING FORWARD

Ongoing research is expected to continue finding more biomarkers in the future. As a result, new drugs targeting specific mutations will likely be developed. As precision cancer care evolves, comprehensive biomarker testing is expected to become more widespread and included as standard of care for diagnosing and treating many types of cancer in the future.

To be fully informed about your treatment options, learn about the types of testing available and the biomarkers for your specific type of cancer. ■

TABLE 2

## HOW BIOMARKERS ARE USED

| Purpose | Description |
|---|---|
| **Screening** | Most biomarkers are not useful for screening; only 1 biomarker (prostate-specific antigen) is used for screening |
| **Aid diagnosis** | Biomarkers can help identify the type of cancer when considered along with other clinical factors, such as symptoms and findings on imaging studies |
| **Determine prognosis** | Some biomarkers are factors considered when determining prognosis or predicting outcome |
| **Guide treatment** | Some biomarkers can provide information about the types of treatment that are more likely to produce a response |
| **Monitor response to treatment** | Biomarkers can monitor the effectiveness of some treatments, especially for advanced cancers |
| **Detect recurrence or progression** | One of the primary uses of biomarkers; if the level of a tumor marker is elevated before treatment, or is low after treatment and then begins to increase after treatment, it is likely that cancer is recurring or progressing |

*(cut along dotted line)*

## HAVE THE GENOMIC CONVERSATION WITH YOUR DOCTOR

▶ You do not need a scientific background to understand how genomic testing results could offer treatment options that you wouldn't know about otherwise. You simply need information. If your doctor has not brought up genomic testing, set up a time to talk about it. Ask these questions, take notes and check the boxes as you go down the list to ensure you gather as much information as you can.

❑ ***Is genomic testing available for my type of cancer?***

❑ ***What risks and benefits should I be aware of?***

❑ ***Does insurance cover genomic testing?***

❑ ***When would this testing occur? Have I already had it as part of my blood work or biopsy? If so, did I have a single test or a comprehensive test?***

❑ ***Will you use a blood or tissue biopsy to do the testing?***

❑ ***How long will it take to get the results?***

❑ ***How will those results affect my treatment options?***

❑ ***Is it safe to wait to begin treatment until I get the results?***

❑ ***Who will help me understand the results?***

❑ ***Will I need to be re-tested again at some point?***

***NOTES:***

*(cut along dotted line)*

# Learn how cells mutate and cause cancer

***Doctors now recognize that*** cancer arises from changes that occur in a person's genes. These changes are known as mutations, and they can cause cells to grow out of control and become cancer cells. The foundation of genomic testing is built on finding these mutations within a cell's DNA. Knowing the mutations involved can help your doctor diagnose your type or subtype of cancer, choose a treatment option designed for a specific mutation and monitor your condition for a possible recurrence.

### CELL BIOLOGY 101

Understanding genomic testing begins with learning about cells, their components and how the genes within the cells mutate and become cancer cells.

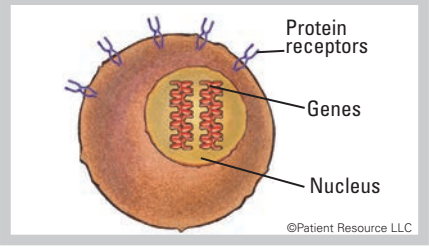
A cell is the smallest structure of the body capable of performing all of the processes that define life (see Figure 1). Almost every cell in the human body contains a complete copy of the genome (genes), which is a complete set of chromosomes containing the DNA code. These are the biological instructions for the various cells in your body that make each person unique. DNA is passed from adults to their children.

A cell has three main parts:

- 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 most of the cell's DNA.
- The cytoplasm is the fluid inside the cell.

FIGURE 1

## NORMAL HEALTHY CELL




A cell's nucleus contains 46 chromosomes — 23 from your mother and 23 from your father. Each chromosome is made up of DNA, which consists of two twisting, paired strands (base pairs) that create a double helix. Base pairs are bonded to one another forming a "rung of the DNA ladder."

Genes are sections of DNA on a chromosome that contain the instructions for making a specific protein that the body needs to function properly. Proteins are the basis of body structures, such as skin and hair, and of other substances such as enzymes, cytokines and antibodies. Each gene must have the correct instructions to make its protein.

### DEFINING MUTATIONS

Cancers are driven by a mixture of specific mutations. Mutations can either be acquired during a person's lifetime from environmental factors, or they are hereditary (inherited from a parent). A mutation is sometimes called a gene or genomic variant.

Testing for acquired and inherited mutations through genomic and genetic testing helps your doctor find the mutations in your genes that are causing your specific cancer.

### HOW MUTATIONS CAUSE CANCER

It is common for a cell to have mutations, but it requires multiple mutations before a tumor is formed. A single mutation likely will not cause cancer.

Mutations or genomic variants that may lead to cancer can occur in DNA, genes or chromosomes. Some common gene mutations include the following (see Figure 2):

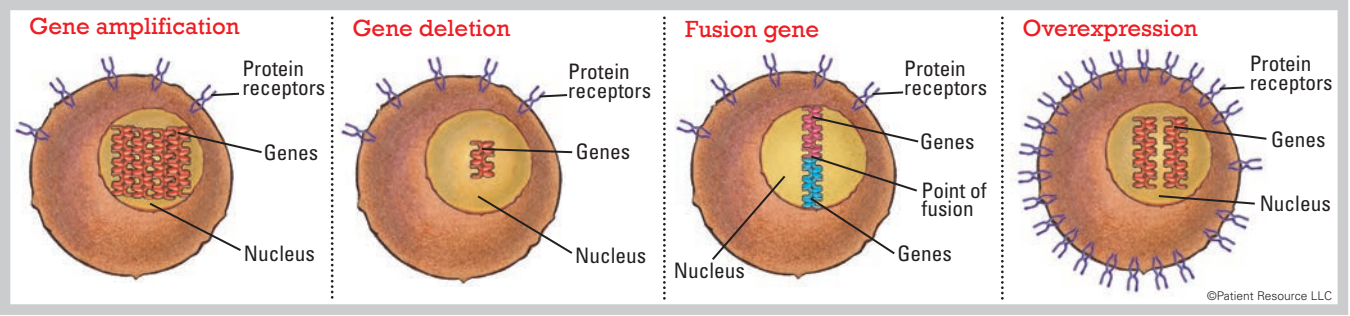
- Gene amplification — An increase in the number of copies of a gene, which is common in cancer cells. Some amplified genes may cause cancer cells to grow or become resistant to anti-cancer drugs.
- Gene deletion — The loss of all or part of a gene.
- Fusion gene — A gene made by joining parts of two different genes. Fusion genes, and the fusion proteins that come from them, may be made when part of the DNA from one chromosome moves to another chromosome. Fusion proteins produced by this change may lead to the development of some types of cancer.
- Overexpression — Too many copies of a protein or other substance.
- Rearrangement — Portions of the chromosome are not in order, which creates a new gene (not shown).

Chromosome mutations or variations that can lead to cancer include the following:

- Deletion — Part of a chromosome is missing or deleted.
- Duplication — Part of the chromosome is duplicated, resulting in extra genetic material.
- Inversion — Part of the chromosome has broken off, turned upside down and reattached.
- Rearrangement — A portion of the chromosome has broken off and reattached, creating a different order of its genes, which may create a new gene.
- Rings — Part of a chromosome has broken off and formed a circle or ring.
- Translocation — Part of a chromosome is transferred to another chromosome. ■

FIGURE 2

## GENE MUTATIONS



# Keep a positive mindset to beat cancer

***Comprehensive biomarker testing guided Michael Stern's doctor in choosing the best treatment for his Stage IV colon cancer. Next-generation sequencing of multiple genes showed he had a mutation in the KRAS gene. Michael recommends other patients have biomarker testing, too, and he shares his optimism and support with other survivors as an ambassador for Fight Colorectal Cancer.***

Symptoms began about a year before I had a colonoscopy. I thought they were due to my diet so I put off having a colonoscopy. Truthfully, I was also afraid of the procedure. Looking back, I wish I had not waited. Originally determined to be Stage II colon cancer, my diagnosis was changed to Stage IV after the test results were re-examined.

