Understanding the Role of Biomarkers in Treating Cancer

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Biomarkers—short for biological markers—are measurements that capture key health-related indicators at a given point in time.

Biomarkers are objective indicators that determine the presence or progression of a specific condition within a person's body and how that condition is responding to treatment. A biomarker does not assess how an individual feels or functions, or what symptoms they may be experiencing.

Some biomarkers are simple—such as blood pressure, heart rate and the results of blood and urine tests. Other biomarkers measure more complex activity that occurs in molecular and cellular forms, including genes, proteins and hormones, as well as genetic material that is shed into the bloodstream from cancer cells.

The value of biomarkers is well-established in research settings (clinical trials, for example) as well as in doctors' offices, hospitals and other treatment centers. The knowledge gained from the use of biomarkers can improve health outcomes for people diagnosed with cancer or other conditions.

Types of Biomarkers

In 2015, a joint leadership council of the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) defined the following biomarker categories:

- **Susceptibility/risk.** Indicates the potential for an individual developing a disease or medical condition that they do not currently have.
- **Diagnostic.** Detects or confirms the presence of a disease or medical condition.
- **Monitoring.** Assesses the status of a disease or medical condition.
- **Prognostic.** Identifies the likelihood of a clinical event (a disease or medical condition) in individuals occurring, recurring (returning) or progressing (becoming more serious).
- **Predictive.** Identifies individuals who are more likely to experience an effect (favorable or unfavorable) from exposure to a medical product.
- **Pharmacodynamic/response.** Shows that a biological response has occurred in an individual who has been exposed to a medical product.
- **Safety.** Indicates the likelihood, presence or extent of an adverse effect after an individual has been exposed to a medical product.

The use of biomarkers in cancer treatment is discussed in the next section. Examples of biomarkers for other conditions include:

- Factor V Leiden to identify individuals with a predisposition to develop deep vein thrombosis ***(susceptibility/risk).***
- Blood sugar or hemoglobin A1c to identify individuals with Type 2 diabetes ***(diagnostic).***
- Hepatitis C virus ribonucleic acid level when assessing treatment response in individuals with chronic hepatitis C ***(monitoring).***
- C-reactive protein to identify individuals with a greater likelihood of recurrent coronary artery disease events ***(prognostic).***
- Mutations related to cystic fibrosis to identify individuals more likely to respond to a particular treatment ***(predictive).***
- Blood pressure when evaluating individuals with hypertension, to assess response to an antihypertensive agent or restriction in sodium consumption ***(pharmacodynamic/response).***
- Serum creatinine when evaluating individuals taking medications that affect kidney function, to assess kidney damage ***(safety).***

Biomarkers in Cancer Treatment

Through ongoing research, the medical community has learned much about how cancer cells develop, grow and spread. In recent years, there has been an increased focus on the role of biomarkers in these processes. Biomarkers can be produced by the cancer itself, or by other cells in the body in response to the cancer.

A diagnosis of cancer and its specific type is made by a pathologist, a doctor who studies cells and tissues under a microscope. Once the diagnosis of cancer is made, biomarker testing can begin. To determine if any cancer biomarkers are present, doctors take a sample of bodily fluid (e.g., blood, pleural fluid from around the lungs, ascites fluid from around the abdominal organs) or tumor tissue. The sample is sent to a laboratory, where profiling tests are conducted that detect and measure the level of cancer biomarkers.

Some biomarkers trigger cells to grow abnormally. An example is the HER2 protein, which helps to control cell growth. If HER2 is "overexpressed" (exists in abundance), cells can grow too quickly and form a cancerous tumor, which has a risk of spreading to other parts of the body. Detection of HER2 overexpression can predict response to certain types of cancer medicines that block the action of HER2.

Other biomarkers support the action of a specific treatment approach. For example, the Secreted Protein, Acidic, Cysteine-Rich (SPARC) gene helps bring a type of protein called albumin into cells. Some chemotherapy drugs are paired with albumin so that they can work more effectively.

Another type of biomarker disrupts the effectiveness of certain treatments. An example is a protein called ERCC1. If high levels of ERCC1 exist, platinum-based chemotherapy is unlikely to be an effective treatment approach.

The information gained from biomarker testing allows doctors to create a personalized treatment plan based on an individual's unique circumstances.

Examples of Cancer Biomarkers

There are many specific types of cancer biomarkers. A few of the most common biomarkers are listed below.

