
Tumor Markers

What Are Tumor Markers?

Tumor markers are substances that can be found in the body when cancer is present. They are usually found in the blood or urine. They can be products of the cancer cells themselves or of the body in response to cancer or other conditions. Most tumor markers are proteins.

There are many different tumor markers. Some are seen only in a single type of cancer, while others can be found in many types of cancer.

To test for a tumor marker, the doctor sends a sample of the patient's blood or urine to a lab. The marker is usually found by combining the blood or urine with manmade antibodies designed to react with that specific protein.

For many reasons, tumor markers by themselves are usually not enough to diagnose or rule out cancer. Most tumor markers can be made by normal cells as well as by cancer cells. Sometimes, non-cancerous diseases can also cause levels of certain tumor markers to be higher than normal. And not every person with cancer may have higher levels of a tumor marker.

For these reasons, only a handful of tumor markers are commonly used by most doctors. When a doctor looks at the level of a certain tumor marker, he or she will consider it along with the results of the patient's history and physical exam and other lab tests or imaging tests.

In recent years, doctors have begun to develop newer types of tumor markers. With advances in technology, levels of certain genetic materials (DNA or RNA) can now be measured. And while it has been hard to identify single substances that provide useful information, doctors are now beginning to look at patterns of genes or proteins in the blood. These new fields of genomics and proteomics, respectively, are discussed further in the section ["What's New in Tumor Marker Research?"](#)

How Are Tumor Markers Used?

Screening and Early Detection of Cancer

Screening refers to looking for cancer in people who have no symptoms of the disease. *Early detection* is finding cancer at an early stage, when it is less likely to have spread and is more likely to respond well to treatment. Although tumor markers were first developed to test for cancer in people without symptoms, very few markers have been shown to be helpful in this way.

The most widely accepted tumor marker is the prostate-specific antigen (PSA) blood test, which is used (along with the digital rectal exam) to screen for prostate cancer. But because it's not always clear what the test results mean, not all doctors agree that PSA screening is appropriate for all men. Newer versions of the PSA test may prove to be more accurate.

Most other tumor markers have not been shown to detect cancer much earlier than they would have been found otherwise.

Diagnosing Cancer

Tumor markers are usually not used to diagnose cancer. In most cases, cancer can only be diagnosed by a biopsy (removal of tumor cells so they can be looked at under a microscope). Still, markers can help determine if a cancer is likely. They can also help diagnose the source of widespread cancer in a patient when the origin of the cancer is unknown. An example is a woman who has cancer throughout the pelvis and abdomen. The presence of a high level of the tumor marker CA 125 will strongly suggest ovarian cancer, even if surgery can't identify the source. This can be important because treatment can then be tailored to this type of cancer.

Determining the Prognosis (Outlook) for Certain Cancers

Some types of cancer grow and spread faster than other types. But even within a cancer type (such as breast cancer), some cancers will grow and spread more quickly or may be more or less responsive to certain treatments. Some newer tumor markers help show how aggressive a person's cancer is likely to be, or even how well it might respond to certain drugs.

Determining the Effectiveness of Cancer Treatment

One of the most important uses for tumor markers is to monitor patients being treated for cancer, especially advanced cancer. If a tumor marker is available for a specific type of cancer, it is much easier to measure it to see if the treatment is working rather than repeating chest x-rays, CT scans, bone scans, or other tests. It also tends to be less expensive.

If the tumor marker level in the blood goes down, it is almost always a sign that the treatment is having an effect. On the other hand, if the marker level goes up, then the treatment probably should be changed. (One exception is if the cancer is very sensitive to a certain chemotherapy treatment. In this case, the chemotherapy can cause many cancer cells to die and release large amounts of the marker into the blood, which will cause the level of the tumor marker to rise for a short time.)

Detecting Recurrent Cancer

Markers are also used to look for cancer that may come back (recur) after initial treatment. Some tumor markers may be useful once treatment is complete and there is no evidence of cancer remaining. These include PSA (for prostate cancer), human chorionic gonadotropin (HCG) (for gestational trophoblastic tumors and germ cell cancers of the ovaries and testicles), and perhaps CA 125 (for epithelial ovarian cancer).