I felt like the world suddenly stopped. I thought about what I would do to prepare to leave my family. I wondered what I would say to my kids and whether I'd ever see them grow up and have families of their own. It was one of the darkest times in my life. But a few weeks later, I came to grips with the diagnosis and chose to fight.

After the diagnosis, I asked my good friends to recommend the top colorectal surgeons and oncologists they knew. I wanted the best. The oncologist I chose from their recommendations was amazing. He had excellent reviews from other patients, and I appreciated his bedside manner and overall knowledge of colon cancer. I trust him 100 percent.

I also relied on the support of my wife. She is my rock. I wouldn't have made it through without her. She helped pull me out of that dark hole and gave me the will to fight. She went to all of the appointments with me and helped make sense of what the doctor was saying. So much of it sounded like a foreign language to me.

The first step was surgery. I hoped for the best, which was for the surgeon to simply remove all of the cancer. However, I woke up with a temporary ileostomy bag. I was devastated. The surgeon had to take out more of my colon than he initially thought because the cancer was more aggressive than expected. He recommended the tumor be tested for mutations with comprehensive biomarker testing. I didn't know what that was, but I didn't question him. We waited two to three weeks for the results before starting any further treatment in case the information changed the treatment strategy.

In the meantime, it was a struggle to get the insurance to pay for the biomarker testing. At one point, my doctor had a peer-to-peer conversation with them to explain why this testing was necessary and that it was not an "elective" procedure. It also made an already stressful time more stressful. Luckily, my doctor fought for me to get the testing covered, and he succeeded.

The testing included next-generation sequencing of the tumor, which looked at multiple genes. Results showed I had a *KRAS* mutation. My oncologist explained that meant certain chemotherapies would be better at treating my colorectal cancer than others. I'm so grateful that I had the testing. He started me on a specific chemotherapy regimen with multiple drugs.

About eight months after the surgery, I was able to have my ileostomy reversed, which was a relief. I finished chemotherapy and was declared no evidence of disease (NED).

Unfortunately, about a year and half later, the cancer returned. The relapse meant I needed surgery to remove my colon and rectum, have a permanent ileostomy and start another chemotherapy regimen.

It was a lot, but I chose to keep a positive attitude because that was the one thing I could control. This whole experience was a wake-up call. Ironically, cancer was one of the worst things that ever happened to me but also was one of the best.

The surgery was successful. I'm again considered NED, and I'm on another chemotherapy regimen to "clean up" any remaining cancer cells. I have regular scans to monitor for a recurrence. Blood tests are performed in between the scans to detect any microscopic circulating tumor cells in my blood. If any are found, my doctor orders a new scan instead of waiting until the scheduled one in case we need to change the treatment strategy. I love his proactive approach.

Having the support of my doctor, wife and family was invaluable, so much so that I created a local support group for other colorectal cancer survivors. A good friend of mine also invited me to a Fight Colorectal Cancer retreat. After that, they asked me to be an ambassador for them. Now I advocate for screening and the importance of it, along with increased funding for more colorectal cancer research. ■

# The role of genomic testing during diagnosis and treatment

***Along with the many blood tests,*** imaging scans, surgical removal of tumors, and/or tumor biopsies that will be performed to diagnose your cancer, stage it and follow its response to treatment, genomic tests may be ordered to identify any biomarkers or mutations that are present in your cancer. Your doctor will review the test results after a pathologist (a doctor specially trained to diagnose disease by looking at cells under a microscope) and/or a molecular pathologist have examined a sample. The results will help your medical team determine whether therapies that are approved for any found mutations should be included in your treatment plan.

During the diagnostic process, your doctor will discuss the possibility of genomic testing with you. It may not be necessary or beneficial for all patients to have genomic testing, but it should be routine in all younger patients, especially if they have a no-smoking or light-smoking history. It is also recommended for patients with advanced or metastatic cancer. If your doctor has not talked with you about the testing, ask whether it is appropriate for you.

The type of test and the sample used for testing will vary, depending on the cancer involved and the information your doctor is seeking.

Results from diagnostic testing may not detect a biomarker or mutation or may discover one that does not yet have an approved treatment. If you are in either of those situations, do not be alarmed. You still have options, such as the current standard of care treatment for your specific diagnosis or a clinical trial. Your doctor will talk with you about all potential therapies as you discuss your treatment plan.

You may have genomic testing at other times during your care. Your doctor may use it if cancer returns or progresses, to determine whether the cancer is responding or to monitor for a recurrence.

### ABOUT THE TESTING PROCESS

In many cases, using a biopsy sample is crucial to diagnosing the type of cancer you have because it will help your doctor determine the most effective type of treatment. In general, your doctor will follow these steps.

**1** **A biopsy of tumor tissue is taken.** It can be done by several methods, and different tests require different amounts of tissue. Ask your doctor how your testing will be done before the biopsy to make sure enough tissue samples will be taken to meet the requirements of all the necessary tests.

**2** **The sample is sent to a laboratory** where a pathologist will look for the presence of cancer cells and document certain characteristics of the tumor cells in the sample.

**3** **If cancer cells are found,** they will be extracted from the sample so the pathologist can determine the histologic type of the cancer. The six major histologic types are carcinoma, sarcoma, myeloma, leukemia, lymphoma and mixed types. In some instances, the pathologist may not be able to identify the histologic type because the tissue sample is too small. When this happens, another biopsy may be necessary.

**4** **Specialized equipment will be used** to sequence the tumor's DNA and find any abnormalities. DNA sequencing determines the order of the four building blocks – referred to as "bases" – that make up the DNA molecule.

**5** **If abnormalities are found, they will** be compared to known mutations of the type or subtype of your particular cancer.

**6** **Results are returned to your doctor** in a pathology report (see *Your Pathology Report,* page 12).

**7** **If a known abnormality is found,** your doctor may suggest treatment options that are approved to target the same mutations.

**8** **If a mutation is found that does not** have a specialized treatment, your doctor may recommend standard of care treatment. It is also possible that a clinical trial that is testing the mutation identified in your tissue sample is underway. Ask your doctor whether that may be an option to consider (see *Clinical Trials*, page 13).

**9** **Genomic testing may be repeated** during follow-up appointments to monitor the effectiveness of your current treatment, or if your doctor suspects a recurrence or resistance because sometimes new mutations can develop. ■

***"Genomic testing saved my life. I truly believe that if my doctor hadn't ordered it, I wouldn't be here today. I recommend everyone get genomic testing even if your doctor doesn't think your cancer has biomarkers."***

*~ **Amy G.,** non-small cell lung cancer survivor*

# When to consider genetic testing

***Genetic testing,*** unlike genomic testing, is used to determine whether a person has inherited a gene that increases their risk for developing certain types of cancer. It may be performed before or after receiving a cancer diagnosis. If your family history involves a particular type of cancer, you may consider genetic testing to find out whether you carry the corresponding risk gene.

Certain risk factors may indicate that you have inherited an abnormal gene, but having one or more of them does not necessarily mean you will develop cancer. It does, however, offer valuable information that you can discuss with your doctor. Together, you can explore ways to lower your risk through lifestyle changes, frequent screenings, medication, and, in some cases, preventive surgery. Preventing or detecting a cancer early offers the best chance of a successful treatment outcome.

Some risk factors include the following:

- Family history of cancer, cancer at an early age, rare or multiple cancers in one relative
- Cancers in your family that are linked to a single gene mutation
- A family member who has had genetic testing revealing a mutation that can be passed to children
- A particular race or ancestry, such as Ashkenazi Jewish heritage, linked to a higher risk of gene mutations

### THE GUIDANCE OF A GENETIC COUNSELOR

If you choose to have genetic testing, ask for a referral to a genetic counselor, either on staff or elsewhere. The genetic counselor will discuss your medical history and cancer screening history, your family's cancer history, the possibility of an inherited cancer risk, the benefits and limitations of genetic testing, and current laws regarding the privacy of genetic information. The counselor can also help find out whether your health insurance will pay for the cost of the test.