Breast cancer

- BReast CAncer genes 1 and 2 (BRCA1/2) mutations as a ***susceptibility/risk*** biomarker to identify people with a predisposition to develop breast cancer.
- BRCA1/2 gene mutations as ***prognostic*** biomarkers when evaluating people with breast cancer, to assess the likelihood of a second breast cancer.
- HER2 as both a ***prognostic*** and ***predictive*** biomarker.
- Estrogen and Progesterone receptors (ER and PR) as both ***predictive and prognostic*** biomarkers.

Cervical cancer

- Infection with certain human papillomavirus (HPV) subtypes as a ***susceptibility/risk*** biomarker to identify women with a predisposition to develop cervical cancer.
- PD-L1 expression as a ***predictive*** biomarker to identify women whose cancers have a higher likelihood of responding to immunotherapy.

Chronic lymphocytic leukemia (CLL)

- Chromosome 17p deletions and TP53 mutations as ***prognostic*** biomarkers when evaluating people with CLL.

Colorectal cancer

- Methylated genes such as MLH1, VIM and SEPT9 as ***diagnostic*** biomarkers for colorectal cancer.
- Mismatch repair protein expression status and microsatellite instability testing as ***susceptibility/risk*** biomarkers for a predisposition to colorectal and other cancers.
- Mismatch repair protein expression status and microsatellite instability testing as ***predictive*** biomarkers to identify people whose tumors may respond to immunotherapy.
- Extended RAS/RAF testing as a ***predictive*** biomarker for determining whether a person with cancer will benefit from EGFR targeted therapy.

Diffuse large B-cell lymphoma (DLBCL)

- Gene expression profiling as a ***diagnostic*** biomarker to separate people with DLBCL into subgroups based on the origin of the cancer cells.
- Standardized uptake value (SUV) as a ***pharmacodynamics/response*** biomarker when evaluating people with DLBCL being treated with chemotherapy and/or targeted therapies.

Endometrial cancer

- Mismatch repair enzyme expression status as a ***susceptibility/risk*** biomarker for a predisposition to developing certain types of endometrial cancer and a ***predictive*** biomarker for identifying people whose tumors may respond to immunotherapy.
- HER2 expression analysis as a ***prognostic*** biomarker to identify women with serous endometrial carcinoma (an aggressive form of the condition) whose tumors may respond to HER2 targeted therapy.

Lung cancer

- Squamous differentiation in non-small cell lung cancer (NSCLC) as a ***predictive*** biomarker to identify people who are likely to have better outcomes with standard chemotherapies such as docetaxel or cisplatin in combination with gemcitabine, as compared to the chemotherapy pemetrexed.
- PD-L1 as a ***predictive*** marker to identify people who are more likely to benefit from immunotherapy.
- Mutations in the EGFR gene as a ***predictive*** marker to determine whether people with NSCLC may benefit from targeted therapy with tyrosine kinase inhibitors (TKIs).

Melanoma

- BRAF mutation testing as a ***predictive*** biomarker to identify people whose tumors may respond to cancer medicines that target BRAF. Other gene mutations, such as KIT, have similar predictive value.

Ovarian cancer

- BReast CAncer genes 1 and 2 (BRCA1/2) mutations as ***predictive*** biomarkers when evaluating women with platinum-sensitive ovarian cancer, to identify those women likely to respond to treatment with PARP inhibitors.
- BRCA1/2 gene mutations as ***susceptibility/risk*** biomarkers to identify women with a predisposition to develop breast and ovarian cancer.
- Cancer antigen 125 (CA 125) as a ***monitoring*** biomarker when assessing disease status during and after treatment in women with ovarian cancer.

Pancreatic cancer

- Carbohydrate antigen (CA) 19-9, a type of antigen released by pancreatic cancer cells, as a ***pharmacodynamic/ response biomarker.***

Prostate cancer

- Prostate-specific antigen (PSA) as a ***monitoring*** biomarker when assessing disease status in men with prostate cancer.
- “Gleason score” (a score that helps predict the aggressiveness of prostate cancer) as a ***prognostic*** biomarker when evaluating men with prostate cancer, to assess the likelihood of cancer progression.

The Importance of Clinical Trials

Clinical trials are the standard by which we measure the worth of new treatments and the quality of life of patients as they receive those treatments. For this reason, doctors and researchers urge people with cancer to take part in clinical trials.

Your doctor can guide you in making a decision about whether a clinical trial is right for you. Here are a few things that you should know:

- Often, people who take part in clinical trials gain access to and benefit from new treatments
- Before you participate in a clinical trial, you will be fully informed as to the risks and benefits of the trial, including any possible side effects.
- Most clinical trials are designed to test a new treatment against a standard treatment to find out whether the new treatment has any added benefit.
- You can stop taking part in a clinical trial at any time for any reason.