Some women who have been treated for breast cancer have yearly blood tests for levels of the tumor marker CA 15-3. This can sometimes detect cancer recurrence before the woman has symptoms or evidence of cancer on imaging tests. Many doctors question the test's value, though, because no one has shown a long-term advantage in finding recurrent breast cancer early. And usually the cancer causes symptoms or can be found by the doctor around the same time that the CA 15-3 level rises. The same is true for carcinoembryonic antigen (CEA), a tumor marker used to monitor colorectal cancer.

Because of this, some doctors and medical groups do not recommend using these tumor markers after treatment aimed at curing these cancers. They are more likely to

be used to monitor more advanced cancer, especially when treatment may not be expected to result in a cure, as mentioned above.

History of Tumor Markers

The first modern tumor marker used to detect cancer was human chorionic gonadotropin (HCG), the substance doctors look for in pregnancy tests. Women whose pregnancy has ended but whose uterus continues to be enlarged are tested for the presence of HCG. A high level of HCG in the blood may indicate the presence of a cancer of the placenta called gestational trophoblastic disease (GTD). This cancer continues to produce HCG. Some testicular and ovarian cancers resemble GTD because they start in reproductive cells called germ cells. These cancers also make HCG, so this marker is used to help diagnose them and monitor their response to therapy.

The hope in the search for tumor markers was that all cancers could someday be detected by a single blood test. Both GTD and germ cell tumors of the ovaries and testicles are too rare to look for these cancers by testing everyone. But other cancers, such as colon, breast, and lung are much more common. A simple blood test that could detect these cancers in their earliest stages could prevent the deaths of millions of people. And so, many scientists began working toward this goal.

The first success in developing a blood test for a common cancer was in 1965, when carcinoembryonic antigen (CEA) was found in the blood of some patients with colon cancer. By the end of the 1970s several other blood tests had been developed for different cancers. The new markers were often given numeric labels. There was CA 19-9 for colorectal and pancreatic cancer, CA15-3 for breast cancer, and CA 125 for ovarian cancer. Many others were also found, but because they did not show an advantage over the already discovered markers, they were not studied any further.

Unfortunately, none of these tumor markers, including CEA, met the original goal of reliably finding cancer at an early stage. There were a few reasons for this:

- Almost everyone has a small amount of these markers in their blood, and it is very hard to spot early cancers by using these tests.
- The levels of these markers tend to get higher than normal only when there is a large amount of cancer present.
- Some people with cancer never have higher levels of these markers.
- Even when levels of these markers are high, they are often not specific enough. For example, the level of the tumor marker CA 125 can be high in women with gynecologic conditions other than ovarian cancer.

Because of this, these markers are used mainly in patients who have already been diagnosed with cancer to monitor their response to treatment or detect the return of cancer after treatment.

The only tumor marker widely used in screening is the prostate-specific antigen (PSA) test. It was discovered around the same time as the others, but it's been in widespread use for screening since the early 1990s because it has certain advantages. First, it is made only by prostate cells, so a rise in PSA is fairly specific to a prostate problem. Also, the PSA level usually rises even in early cancers, so most prostate cancers can be found at an early stage, when they are most likely to be curable. The test is not perfect, however. Some men may have an elevated PSA because of other prostate conditions or a prostate cancer that would never need

treatment, and some men with prostate cancer may not have an elevated PSA. Because of this, doctors and medical organizations do not agree about whether all men should be tested.

Many other tumor markers have been found in recent years and are now under study. Some of these are different from traditional markers, which were proteins found in the blood.

Specific Tumor Markers

This section focuses on the most commonly used tumor markers.

There are many other markers being made by commercial testing labs that are not commonly used. They are sometimes advertised as being better than the commonly used markers but then often fall out of use when they show no advantage over the others. There are also other markers that are used by researchers. These are often not available to doctors or hospital labs. If research does show that they are useful, they are then made available to doctors and their patients. This list is limited to those tumor markers available to most doctors and for which there is reliable scientific information showing that they are useful.