Your counselor can help you understand the often-complicated results and what they mean for you, and for your family members and their future health. Family members may also be offered genetic testing if a mutation is found. ■

## Avoid home-based kits for cancer answers

**Although you may feel a sense of urgency and want to know "right away" if you may have cancer, using this type of genetic test without your doctor's involvement is not recommended for many reasons:**

- **The sensitivity of these tests is unknown compared to those used by doctors.**
- **The tests may not screen for all the possible genes and mutations for a particular cancer.**
- **The tests do not offer information on your overall risk for developing cancer.**
- **You would not have the benefit of using a special laboratory used by doctors, which is regulated to meet standards for accuracy and reliability.**

## GLOSSARY ➥ *Terms to know*

**Adjuvant therapy:** Additional cancer treatment given after primary treatment to lower the risk the cancer will come back.

**Cytogenetics:** The study of chromosomes to look for changes, including broken, missing, rearranged or extra chromosomes.

**DNA:** Deoxyribonucleic acid. The molecules inside cells that carry genetic information that is passed from one generation to the next.

**DNA sequencing:** A laboratory process used to find DNA mutations (changes) that may cause diseases, such as cancer.

**First-line therapy:** The first treatment used.

**Fluorescence in situ hybridization (FISH):** FISH can be used to identify where a specific gene is located on a chromosome, how many copies of the gene are present and any chromosome abnormalities.

**Genome:** The complete set of DNA (genetic information) in an organism.

**Genomic sequencing:** A procedure that determines the entire genetic makeup of an organism or cell type to diagnose and treat cancer.

**Histologic grade:** Description of a tumor based on how abnormal the cancer cells and tissue look under a microscope. It also helps determine how quickly the cancer cells are likely to grow and spread.

**Immunotherapy:** Also referred to as immune-oncology, treatment designed to enhance the patient's own immune system to fight the cancer.

**Liquid biopsy:** A test done on a sample of blood to look for cancer cells or pieces of DNA from a tumor that are circulating in the blood. May be used to help plan treatment, determine treatment effectiveness and identify cancer that has returned.

**Local treatment:** Directed to a specific organ or limited area of the body; includes surgery, radiation therapy and topical therapy (a lotion or cream that is applied to the skin).

**Molecular testing:** Uses a sample of tissue, blood or other body fluid to check for certain genes, proteins or other molecules; also looks for gene or chromosome changes that may affect the chance of developing cancer. Helps diagnose some types of cancer, plan treatment, monitor treatment effectiveness or predict outcome.

**Mutations:** Changes from an individual's genetic code when compared to the human reference sequence.

**Neoadjuvant therapy:** Treatment given to shrink a tumor before the main treatment (usually surgery) is given.

**Next-generation sequencing (NGS):** Tests that detect sections of DNA that represent changes, including insertions or deletions, in a specific DNA sequence.

**Pathologic stage:** The stage of cancer based on histologic grade.

**Second-line therapy:** Given when the first-line therapy does not work or is no longer effective.

**Standard of care:** The most widely accepted treatment known for the type and stage of a particular cancer.

**Systemic therapy:** Drug therapy that travels throughout the body.

**Tumor microenvironment:** The cells, molecules and structures that surround and support a tumor.

# Multiple strategies available for treating mutation-driven cancer

***Advances by cancer researchers*** who are focused on finding mutations that create and drive cancer are resulting in new types of drugs, innovative combination therapies and additional clinical trials. This personalized treatment strategy is offering people facing cancer more options and, ultimately, more hope for a prolonged life or even cure.

Your genomic testing results will indicate whether you have a specific mutation for which a treatment is available. Keep in mind that it is possible a mutation will not be detected, or that a mutation will be identified that does not have an approved treatment. In either of those cases, your doctor will discuss the other treatment options that are available. Those may include a clinical trial, as many are underway to continue finding effective treatments for additional mutations.

Should a mutation or abnormality be detected, your doctor will consider many factors before recommending a treatment plan tailored just for you. Those factors will include the tumor's stage, grade and biomarker status; your general health; and your preferences concerning quality of life in regard to potential treatment side effects.

Take this opportunity to ask questions about the proposed plan. Before beginning any therapy, discuss the following:

1. The side effects that may accompany each treatment option. Some may be mild while others may be severe. Ask your medical team what to watch for and what you should do if side effects occur. Some may prompt treatment to prevent more serious complications.
2. The importance of medication adherence. Most cancer therapies are designed to maintain a specific level of drugs in your system for a certain time. To be fully effective, every dose must be taken exactly as prescribed, whether you receive it via IV, injection or pill form. Non-adherence can be serious, even life-threatening. Make sure you are capable of sticking to your medication and appointment schedules.
3. How treatment effectiveness will be monitored. Your doctor will continually monitor your condition and make adjustments. Sometimes a therapy becomes less effective over time; other times, a new mutation may be discovered and a different therapy may offer more promise; or you may reach remission, among other things. When cancer cells stop responding to a drug, it is known as drug resistance, which is known to happen with some targeted therapies. In some cases, patients will have access to other targeted therapies that are designed for other substances within the cancer.

## TYPES OF TREATMENT

Following are descriptions of therapies that are available to treat some mutations. These drugs can be given orally, intravenously or subcutaneously (see Figures 1 and 2).

FIGURE 1

### SYSTEMIC THERAPY

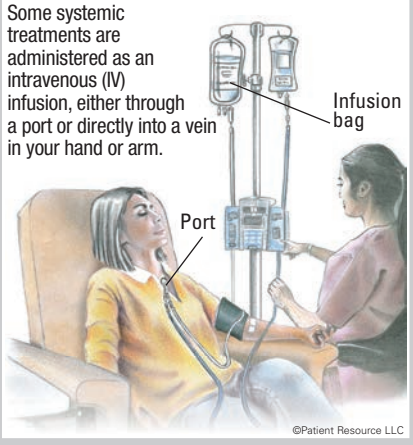
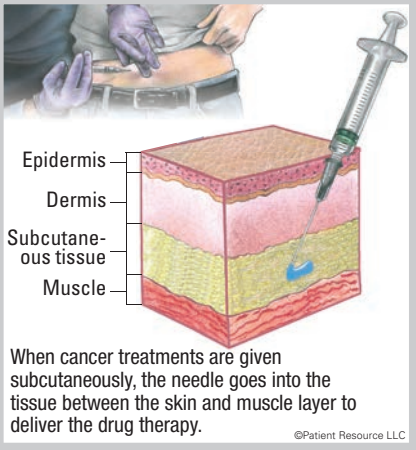



FIGURE 2

### SUBCUTANEOUS INJECTION




## TARGETED THERAPY

This strategy uses the results from genomic testing to target specific genes, receptors, proteins, mutations, abnormalities or other factors involved in the development and support of the tumor. Because this therapy focuses on its target only, it typically does not damage nearby healthy cells, generally resulting in fewer side effects than traditional chemotherapy. They can attack cancer in the following ways:

- Preventing cancer cells from growing and from living longer than normal
- Blocking or stopping signals that help form blood vessels to the tumor
- Delivering cell-killing substances to cancer cells
- Causing cancer cell death
- Starving cancer of the hormones it needs to grow

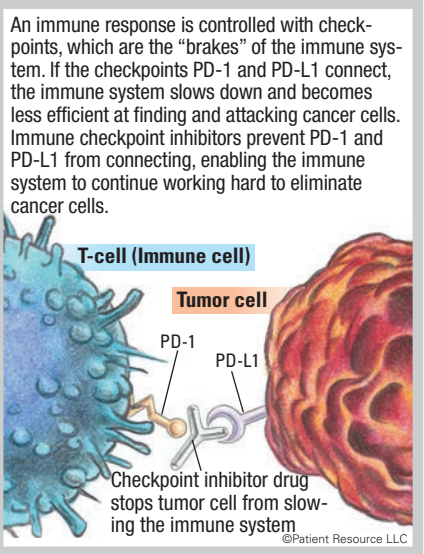
Targeted therapies work in different ways and can be classified as small molecule drugs, angiogenesis inhibitors and monoclonal antibodies (mAbs). Some mAbs are also considered immunotherapy (see page 11).