Treatment Approaches and Common Side Effects

The medicines used to treat cancer fall into the following main categories:

Chemotherapy is the use of medication to treat cancer by stopping the ability of cancer cells to grow and divide.

Targeted therapies focus on specific molecules and cell mechanisms that are important for cancer cell survival and growth.

Immunotherapy uses our own immune system—a complex network of organs, cells and molecules—against the cancer.

All cancer treatments can cause side effects. It's important that you report any side effects you experience to your health care team so they can help you manage them. Report them right away—don't wait for your next appointment. Early reporting can help improve your quality of life and allow you to stick with your treatment plan.

This section provides tips and guidance on how to manage certain common side effects should they occur.

Managing Digestive Tract Symptoms

Nausea and vomiting

- Eat small, frequent meals.
- Avoid food with strong odors, as well as overly sweet, greasy, fried or highly seasoned food.
- Having something in your stomach when you take medication may help ease nausea.
- Do not lie down within two hours after eating.

Diarrhea

- Drink plenty of water. Ask your doctor about using drinks such as Gatorade, which provide electrolytes. Electrolytes are body salts that must stay in balance for cells to work properly.
- Over-the-counter medicines such as loperamide (Imodium A-D and others) and prescription drugs are available for diarrhea but should be used only if necessary and with your health care team's guidance. If the diarrhea is bad enough that you need medicine, contact a member of your health care team.
- Choose foods that contain soluble fiber, like whole grain products, oat cereals and flaxseed, and high-pectin foods such as peaches, apples, oranges, bananas and apricots.
- Avoid food high in refined sugar and those sweetened with sugar alcohols such as sorbitol and mannitol.

Constipation

- As hydration is important to avoid constipation, make sure to drink plenty of fluids. Also, limit your intake of caffeine and alcoholic beverages, as they can cause dehydration.
- Include foods high in fiber in your daily diet, such as fruit (especially pears and prunes), vegetables and cereals. If your health care team approves, you may want to add synthetic fiber to your diet, such as Metamucil, Citrucel or FiberCon.
- Be as physically active as you can, after checking with your health care team on the level of physical activity that is right for you.
- If your doctor has prescribed a "bowel regimen," make sure to follow it exactly.

Loss of appetite

- Eating small meals throughout the day is an easy way to take in more protein and calories, which will help maintain your weight. Try to include protein in every meal. Nutrition shakes or protein drinks are a way to add calories to your daily diet.
- To keep from feeling full early, avoid liquids with meals or take only small sips (unless you need liquids to help swallow). Drink most of your liquids between meals.
- Keep high-calorie, high-protein snacks on hand such as hard-boiled eggs, peanut butter, cheese, ice cream, granola bars, liquid nutritional supplements, puddings, nuts, canned tuna and trail mix.
- If you are struggling to maintain your appetite or weight, talk to your health care team about a referral to a dietician or nutritionist who has specialist-level oncology knowledge. You can also ask your doctor whether appetite-building medication could be right for you.

Managing Pain

There are a number of options for pain relief, including prescription and over-the-counter medications. It's important to talk to a member of your health care team before taking any over-the-counter medication to determine if it is safe and will not interfere with your treatment. Many pain medications can lead to constipation. Your doctor can recommend over-the-counter or prescription medications that help to avoid or manage constipation.

Physical therapy, acupuncture, progressive muscle relaxation exercises and massage may also be of help in managing your pain. Consult with a member of your health care team before beginning any of these activities.

Managing Fatigue

Fatigue (extreme tiredness not helped by sleep) is one of the most common side effects of cancer and many cancer treatments. If you are very fatigued while on treatment, your doctor may change the dose or schedule of the drug(s) you are taking, as long as that does not make the treatment less effective. If you are experiencing fatigue, talk to your doctor about whether a dose change is right for you.

There are a number of other tips for reducing fatigue:

- Take several short naps or breaks during the day.
- Take walks or do some light exercise, if possible.
- Try easier or shorter versions of the activities you enjoy.
- Ask your family or friends to help you with tasks you find difficult or tiring.

There are also prescription medications that may help. Your health care team can provide guidance on whether medication is the right approach for your individual circumstances.

Managing Side Effects of Radiation Therapy

Radiation therapy is used to treat certain types of cancer in specific circumstances. Changes to the skin are the most common side effects of radiation therapy. Those changes can include dryness, swelling, peeling, redness and blistering. If a reaction occurs, contact your health care team so the appropriate treatment can be prescribed. It's especially important to contact your health care team if there is any open skin or painful area, as this could indicate an infection. Infections can be treated with an oral antibiotic or topical antibiotic cream.