The cancers described in these brief summaries are those for which the marker is usually used. These marker levels may be increased in other kinds of cancer as well, which is why they are not used to diagnose which type of cancer a person has.

As with other kinds of lab tests, different labs may consider slightly different marker levels to be normal or abnormal. This can depend on a number of factors, including a person's age and gender, which test kit the lab uses, and how the test is performed. *The values listed below are average values, but most labs will list their own "reference ranges" along with any test results you receive.* If you are being tested for a tumor marker, be sure to ask your doctor about what your results mean.

Alpha-fetoprotein (AFP): AFP is most useful in following the response to treatment for *liver cancer (hepatocellular carcinoma)*. Normal levels of AFP are usually less than 20 nanograms per milliliter (ng/mL). A nanogram is one-billionth of a gram. AFP levels are higher than normal in about 2 out of 3 patients with liver cancer. The level increases with the size of the tumor. In most patients with liver cancer, the level is more than 500 ng/mL. In very small tumors the levels may be less than 20 ng/mL. AFP is also elevated in acute and chronic hepatitis, but is seldom above 100 ng/mL in these diseases.

AFP is also higher in certain *testicular cancers* (embryonal cell and endodermal sinus types) and is used for follow-up of these cancers. Elevated AFP levels are also seen in a certain rare types of ovarian and testicular cancer called *yolk sac tumor* or *mixed germ cell cancer*.

Beta-2-microglobulin (B2M): B2M blood levels are elevated in *multiple myeloma*, *chronic lymphocytic leukemia (CLL)*, and some *lymphomas*. Levels may also be higher in some non-cancerous conditions, such as kidney disease. Normal levels are usually below 2.5 micrograms per milliliter (ug/mL). A microgram is one-millionth of a gram. B2M is useful in helping to determine prognosis (long-term outlook for survival) in some of these cancers. Patients with higher levels of B2M usually have a poorer prognosis.

Beta-HCG: see human chorionic gonadotropin (HCG) below.

Bladder tumor antigen (BTA): BTA is found in the urine of many patients with *bladder cancer*. It may be present in some non-cancerous conditions too. The results of the test are reported as either positive (BTA is present) or negative (BTA is not present). It is being used along with NMP22 (see below) to test patients for recurrent cancer. This test is not widely used but is still being studied. It is not certain whether it is as sensitive as cystoscopy (looking directly into the bladder through a thin, lighted tube). Most experts still recommend cystoscopy for diagnosis and follow-up of bladder cancer.

CA 15-3: CA 15-3 is used mainly to monitor patients with *breast cancer*. Elevated blood levels are found in less than 10% of patients with early disease and in about 70% of patients with advanced disease. Levels usually drop following effective treatment, although they may spike in the first few weeks after treatment is started, a result of dying cancer cells spilling their contents into the bloodstream.

The normal level is usually less than 25 U/mL (units/milliliter), depending on the lab. But levels as high as 100 U/mL can sometimes be seen in women who do not have cancer. Levels of this marker can also be higher in other cancers and in some non-cancerous conditions such as benign breast conditions and hepatitis.

CA 27.29: CA 27.29 is another marker used to follow patients with *breast cancer* during or after treatment. This test measures the same marker as the CA 15-3 test, but in a different way. Although it is a newer test than CA 15-3, it does not appear to be any better in detecting either early or advanced disease. It may be less likely to be positive in people without cancer. The normal level is usually less than 38 to 40 U/mL (units/milliliter), depending on the testing lab. This marker can also be elevated in other cancers and in some non-cancerous conditions, and it may not be elevated in some women with breast cancer.

CA 125: CA 125 is the standard tumor marker used to follow women during or after treatment for *epithelial ovarian cancer* (the most common type of ovarian cancer). Normal blood levels are usually less than 30 to 35 U/mL (units/milliliter). More than 90% of patients have higher levels of CA 125 when the cancer is advanced.