**Small molecule drugs** are able to get inside a cell and target its internal components. They can target the cancer's gene expression, enzymes that affect the tumor or certain proteins.

- Apoptosis inducers cause cancer cells to undergo a process of controlled cell death called apoptosis.

FIGURE 3

### IMMUNE CHECKPOINT INHIBITORS



- Gene expression modulators modify the function of proteins that play a role in controlling gene expression.
- Histone deacetylase (HDAC) inhibitors affect gene expression inside tumor cells.
- Kinase inhibitors block a type of enzyme known as a kinase. Certain kinases are more active in some types of cancer cell.
- Proteasome inhibitors target proteins to kill cancer cells.
- Selective inhibitors of nuclear export (SINE) enhance the anti-cancer activity of certain proteins in a cell.
- Signal transduction inhibitors block signals passed from one molecule to another inside a cell. Blocking these signals can affect many functions of the cell and may kill cancer cells.

**Angiogenesis inhibitors** block new blood vessel growth that feeds tumor cells. Tumors need a blood supply to survive and grow. Without it, the tumor cells cannot survive.

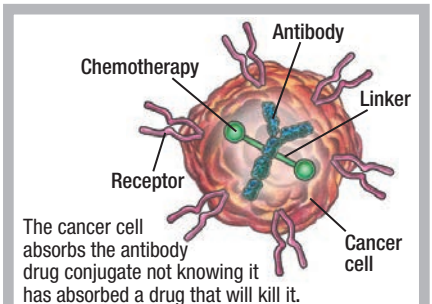
**Monoclonal antibodies (mAbs)** are proteins produced in a laboratory that are designed to attach to specific targets found on cancer cells. They can directly stop cancer cells from growing, cause them to self-destruct or deliver therapeutic agents directly to targeted cancer cells.

Many mAbs work by themselves. Others have a chemotherapy drug or a radioactive particle attached to them. Known as conjugated mAbs, they deliver treatment to the cancer cells. Types include radiolabeled antibodies, which deliver radioactive particles, and antibody drug conjugates, which deliver a chemotherapy drug (see Figure 4).

Another type, bispecific mAbs, are made up of two different mAbs that can attach to two different antigens at the same time.

FIGURE 4

## ANTIBODY DRUG CONJUGATE

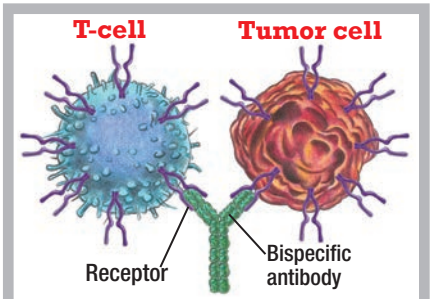



The cancer cell absorbs the antibody drug conjugate not knowing it has absorbed a drug that will kill it.



FIGURE 5

## BISPECIFIC ANTIBODY




A bispecific antibody can bind to two different antigens at the same time, connecting a T-cell with a tumor cell. A T-cell is a type of white blood cell, which is part of the immune system. Normally, a T-cell can only interact with a tumor cell if it finds an antigen on a tumor cell and connects to it. A bispecific antibody skips this step and brings the T-cell directly to the tumor cell to release chemicals or other therapeutics to attack the tumor cell.



### IMMUNOTHERAPY

A rapidly advancing and promising field in cancer treatment, immunotherapy recognizes and destroys cancer cells by harnessing the potential of the body's own immune system. You may be a candidate for immunotherapy if your genomic testing results identify specific biomarkers such as PD-L1 expression, tumor mutational burden (TMB) and microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR).

Clinical trials are actively exploring the use of tumor-infiltrating lymphocytes (TILs) and chimeric antigen receptor T-cell (CAR-T) adoptive cell therapies. You may hear these cell-based therapy terms discussed and be a candidate for such immune system based treatments. The types of immunotherapy include immune checkpoint inhibitors and monoclonal antibodies.

**Immune checkpoint inhibitors** prevent the immune response from slowing down, which allows the immune cells to continue fighting cancer. They also help the immune system to recognize cancer cells as foreign cells. Normally, the immune system is kept in check through biological checks and balances called checkpoints. Checkpoint-inhibiting drugs prevent connections between checkpoints so that the immune system does not slow down and can keep up its fight against cancer (see Figure 3).

Some immune checkpoint inhibitors are also approved as tumor-agnostic treatment, which means they are approved to treat any cancer that has the molecular alterations known as microsatellite instability-high (MSI-H), deficient mismatch repair (dMMR) or tumor mutational burden-high (TMB-H).

MSI-H describes cancer cells that have a greater-than-normal number of genetic markers called microsatellites, which are short, repeated sequences of DNA. Every time a cell reproduces itself, it makes a copy of its genes and DNA. During the process, errors in duplication can be made, much like a misspelled word. The body normally corrects the error, but sometimes it is not caught and fixed (dMMR). It then becomes a mutation that is reproduced in later versions of the cell.

Cancer cells that have large numbers of microsatellites may have defects in the ability to correct mistakes that occur when DNA is copied. When cancer cells have this feature, they are more sensitive to destruction by immune checkpoint inhibitors. MSI is also tested to determine which tumors may have developed because of a deficiency in correcting cell division errors.

TMB measures the number of mutations within a tumor to predict a patient's response to immune checkpoint inhibitor treatment. TMB-H describes cancer cells that have a high number of gene mutations.

**Monoclonal antibodies (mAbs)** are antibodies made in a laboratory that target specific tumor antigens. Some mAbs mark cancer cells so that the immune system will better recognize and destroy them. Other mAbs bring T-cells, a type of white blood cell, close to cancer cells, helping the immune cells kill the cancer cells. They can also carry cancer drugs, radiation particles or laboratory-made cytokines (proteins that enable cells to send messages to each other) directly to cancer cells.

When used as an immunotherapy, a bispecific mAb engages and activates immune cells, such as T-cells, to attack a tumor, block dual signaling pathways, block immune checkpoints, or form a way to replace a missing functional protein (see Figure 5). These should not be confused with mAbs used as targeted therapy, which directly attack certain components in or on cancer cells.

### HORMONE THERAPY

This treatment targets specific hormones and can be used to block the body's ability to produce them and interfere with how they behave in the body.

### CHEMOTHERAPY

Your doctor may use your genomic test results to see whether chemotherapy may be an effective treatment option for you. ■

# The comprehensive results that guide your treatment

***The pathology report is developed by*** a surgical pathologist who is specially trained and a critical member of the cancer management team. The surgical pathologist and members of the pathology team assist in defining the extent of the cancer, the tumor grade (low vs. high) and the potential for surgical removal of the tumor, as well as other histologic features of the tumor.

Although it is common for people diagnosed with cancer to have a pathology report, it is not typically shared with them. It is not a secret, and you can request a copy at any time. It is a behind-the-scenes document that helps guide your medical team as they diagnose and plan the treatment, which may include clinical trials, most likely to be effective for you.

Surgical biopsies obtain tissue or lymph nodes, and liquid biopsies use a sample of blood or other body fluid to characterize cancer cells contained in the blood or fluid and test for pieces of DNA that are released from tumor cells. Once a biopsy of a tumor is taken, the specimen is sent to be examined by a specially trained doctor called a surgical pathologist, or by a molecular or genomic pathologist.

The pathologist studies the specimen with and without a microscope, documents its size, describes its location and appearance, and performs special testing, such as molecular testing. Those tests may include cytogenetics studies, flow cytometry and immunohistochemistry. Testing for microsatellite instability (MSI) and tumor mutational burden (TMB) may be included. These tests assess the number of genetic mutations in a tumor. Specific molecular tests are used for certain biomarkers.