Communicating With Your Health Care Team

As you manage your cancer treatment, it's important to remember that you are a consumer of health care. The best way to make decisions about health care is to educate yourself about your diagnosis and get to know the members of your health care team, including doctors, nurse practitioners, physician assistants, nurses, dietitians, social workers and patient navigators.

Here are some tips for improving communication with your health care team:

Start a health care journal. Having a health care journal or notebook (either on paper or in a digital format) will allow you to keep all of your health information in one place. You may want to write down the names and contact information of the members of your health care team, as well as any questions for your doctor.

Prepare a list of questions. Before your next medical appointment, write down your questions and concerns. Because your doctor may have limited time, ask your most important questions first and be as specific as possible.

Bring someone with you to your appointments. Even if you have a journal and a prepared list of questions or concerns, it's always helpful to have support when you go to your appointments. They may also think of questions to ask your doctor or remember details about your symptoms or treatment that you may have forgotten.

Write down your doctor's answers. Taking notes will help you remember your doctor's responses, advice and instructions. You can also ask the person who accompanies you to take notes for you. If you have a mobile device, ask if you can use it to take notes or record the discussion, which will help you review the information later.

Remember, there is no such thing as over-communication.

Treatment Summaries

Keeping your own records up-to-date in the form of a treatment summary can be helpful, as it allows you and your family members to have instant access to the specifics of your cancer diagnosis and treatment.

A treatment summary should include:

- Your name and date of birth
- Date of diagnosis
- Prescribed therapy/therapies, including dates started and stopped and dosages when appropriate
- Dates and types of baseline and post-diagnosis testing and the results of these tests
- Other medications and supplements you are taking
- Names, affiliations and contact information of all members of your health care team

Ask the members of your health care team what they suggest be included. Take your personal record with you when you visit any doctor, not just your oncologist.

Cancer*Care's* Free Support Services and Programs

It can be very difficult to receive a diagnosis of cancer, and adjusting to the necessary changes in your life can be challenging.

Cancer*Care*® can help. We are a national nonprofit organization providing free, professional services to anyone affected by cancer. Our licensed oncology social workers can provide support and education, help in navigating the complicated health care system and offer information on support groups and other resources.

To learn more about how Cancer*Care* helps, call us at 800-813-HOPE (4673) or visit www.cancercare.org.

You will likely also build your own personal support network composed of family and friends. In doing so, it's best to take some time to think about the people in your life and how they are best suited to help. Match the task to their strengths—ask a family member who loves to shop to pick up something for you at the store, or ask a friend who's a good listener to come over for a chat.

Frequently Asked Questions

Q: What questions should I ask about biomarkers?

A: Specific questions to ask your doctor or another member of your health care team about biomarkers include:

- Is there a biomarker test for my type of cancer?
- How is that test administered?
- How will that test help in the diagnosis or treatment of my cancer?
- How accurate is the test?
- Can I get a copy of the pathology report and the results of biomarker tests?
- Should my biomarker testing be repeated? If so, when?

Additional questions will likely arise in the course of your discussion.

Q: What is a proteomic biomarker?

A: The "proteome" (a blend of the words "protein" and "genome") is all the proteins our genes make. Proteins do most of the work in cells; the genome is our complete genetic material. Proteomic biomarkers use technologies that can analyze many proteins simultaneously, such as protein microarray and mass spectrometry. With proteomics, doctors can also identify the proteins that govern how each person will metabolize (process) drugs. This is another important factor in choosing an effective treatment.

Q: Should I get a second opinion on the pathology of my tumor and/or biomarker testing?

A: It is standard practice in many laboratories to have more than one pathologist review the results of an initial diagnosis of cancer. Ask your doctor whether they think a second opinion on your pathology diagnosis would be helpful, especially if the diagnosis was difficult or unusual. Obtaining a second opinion on your pathology diagnosis can be as important as a second opinion on a medical diagnosis or a recommended treatment approach.

Biomarker results are more standardized than pathology interpretation, but it's important to ensure that your tests are being carried out in a laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA). Your doctor can help you choose a certified laboratory for your biomarker testing.

Resources

CancerCare®
800-813-HOPE (800-813-4673)
www.cancercare.org

American Cancer Society
800-227-2345
www.cancer.org

Cancer.Net
Patient information from the American Society of Clinical Oncology
888-651-3038
www.cancer.net

National Cancer Institute
800-422-6237
www.cancer.gov

Cancer Support Community
888-793-9355
www.cancersupportcommunity.org

National Coalition for Cancer Survivorship
877-622-7937
www.canceradvocacy.org

CLINICAL TRIALS WEBSITES

EmergingMed
www.emergingmed.com

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