Levels are also elevated in about half of women whose disease is still confined to the ovary. Because of this, CA 125 is being studied as a screening test. The problem with using it as a screening test is that it would still miss many early cancers, and conditions other than ovarian cancer can cause an elevated CA 125 level. For example, it is also often higher in women with uterine fibroids or endometriosis (having uterine cells in abnormal locations), in men and women with lung cancer, and in people who have had cancer in the past. Because ovarian cancer is a relatively rare disease, an increased CA 125 level is more likely to be caused by something other than ovarian cancer.

CA 72-4: CA 72-4 is a newer test being studied in *ovarian* and *pancreatic cancer* and cancers starting in the digestive tract, especially *stomach cancer*. There is no evidence that it is better than current tumor markers, but it may be valuable when used along with other tests. Studies of this marker are still in progress.

CA 19-9: Although the CA 19-9 test was first developed to detect colorectal cancer, it is more sensitive to *pancreatic cancer*. It will not usually detect very early disease, which is why it is not used as a screening test. But it is now considered the best

tumor marker for following patients with cancer of the pancreas.

Normal blood levels of CA 19-9 are below 37 U/mL (units/milliliter). A high CA 19-9 level in a newly diagnosed patient usually means the disease is advanced.

CA 19-9 can also be used to monitor *colorectal cancer*, but because it is less sensitive than the CEA test, most medical groups recommend CEA testing when following this disease.

CA 19-9 can also be elevated in other forms of digestive tract cancer, especially cancers of the stomach and bile ducts, and in some non-cancerous conditions such as pancreatitis (inflammation of the pancreas).

Calcitonin: Calcitonin is a hormone produced by certain cells (called parafollicular C cells) in the thyroid gland. It normally helps regulate blood calcium levels. In cancer of the parafollicular C cells, called *medullary thyroid carcinoma (MTC)*, blood levels of this hormone are elevated.

This is one of the rare tumor markers that can be used to help detect early cancer. Because MTC is often inherited, blood calcitonin can be measured to detect the cancer in its very earliest stages in family members who are at risk. Other cancers, particularly lung cancers, can also cause calcitonin levels to be elevated, but measurement of its level in the blood is not usually used to follow these cancers.

Carcinoembryonic antigen (CEA): CEA is the preferred tumor marker for following patients with *colorectal cancer* during or after treatment, but it is not useful as a screening or diagnostic test. The normal range of blood levels varies from lab to lab, but levels higher than 5 nanograms per milliliter (ng/mL) are generally considered abnormal. The higher the CEA level at the time colorectal cancer is detected, the more likely it is that the cancer is advanced.

Many doctors use this marker to follow other cancers, such as *lung cancer* and *breast cancer*. CEA levels are also elevated in many other cancers such as those of the thyroid, pancreas, liver, stomach, ovary, and bladder. They are elevated in some non-cancerous diseases and in otherwise healthy smokers, too.

Chromogranin A (CgA): Chromogranin A is made by *neuroendocrine tumors*, which include *carcinoid tumors*, *neuroblastoma*, and *small cell lung cancer*. The blood level of CgA is often elevated in people with these diseases. It is probably the most sensitive tumor marker for carcinoid tumors, being abnormal in 1 out of 3 people with localized disease and 2 out of 3 of those with metastatic cancer. Levels can also be elevated in some advanced forms of prostate cancer that have neuroendocrine features. The range of normal blood levels varies between testing centers, but is generally less than 76 nanograms per milliliter (ng/mL) in men and less than 51 ng/mL in women.

Estrogen receptors/progesterone receptors: Breast tumor samples--not blood samples--from women and men with *breast cancer* are commonly tested for these markers. Breast cancers that contain estrogen receptors are often referred to as "ER-positive," while those with progesterone receptors are "PR-positive." About 7 out of 10 breast cancers test positive for at least one of these markers. These cancers tend to have a better prognosis than cancers without these receptors and are much more likely to respond to hormonal therapy such as tamoxifen or aromatase inhibitors.