Your pathologist may review tests on cells that are present in bodily fluids, such as urine, cerebrospinal fluid (the fluid around the brain and spinal cord), sputum (mucus from the lungs), peritoneal (abdominal cavity) fluid, pleural (chest cavity) fluid, cervical/vaginal smears, and bone marrow.

The pathologist prepares the pathology report containing the primary results, which is a final diagnosis of your cancer. Secondary (or incidental) findings are medically meaningful but unrelated to the reason for testing, and may also be included in the report. Secondary findings may include genetic risks for future disease, carrier status (carrying a gene for, but not exhibiting, a condition) and findings related to differences in how you may process medications.

The format of a pathology report may be different for each facility but generally includes the following categories.

**Clinical history:** Contains a brief summary of essential clinical information provided to the surgical pathologist by the oncology team when submitting a specimen for analysis.

**Gross description:** Includes the color, weight and size of a tissue sample as seen by the naked eye. It may also include the shape of the tissue sample and any visible abnormalities. Also documented are the site(s) from where the tissue was taken, the number of samples taken and whether any lymph nodes were removed.

**Microscopic description:** Includes information about the appearance of the cells after they have been stained and viewed under the microscope. Staining helps identify different cells and tissues and provides important information about the pattern and shape of cells, the structure of the tissue, the type and number of cells seen in the tissue sample, how abnormal the cells look (also called the tumor grade), and whether there are notable cell features (such as their arrangement and behavior).

**Histologic grade:** Based on how closely the tumor cells resemble normal cells.

**Surgical margins:** Indicate whether cancer cells are found in the normal tissue around the edges of the tumor. If they are, additional treatment (surgery or radiation therapy, for example) may be needed.

**Extent of invasion:** Shows the other nearby structures affected by the tumor. This is a factor in staging and determining treatment.

**Lymph node status:** Indicates whether the cancer has spread and helps determine how extensive the cancer is. ■

## MULTIDISCIPLINARY TEAM — Meet your team members

***Highly skilled health care professionals will examine, treat, educate, guide and comfort you. Your team may include the following.***

- **Case managers** and **social workers** act on your behalf by collaborating with health care professionals and non-medical personnel to help you overcome various barriers to care.
- **Financial counselors** address cancer-related financial concerns, such as insurance coverage and out-of-pocket expenses.
- **Genetic counselors** explain what your test results may mean to you or your family.
- **Medical oncologists** treat cancer patients using drug therapies and manage your course of treatment.
- **Molecular pathologists,** also called genomic pathologists, study tissue and blood samples on a molecular level to provide information about your diagnosis, treatment and prognosis.
- **Nurse navigators** collaborate with your health care team from diagnosis through survivorship and will know you the best.
- **Oncology nurses** may be registered nurses, clinical nurse specialists, advanced practice nurses, radiation therapists, chemotherapy nurses, oncology social workers, case managers, educators or consultants.
- **Pathologists** identify diseases by studying cells and tissues under a microscope.
- **Pharmacists** prepare and dispense prescriptions, ensure medicines and doses are correct, and prevent harmful drug interactions.
- **Radiation oncologists** use radiation therapy to treat and reduce the symptoms of cancer.
- **Radiologists** create and interpret pictures of areas inside the body that are made with X-rays, sound waves or other types of energy.
- **Rehabilitation specialists** include physical, occupational and speech therapists.
- **Surgical oncologists** use surgery to remove tumors or repair a part of the body affected by cancer.

# Doing the work to find new and additional biomarkers

***Research studies known as clinical trials*** identify new and better ways to treat cancer and its symptoms and side effects. They have traditionally tested medical approaches and researched new drugs, drug combinations, medical procedures or devices. In the past few years, to support the emphasis on patient-centered cancer care, significantly more clinical trials have focused on biomarkers, giving some patients the opportunity to access the latest developments in targeted treatments.

These types of clinical trials are designed to help researchers learn more about the way biomarkers influence how cancer begins, grows and reacts to treatment. As a result, more prevention, diagnosis and treatment options are becoming available for people with cancer.

For some people, the results of biomarker testing may indicate they are eligible for a treatment used in a clinical trial that is based on the biomarkers in their cancer instead of where in the body the cancer began. These are called "basket trials." Other people may be eligible for "umbrella trials," which test how well new drugs or other substances work in people who have the same type of cancer but different mutations or biomarkers.

Talk with your doctor before treatment begins, if possible, about whether you should consider a clinical trial. There is evidence that patients who are able to participate in clinical trials as part of their treatment may do better and live longer.

### SEARCHING FOR A CLINICAL TRIAL

You can be proactive and help your medical team look for clinical trials. Not only will you become more informed about available research studies, you may find the next step in your treatment plan.

To get started:

**Step 1:** Have available your exact diagnosis, biomarker test results, pathology report and details of previous treatments (if applicable). These will help you narrow the list of trials that may be a good fit for you.

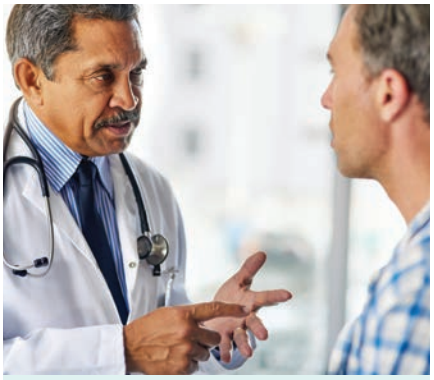
**Step 2:** Decide whether to search online or by phone. Some clinical trial search websites are customized to a certain cancer type; others are much broader. No single list contains every open clinical trial, and new trials are continually being added, so check back often. See *Assistance*, page 17, for websites and telephone numbers.

**Step 3:** Depending on your diagnosis, there could be many trials to explore. That can be time-consuming. Consider asking friends and family members to help.

**Step 4:** As you search, keep in mind that every trial has eligibility criteria, such as cancer type, subtype, stage, biomarker status and treatment history, to ensure the data gathered during the trial are valid. You may not qualify for every trial that appeals to you. Some may be closed, or you may not meet the eligibility criteria. Under certain extreme conditions, you and your doctor may apply to the U.S. Food and Drug Administration (FDA) to join a clinical trial that is closed or otherwise inaccessible. This is known as Expanded Access, also called Compassionate Use.

**Step 5:** Once you find a trial that you think may be a good addition to your treatment plan, discuss it with your doctor or contact the clinical trial investigators, staff or sponsors listed. They are experts who may be able to provide more details and answer questions about the study.

**Step 6:** If it is determined that you meet the criteria to join the trial, you will be given the Informed Consent document. This contains detailed information, including the goal of the study, the required schedule, associated costs and more. Review this document closely with your loved ones, and ask the clinical trial team any questions. Once you sign the form, you will become part of the trial. ■



## Multiple reasons to get a second opinion

***When it comes to cancer,*** information is power. The more you know, the better prepared you will be to make the important decisions ahead. One way to do that is to seek a second opinion from another doctor (often a specialist in your type of cancer) who reviews your medical records and gives an opinion about your health problem and how it should be treated. You can get a second opinion either before or after diagnosis, and even after you begin treatment.

Realistically, you may feel overwhelmed and wonder whether getting a second opinion is even worth it. It most definitely is. Here are several reasons why:

- To verify the pathology report and diagnosis. This is especially important if there was any difficulty or controversy in interpreting the findings, and if the cancer has metastasized (spread).
- To confirm the treatment plan or learn about alternatives, including clinical trials that the first doctor may not be aware of.
- You may live in a small town or rural area where there may not be many oncology specialists. Because the goal is for you to get the best care possible, your doctor should be pleased to help you locate a specialist. Second opinions allow you to benefit from the collective wisdom of experts.
- You may need highly specialized or complicated care. If so, reach out to a larger medical center or comprehensive cancer center with expertise in treating your type of cancer.
- It offers the opportunity to decide whether a different doctor, health care team or treatment center is a better fit for you.