HER2 (also known as HER2/neu, erbB-2, or EGFR2): HER2 is a marker that is elevated in some *breast cancer* cells. Higher than normal levels are also found in some other cancers. The HER2 level is usually found by testing a sample of the cancer tissue itself, not the blood. About 1 in 5 people with breast cancer test positive for HER2. Its main use is as a predictor of prognosis (outlook for survival). Those whose cancers are positive for this marker don't respond as well to chemotherapy, and in the past were thought to have a less favorable outlook. But this may be changing, as these cancers are more likely to respond to newer treatments such as trastuzumab (Herceptin[®]) and lapatinib (Tykerb[®]), which work against the HER2 receptor on breast cancer cells.

Human chorionic gonadotropin (HCG): HCG (also known as beta-HCG) blood levels are elevated in patients with some types of *testicular* and *ovarian cancers* (germ cell tumors) and in *gestational trophoblastic disease*, mainly *choriocarcinoma*. They are also higher in some men with certain cancers in the middle of their chest (mediastinum) that start in the same cells as testicular cancer (*mediastinal germ cell neoplasms*). Levels of HCG can be used to help diagnose these conditions and can be followed over time to monitor how well treatment is working. They can also be used to look for cancer recurrence once treatment has ended.

An elevated blood level of this marker will also raise suspicions of cancer in certain situations. For example, in a woman who continues to have a large uterus after pregnancy has ended, a high blood level of this marker is a possible sign of a cancer. This is also true of men with an enlarged testicle or with a mass in their chest. The definition of a normal level is hard to determine because there are different methods of testing for this marker and each has its own normal value.

Immunoglobulins: Immunoglobulins are not really tumor markers but antibodies, which are blood proteins normally made by immune system cells to help fight germs. There are many types of immunoglobulins, including IgA, IgG, IgD, and IgM. Bone marrow cancers such as *multiple myeloma* and *Waldenstrom macroglobulinemia* often result in too many immunoglobulins in the blood (and in the urine). A high level of immunoglobulins may indicate the presence of one of these diseases.

There are normally many different immunoglobulins in the blood, with each one differing very slightly from the others. A classic sign in patients with myeloma or macroglobulinemia is a very high level of one specific (monoclonal) immunoglobulin. This can be seen on a test called protein electrophoresis, which separates the globulins by electrical current. With myeloma or macroglobulinemia, the globulins (also called monoclonal proteins or M proteins) stick together and form a monoclonal "spike" (often called the M spike) on the readout of the test. The level of the spike is important, because older people may show low levels of a spike without having myeloma or macroglobulinemia. The diagnosis, however, must be confirmed by a biopsy of the bone marrow.

Immunoglobulin levels can also be followed over time to help determine how well treatment is working.

Lipid associated sialic acid in plasma (LASA-P): LASA-P has been studied as a marker for *ovarian cancer* as well as some other cancers. Generally it has not proven valuable, however, and it has been replaced by more specific marker tests. It is not specific for any particular cancer or even for cancer in general, as it can also be elevated in some non-cancerous conditions. It is sometimes used along with other

tumor markers to follow response to treatment.

Neuron-specific enolase (NSE): NSE, like chromogranin A, is a marker for *neuroendocrine tumors* such as *small cell lung cancer*, *neuroblastoma*, and *carcinoid tumors*. It is not used as a screening test. It is most useful in the follow-up of patients with small cell lung cancer or neuroblastoma (while chromogranin A seems to be a better marker for carcinoid tumors). Elevated levels of NSE may also be found in some non-neuroendocrine cancers. Abnormal levels are usually higher than 9 micrograms per milliliter (ug/mL).

NMP22: NMP22 is a protein found in the nucleus (control center) of cells. Levels of NMP22 are often elevated (more than 10 U/mL or units/milliliter) in the urine of people with *bladder cancer*. So far it hasn't been found to be sensitive enough to be used as a screening tool. It is most often used to look for cancer recurrence after treatment. This is a less invasive form of monitoring than cystoscopy (looking into the bladder with a thin, lighted tube), but it's not clear whether it is as accurate, so it is not as widely used. NMP22 levels can also be higher than normal due to non-cancerous conditions or recent treatment with chemotherapy.

Prostate-specific antigen (PSA): PSA is a tumor marker for *prostate cancer*. It is the only marker used to screen for a common type of cancer (although some medical groups do not recommend its use). It is a protein made by cells of the prostate gland in men, which is responsible for making some of the liquid in semen. The level of PSA in the blood can be elevated in prostate cancer, but PSA levels can be affected by other factors, too. Men with benign prostatic hyperplasia (BPH), a non-cancerous growth of the prostate, often have higher levels. The PSA level also tends to be higher in older men and those with larger prostates, and it can be elevated for a day or two after ejaculation.

When the PSA test is used for screening, it should be done along with a digital rectal exam. For this test the doctor inserts a gloved, lubricated finger into the rectum to feel the prostate gland for any abnormalities.

PSA is measured in nanograms per milliliter (ng/mL). Most doctors feel that a blood PSA level below 4 ng/mL means cancer is unlikely, while levels greater than 10 ng/mL mean cancer is likely. The area between 4 and 10 is a gray zone. Doctors often recommend a prostate biopsy (getting samples of prostate tissue to look for cancer) for men with a level above 4 ng/mL.

But there is some controversy surrounding these cutoff points. Some men with prostate cancer do not have an elevated PSA level, while some others with a borderline or elevated level will not have cancer. Some doctors are now recommending following the PSA level over time (*PSA velocity*) because an increase from one year to the next may mean prostate cancer is more likely. Doctors are also looking at the PSA level in other ways to see if it might be more useful.

A helpful test when a PSA value is between 4 ng/mL and 10 ng/mL is to measure the *free PSA* (or *percent-free PSA*). PSA in the blood exists in 2 forms – some is bound to a protein and some is free. As the amount of free PSA goes up, the less likely it is that there is prostate cancer. When the free PSA makes up more than 25% of the total PSA, prostate cancer is unlikely. If the free PSA is below 10%, the chance of prostate cancer is much higher.

The PSA test is very valuable in the follow-up of patients with prostate cancer. For

patients who have been treated with surgery meant to cure the disease, the PSA should fall to an undetectable level. Those treated with radiation therapy should also have a significant drop in PSA after treatment. A rise in the PSA level may be a sign the cancer is coming back. The PSA can also be used to follow the response to treatment for more advanced disease. For more information about the PSA test, see our [Prostate Cancer](#) document.

Prostatic acid phosphatase (PAP): PAP (not to be confused with the Pap test for women) is another test for *prostate cancer*. It was used before the PSA test was developed but is rarely used now because the PSA test is much more sensitive.

Prostate-specific membrane antigen (PSMA): PSMA is a substance found in all prostate cells. Blood levels increase with age and with *prostate cancer*. PSMA is a very sensitive marker, but so far it has not proven to be better than PSA, and its use in detecting or monitoring cancer is still being studied. Its current use is limited to being part of a nuclear scan (a type of imaging test) to look for the spread of prostate cancer in the body. Some potential immunotherapy treatments for prostate cancer based on this substance are now under study.

S-100: S-100 is a protein found in most *melanoma* cells. Tissue samples of suspected melanomas are often tested for this marker to help in diagnosis.

Some studies have shown that blood levels of S-100 are elevated in most patients with metastatic melanoma. The test is sometimes used to look for melanoma spread before, during, or after treatment.

TA-90: TA-90 is a protein found on the outer surface of *melanoma* cells. Like S-100, TA-90 can be used to look for the spread of melanoma. Its value in following melanoma is still being studied, and it is not widely used at this time. It is also being studied for use in other cancers such as colon and breast cancer.

Thyroglobulin: Thyroglobulin is a protein made by the thyroid gland. Normal blood levels depend on a person's age and gender. Thyroglobulin levels are elevated in many thyroid diseases, including some common forms of *thyroid cancer*.

Treatment for thyroid cancer often involves removal of the entire thyroid gland, sometimes along with radiation therapy. Thyroglobulin levels in the blood should fall to undetectable levels after treatment. A rise in the thyroglobulin level suggests the cancer may have returned. In people with metastatic thyroid cancer, thyroglobulin levels can also be followed over time to evaluate the results of treatment.