FICTIONAL CASE STUDY / LUNG CANCER

*Carlos is not a real patient.

**Name:** Carlos*
**Age:** 66
**Diagnosis:** Stage IV Non-Small Cell Lung Cancer
**Mutation:** *NTRK* fusion
**Family history of cancer:** No
**Treatment:** Targeted therapy

***In this fictional scenario, Carlos is a patient initially diagnosed with Stage IV non-small cell lung cancer. Results of his genomic testing show he has a rare NTRK mutation.***

### What are Carlos' initial symptoms?

When Carlos experiences shortness of breath and begins coughing, he makes an appointment at an urgent care clinic. He shares his symptoms with the doctor, who performs a physical examination. He listens to his lungs and then orders an X-ray. Results show a mass in the upper right lobe of his lung. The doctor refers him to a local oncologist for further testing.

### How is his cancer diagnosed?

The oncologist orders a CT, which shows a right upper lung mass and enlarged hilar and mediastinal lymph nodes, so the oncologist orders a CT-guided biopsy. The tissue specimen is examined by a pathologist, who confirms that the mass is an adenocarcinoma of the lung, which is the most common form of non-small cell lung cancer.

His oncologist also orders a contrast-enhanced MRI of his brain to check for any metastases (spread) of the cancer. The MRI shows one small metastatic lesion of less than 1 centimeter in his brain. Carlos is diagnosed with Stage IV adenocarcinoma of the lung (non-small cell lung cancer).

### What additional testing is needed?

The oncologist explains that although initial testing indicates lung cancer, she will request genomic profiling on both a blood sample and on the tissue biopsy to find out whether his cancer has any mutations. She explains that the blood testing will provide results several weeks before the tissue testing. She also explains that a positive result will lead to a specific therapy in the shortest time frame. However, the tissue testing is more sensitive as there is more DNA. Thus, if the blood test is negative, they will await the tissue test results before selecting therapy.

She tells Carlos she's ordering next-generation sequencing of his samples because many different mutations have been discovered in lung cancer, and this type of test looks for more than one mutation. The testing looks for mutations in the following genes: *ALK, BRAF, EGFR, HER2, KRAS, MET, NTRK, RET, ROS1* and *STK11*. She also includes testing for levels of PD-L1, PD1 and tumor mutational burden (TMB).

If he has a mutation that has approved treatments available, Carlos may have more treatment options, such as an oral targeted therapy pill or an immunotherapy, which may have fewer side effects than traditional chemotherapy. Carlos likes this idea.

He is nervous about waiting, but she assures him that, in his case, delaying the start of treatment for two to three weeks is not likely to affect the outcome.

### What are the results of his genomic testing?

Results of the comprehensive biomarker testing show that Carlos has an *NTRK* fusion, which is fairly rare in non-small cell lung cancer. His oncologist explains that fewer than two percent of non-small cell lung cancers contain the *NTRK* fusion.

Carlos is concerned that this biomarker is too rare to have a targeted or molecular therapy available, but his doctor assures him that there are some molecular therapies that target the *NTRK* mutation.

### What are his treatment options?

His oncologist explains that she thinks the best course of treatment is to prescribe a molecular therapy known as a tropomyosin receptor kinase (TRK) inhibitor, which is an oral pill, even though he has one lesion in his brain.

She also believes the molecular therapy will help control the brain metastasis because he does not have severe symptoms, and the pill can cross the blood-brain barrier and treat the brain metastasis as well as the lung mass and lymph node metastases.

### How does Carlos do on treatment?

Carlos tolerates the drug well and has few side effects. He is grateful he did not have to have chemotherapy and that he is not losing his hair.

Follow-up testing shows the cancer responds well to the treatment. However, Carlos begins having trouble breathing again after nine months of treatment. His oncologist orders a repeat chest CT scan and discovers that the tumor in his lung is back. She suspects the cancer has developed resistance to the TRK inhibitor and appears to be no longer working to control the cancer.

### What treatment options are available now?

The oncologist explains that it is common for cancer to develop resistance to a TRK inhibitor, and she reassures him that other options are available. She explains that the first drug he took was considered a first-generation TRK inhibitor and they can try a newer second-generation TRK inhibitor. That is the therapy she prescribes.

### How does Carlos respond to the new inhibitor?

He tolerates the new drug well with very few side effects. Follow-up testing three months later shows the new drug is controlling his cancer, and he is feeling much better. The plan is to remain on this drug for as long as it is effective.

### What is next for Carlos?

His oncologist explains that it is possible he could develop resistance to the second drug, but not to worry. New next-generation TRK inhibitors are being researched in clinical trials and he may qualify for one in the future. In addition, his blood and tissue will be retested at that time because there may be new molecular changes for which a different type of treatment may work.

*Keiko is not a real patient.

**Name:** Keiko*
**Age:** 42
**Diagnosis:** Stage IV Medullary Thyroid Cancer
**Mutation:** *RET* gene
**Family history of cancer:** Yes
**Treatment:** Surgery, hormone therapy, bone radiotherapy and targeted therapy

***In this fictional scenario, Keiko is a patient initially diagnosed with Stage II medullary thyroid cancer. Comprehensive biomarker testing helps her doctor confirm the diagnosis and offers valuable information that may affect her treatment as well as the health of her family.***

### How is Keiko diagnosed?

For four months, Keiko has noticed a swelling on the right side of her neck that moves when she swallows. Over time, it gradually enlarges but does not cause her any discomfort or pain and does not interfere with her swallowing. Still, concerned that it is not going away, she makes an appointment with her primary care doctor.

Her doctor is able to feel the lump and orders blood tests that show she has elevated levels of calcitonin and carcinoembryonic antigen (CEA), which may indicate cancer. She is referred to a head and neck surgeon.

The surgeon orders an ultrasound and a fine-needle aspiration biopsy of the lump. The ultrasound reveals a 2.5 centimeter tumor. Pathologic testing of the biopsy sample combined with the ultrasound imaging conclude she has Stage II medullary thyroid cancer. The doctor then orders comprehensive biomarker testing.

### Keiko is unfamiliar with biomarker testing and asks her doctor to explain what it is and why he recommends it.

He explains that genomic testing is typically performed to identify mutations in blood or tissue samples. For thyroid cancer, it is used to determine whether she has medullary thyroid cancer, which can be inherited through a mutated *RET* gene.

### What do the results show?

Keiko has a mutation in the *RET* gene. Because some medullary thyroid cancers are known to be inherited, he asks whether she has a family history of thyroid cancers. Keiko's aunt had thyroid cancer, so genetic testing is ordered.

Results show she is also positive for the *V804M RET* germline (inherited) mutation, which can cause the growth of cancer cells. She also has multiple endocrine neoplasia type 2 (MEN2), a hereditary condition found in some medullary thyroid cancer patients who have a mutated *RET* gene.

This information allows him to counsel her about her family's risk of other tumors, such as pheochromocytoma, and the risks of her family members developing cancer.

### What is Keiko's treatment plan?

Her doctor explains that although a targeted therapy to treat the *RET* mutation exists, it is only available if a patient cannot have surgery, or the disease is worsening or has spread to other parts of the body. As a result, she does not qualify for the targeted therapy at this time. The standard of care at Stage II is surgery to remove her thyroid.

Her surgeon recommends a thyroidectomy (complete removal of her thyroid) with a neck dissection to determine whether any lymph nodes are involved. Immunohistochemical staining is performed on the tumor, and it is positive for calcitonin, which is consistent with medullary thyroid cancer. None of the removed lymph nodes contain cancer cells.

After surgery, Keiko is prescribed thyroid replacement medication. She has routine monitoring blood work and imaging scans every three months.

### Should her family members have genetic testing?

Yes. Because medullary thyroid cancer can be inherited, her doctor recommends that she encourage her family to get genetic testing. Her mother, father and sister are tested. Results show her sister also has the *V804M RET* mutation. She is referred to a thyroid oncologist for further evaluation and management.

### What happens next?

Keiko will need follow-up testing for the rest of her life to monitor for recurrence. Ongoing monitoring will include testing her blood for biomarkers and checking her levels of calcitonin and CEA. Imaging scans will also be used.

### What are the results of her follow-up testing?

Gradually, Keiko's calcitonin and CEA levels begin to increase, indicating her cancer may be returning. During a physical exam, her oncologist feels a swollen lymph node on the right side of her neck. He suspects her cancer has returned and metastasized to a lymph node. She returns to her head and neck surgeon for a lymph node dissection. Testing of the lymph node shows it is positive for medullary thyroid cancer. Her disease has progressed to Stage IVA medullary thyroid cancer.

Despite removal of the cancerous lymph node, four months later, her calcitonin and CEA levels remain steady but have not decreased. Her doctor continues to monitor these levels.

About a year later, follow-up testing shows her calcitonin and CEA levels are increasing. An MRI shows multiple metastases in the cervical lymph nodes and bone lesions in the thoracic region of the spine.

### How is her recurrence treated?

Keiko has external bone radiotherapy to reduce the bone lesions. Despite treatment, several months later, her calcitonin and CEA levels increase sharply. Her doctor reminds her of the targeted therapy for the *RET* mutation they discussed early on. He recommends treatment with a tyrosine kinase inhibitor.

She tolerates the targeted therapy well and continues having routine follow-up appointments to make sure her body is tolerating the drug. Her calcitonin and CEA levels decrease on this treatment, and her doctor is happy with the results.

FICTIONAL CASE STUDY / BREAST CANCER

*Monica is not a real patient.

**Name:** Monica*
**Age:** 59
**Diagnosis:** Stage IV Breast Cancer
**Mutation:** *PIK3CA* gene
**Family history of cancer:** Yes
**Treatment:** Surgery, radiation therapy, hormone therapy, targeted therapy and a clinical trial

***In this fictional scenario, Monica is a patient initially diagnosed with Stage II invasive ductal carcinoma breast cancer. After hormone therapy, her cancer becomes resistant, prompting the need for genomic testing. Testing reveals a PIK3CA gene mutation, which gives her access to a targeted therapy.***

### What are Monica's first symptoms?

One morning while showering, Monica feels an unusual lump in her right breast. She routinely does breast self-exams and has not felt this lump before. Her last mammogram did not detect any abnormalities. Concerned, she calls her doctor. He orders a new mammogram.

### What is Monica's diagnosis?

Results of the mammogram show a 22-millimeter lump. Her doctor also orders an ultrasound of the lump followed by a fine-needle aspiration biopsy. Biopsy results confirm it is breast cancer. Monica's doctor refers her to a local oncologist.

The oncologist reviews the findings and orders a core needle biopsy with enough tissue to do additional testing for three main biomarkers: hormone receptor status (*ER/PR*) and *HER2* status. The testing confirms that she has Stage II invasive ductal carcinoma breast cancer that is *HR* positive and *HER2* negative.

The doctor asks her whether she has any history of cancer in her family. She does. Her older sister died of ovarian cancer at the age of 43 and her father died of lung cancer at 51. Because of this, he also orders germline genetic testing to see whether she has inherited a mutation that may be causing the breast cancer. Results show she does not have a mutated form of the *BRCA1* or *BRCA2* gene.

### How will Monica's breast cancer be treated?

Her oncologist recommends a partial mastectomy (also known as breast-conserving surgery) and a sentinel lymph node biopsy followed by radiation therapy and hormone therapy (an aromatase inhibitor). Her sentinel lymph node biopsy shows no spread to nearby lymph nodes.

### What are the results of treatment?

Monica successfully completes treatment, continues on hormone therapy and is cancer-free for 2 years. At a follow-up appointment, she tells her oncologist she has had a persistent cough for several weeks. When her oncologist performs a physical exam, he notices a new lump under her right arm and asks her about it. She says it has felt a little tighter than usual but thought that was a long-term effect of radiation therapy. He orders new imaging tests, which show several lumps under her right arm and a spot on her right lung.

After performing biopsies of the lumps and the spot on her lung, he determines the cancer has returned. Her cancer is restaged to Stage IV.

### What happens now?

Monica is alarmed that her cancer has spread. Her oncologist assures her there are options. He suspects the hormone therapy has failed and he wants to try to find out why. He wants to test her recent biopsy tissue for genomic mutations to determine whether she is eligible for more personalized treatments.

She asks her doctor to explain what genomic testing is and how it is different than the genetic testing she previously had. He explains that the initial testing was performed to find whether she had inherited a gene from her family that increased her risk of breast cancer. This testing looks specifically at the tumor tissue to find the mutations driving the growth of the cancer. He also says her recurrence and progression are likely caused by acquired mutations, which are not passed down from parents.

### What are the results of her genomic testing?

Next-generation sequencing, which examines hundreds of genes, finds a mutation in Monica's *PIK3CA* gene. The oncologist tells Monica that some patients who develop resistance to hormone therapy have a mutation in this gene. He reassures her that this means she qualifies for a type of targeted therapy known as a *PIK3CA* inhibitor that can be taken with an estrogen receptor antagonist.

### How does she tolerate the new treatment?

Follow-up testing shows this treatment regimen is increasing her blood sugar levels. Her doctor explains this may indicate a need for more frequent blood tests. She also reports bouts of diarrhea that are difficult to control. He prescribes a medication to help. This intervention helps her tolerate the medication better, and her cancer stabilizes.

Sixteen months later, routine follow-up testing indicates her cancer returned. Her oncologist discovers her latest treatment is unable to control the cancer.

### What are her options now?

The oncologist tells her that she may qualify for a clinical trial because other *PIK3CA* inhibitors are currently being tested. These new treatments may be able to control her cancer. Monica is eager to hear more and asks her doctor to help her find a clinical trial she may qualify for. He refers her to the cancer center's clinical trials research coordinator, Janet.

Monica meets with Janet, who is able to find a clinical trial nearby that is testing another type of *PIK3CA* inhibitor. Monica is eligible for the trial, so after reading and agreeing to the Informed Consent form, she joins the trial.

She is responding well to treatment in the clinical trial. She is happy to be receiving the extra monitoring provided in the clinical trial and is excited that she is helping future metastatic breast cancer patients by participating in this study. ■

# Support and financial resources available for you

## CANCER EDUCATION

Alex's Lemonade Stand Foundation for Childhood Cancer.... www.alexslemonade.org, 866-333-1213
American Cancer Society.....www.cancer.org, 800-227-2345
American Society of Clinical Oncology.....www.cancer.net, 888-651-3038
CANCER101 ..... www.cancer101.org, 646-638-2202
Cancer*Care* ..... www.cancercare.org, 800-813-4673
Cancer Support Community .....www.cancersupportcommunity.org, 888-793-9355
Centers for Disease Control and Prevention (CDC)..... www.cdc.gov, 800-232-4636
The Gathering Place ..... www.touchedbycancer.org, 216-595-9546
Get Palliative Care..... www.getpalliativecare.org
Global Resource for Advancing Cancer Education (GRACE)..... www.cancergrace.org
The Hope Light Foundation .....www.hopelightproject.com
National Cancer Institute ..... www.cancer.gov, 800-422-6237
National Comprehensive Cancer Network (NCCN)..... www.nccn.org, 212-690-0300
National LGBT Cancer Network.....www.cancer-network.org
NCI Cancer Information Service.....800-422-6237
Patient Resource.....www.patientresource.com, 800-497-7530
Scott Hamilton CARES Foundation..... www.scottcares.org, 844-726-8884
Triage Cancer .....www.triagecancer.org, 424-258-4628
Union for International Cancer Control.....www.uicc.org
U.S. National Library of Medicine ..... www.nlm.nih.gov

## CAREGIVERS & SUPPORT

BeholdBeGold .....www.beholdbegold.org
Cactus Cancer Society.....www.cactuscancer.org
CanCare ..... www.cancare.org, 713-461-0028
CANCER101 ..... www.cancer101.org, 646-638-2202
Cancer and Careers .....www.cancerandcareers.org, 646-929-8032
Cancer*Care* ..... www.cancercare.org, 800-813-4673
Cancer Connection .....www.cancer-connection.org, 413-586-1642
Cancer Hope Network ..... www.cancerhopenetwork.org, 877-467-3638
Cancer Really Sucks!.....www.cancerreallysucks.org
Cancer Support Community .....www.cancersupportcommunity.org, 888-793-9355
Cancer Support Services..... www.cancersupportservices.org, 877-593-4212
Cancer Survivors Network .....csn.cancer.org
Caregiver Action Network.....www.caregiveraction.org, 855-227-3640
CaringBridge .....www.caringbridge.org, 651-789-2300
Center to Advance Palliative Care .....www.capc.org, 347-835-0658
Chemo Angels.....www.chemoangels.com
The Children's Treehouse Foundation..... www.childrenstreehousefdn.org, 303-322-1202
Cleaning for a Reason ..... www.cleaningforareason.org
Connect Thru Cancer .....www.connectthrucancer.org, 610-436-5555
Cooking with Cancer ..... www.cookingwithcancer.org, 205-978-3570
Family Caregiver Alliance..... www.caregiver.org, 800-445-8106
Fight Colorectal Cancer .....www.fightcolorectalcancer.org
Friend for Life Cancer Support Network..... www.friend4life.org, 866-374-3634
The Gathering Place ..... www.touchedbycancer.org, 216-595-9546
$GO_2$ for Lung Cancer .....www.go2.org, 202-463-2080
Guide Posts of Strength, Inc. ..... www.cancergps.org, 336-883-4483
Imerman Angels .....www.imermanangels.org, 866-463-7626
Livestrong Foundation .....www.livestrong.org, 855-220-7777
Living Hope Cancer Foundation .....www.getupandlive.org
Lotsa Helping Hands ..... www.lotsahelpinghands.com
MyLifeLine .....www.mylifeline.org, 888-793-9355
National LGBT Cancer Project..... www.lgbtcancer.org, 917-301-1913
Patient Empowerment Network .....www.powerfulpatients.org, 833-213-6657
SHARE Caregiver Circle..... www.sharecancersupport.org/caregivers-support, 844-275-7427
Stronghold Ministry.....www.mystronghold.org, 877-230-7674
Triage Cancer .....www.triagecancer.org, 424-258-4628
Walk with Sally ..... www.walkwithsally.org, 310-322-3900
Well Spouse Association ..... www.wellspouse.org, 732-577-8899
WeSPARK Cancer Support Center..... www.wespark.org, 818-906-3022
Wigs & Wishes ..... www.wigsandwishes.org, 856-582-6600
ZERO Prostate Cancer .....www.zerocancer.org

## CLINICAL TRIALS

Be the Match | Jason Carter Clinical Trials Search & Support.....
www.ctsearchsupport.org, 888-814-8610
Breastcancer.org Metastatic Breast Cancer Trial Search.....
www.breastcancer.org/metastatic-trials-tool, 610-642-6550
BreastCancerTrials.org ..... www.breastcancertrials.org, 888-282-7099
Cancer Support Community ..... www.cancersupportcommunity.org/find-clinical-trial, 888-793-9355
Center for Information & Study on Clinical Research Participation .....
www.searchclinicaltrials.org, 877-633-4376
ClinicalTrials.gov.....www.clinicaltrials.gov
Fight Colorectal Cancer .....trialfinder.fightcrc.org, 877-427-2111
$GO_2$ for Lung Cancer LungMATCH .....800-298-2436
Head and Neck Cancer Alliance ..... www.headandneck.org/clinical-trials, 866-792-4622
Lazarex Cancer Foundation ..... www.lazarex.org, 877-866-9523, 925-820-4517
The Leukemia & Lymphoma Society.....
www.lls.org/treatment/types-of-treatment/clinical-trials/finding-a-clinical-trial, 800-955-4572
LUNGevity Clinical Trial Finder..... clinicaltrials.lungevity.org, 312-407-6100, 240-454-3100
MM Research Foundation..... www.themmrf.org/resources/clinical-trial-finder, 203-229-0464
National Cancer Institute ..... www.cancer.gov/clinicaltrials, 800-422-6237
NCI Cancer Information Service.....800-422-6237
Sarcoma Alliance for Research through Collaboration (SARC)..... www.sarctrials.org, 734-930-7600
ThyCa: Thyroid Cancer Survivors' Association, Inc .....
www.thyca.org/about/clinical-trials, 877-588-6078
TNBC Foundation Clinical Trials Matching Service.....
www.tnbcfoundation.org/research/clinical-trials, 355-731-6036
WCG CenterWatch.....www.centerwatch.com, 866-219-3440

## GOVERNMENT ASSISTANCE

Benefits.gov ..... www.benefits.gov
Centers for Medicare & Medicaid Services.....www.cms.gov
Disability Benefits Center .....www.disabilitybenefitscenter.org
Eligibility.com (Medicare resources).....www.eligibility.com/medicare
Hill-Burton Program..... www.hrsa.gov/get-health-care/affordable/hill-burton, 800-638-0742
InsureKidsNow.gov..... www.insurekidsnow.gov, 877-543-7669
Legal Services Corporation ..... www.lsc.gov, 202-295-1500
Medicare Rights Center ..... www.medicarerights.org, 800-333-4114
National Breast and Cervical Cancer Early Detection Program.....
www.cdc.gov/cancer/nbccedp, 800-232-4636
National Council on Aging ..... www.ncoa.org, 571-527-3900
State Health Insurance Assistance Programs..... www.shiphelp.org, 877-839-2675
U.S. Department of Veterans Affairs.....www.va.gov/health

## MENTAL HEALTH SERVICES

American Psychosocial Oncology Society Helpline .....866-276-7443

## PATIENT ADVOCACY

American Cancer Society Cancer Action Network .....www.fightcancer.org, 202-661-5700
Cancer Legal Resource Center.....www.thedrlc.org/cancer, 866-843-2572
Cancer Support Community .....www.cancersupportcommunity.org, 888-793-9355
Dream Foundation .....www.dreamfoundation.org, 888-437-3267
Firefighter Cancer Support Network..... www.firefightercancersupport.org, 866-994-3276
Friend for Life Cancer Support Network..... www.friend4life.org, 866-374-3634
The Gathering Place ..... www.touchedbycancer.org, 212-595-9546
Gems of Hope, Inc. ..... www.gemsofhope.com, 319-393-9681
National Coalition for Cancer Survivorship..... www.canceradvocacy.org, 877-622-7937
Office of Cancer Survivorship ..... www.cancercontrol.cancer.gov/ocs, 800-422-6237
Patient Advocate Foundation..... www.patientadvocate.org, 800-532-5274
Research Advocacy Network.....www.researchadvocacy.org, 877-276-2187

## PATIENT ASSISTANCE RESOURCES

AbbVie.....www.abbviepaf.org, 800-222-6885
Astellas Pharma..... www.astellaspharmasupportsolutions.com/patient, 800-477-6472
AstraZeneca..... www.myaccess360.com/patient, 844-275-2360
Bristol-Myers Squibb.....www.bmsaccesssupport.com, 800-861-0048
Genentech..... www.genentech-access.com/patient, 877-436-3683
Janssen..... www.janssencarepath.com, 877-277-3728
Jazz Pharmaceuticals .....www.jazzpharma.com/our-purpose/patient-support, 833-533-5299
Lilly.....www.lillyoncologysupportcenter.com, 866-472-8663
Merck.....www.merckhelps.com, 800-727-5400
Novartis..... www.patientassistancenow.com, 800-245-5356
Pfizer .....www.pfizeroncologytogether.com, 877-744-5675
Takeda Oncology.....www.here2assist.com, 844-817-6468

➥ *For more resources, go to* PatientResource.com

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*Where information equals hope*