Some people's immune systems make antibodies against thyroglobulin, which can affect test results. Because of this, levels of anti-thyroglobulin antibodies are often measured at the same time.

Tissue polypeptide antigen (TPA): TPA is a protein marker that is present in high levels in many rapidly dividing cells (such as cancer cells). The TPA blood test is sometimes used along with other tumor markers to help follow patients being treated for *lung, bladder*, and many other cancers. TPA levels are also elevated in some non-cancerous conditions.

Common Cancers and Associated Tumor Markers

Bladder Cancer

No urinary tumor markers are recommended for bladder cancer screening. But the *bladder tumor antigen (BTA)* and the *NMP22* tests can be used along with cystoscopy (using a thin, lighted tube to look in the bladder for cancer) in diagnosing it.

These tests are also being used to follow some patients after treatment, though cystoscopy and urine cytology (using a microscope to look for cancer cells in the urine) are still recommended as the standard tests for diagnosis and follow-up. It is too early to tell if these tests will take the place of urine cytology and cystoscopy or if they will best be used along with these tests. Other tumor markers are also being studied in this setting.

For advanced cancer, some of the markers used for other cancers such as *CEA*, *CA 125*, *CA 19-9*, and *TPA* may be elevated and can be used to follow patients during and after treatment.

(For more information refer to the ACS document [Bladder Cancer](#).)

Breast Cancer

No tumor marker has been found to be useful for screening or for the diagnosis of early stage breast cancer.

At the time of diagnosis, breast cancer tissue is often tested for *estrogen* and *progesterone receptors*, as well as the *HER2/neu* antigen. These markers provide some information on how aggressive the cancer may be and how likely it is to respond to certain treatments.

The markers most commonly used to follow patients with advanced cancer or to detect recurrence are *CA 15-3* and *CEA*. The *CA 27.29* test is also used by some doctors. The *CA 15-3* and *CA 27.29* are probably equally sensitive, while the *CEA* is less sensitive.

These markers are most useful in measuring the results of treatment for patients with advanced disease. Generally speaking, blood levels go down if the cancer responds to treatment and rise if the cancer progresses.

Some doctors use these tests to look for signs of recurrence in women who have no symptoms of cancer after their first treatment. But most professional groups do not recommend using these markers to follow women already treated for early stage disease.

(For more information refer to the ACS document [Breast Cancer](#).)

Colorectal Cancer

The markers most often elevated in advanced colorectal cancer are *CEA* and *CA 19-9*, but neither of these is useful as a screening test for colorectal cancer.

An elevated CEA before surgery may indicate a poorer prognosis. If it is high before surgery, the CEA should return to normal levels in about 4 to 6 weeks if all of the cancer has been removed.

Many doctors follow patients after surgery with CEA tests every 3 to 6 months or so to look for the return of the cancer. Patients are sometimes helped by finding a recurrence early so it can be removed by surgery, but for most patients the recurrence may be too widespread to be removed.

CEA is also used to follow patients who are being treated for advanced or recurrent disease. The CEA level will go down if the treatment is working and will rise if the cancer progresses.

If the CEA is not elevated in patients with advanced or recurrent cancer, sometimes the CA 19-9 can be used to follow the disease.

(For more information refer to the ACS document [Colorectal Cancer](#).)

Gestational Trophoblastic Disease

Trophoblastic tumors include molar pregnancies (a pregnancy that results in a tumor of the placenta) and the more aggressive choriocarcinoma. *Human chorionic gonadotropin (HCG)* is elevated in these tumors. HCG testing can be used to detect these cancers in women who are no longer pregnant and whose wombs do not shrink to normal size.

Measurements of HCG during treatment for trophoblastic disease are very useful in determining response to treatment.

(For more information refer to the ACS document [Gestational Trophoblastic Disease](#).)

Liver Cancer

Cancer that starts in the liver (known as *hepatocellular carcinoma*) is linked with chronic infections caused by hepatitis B and C viruses and with cirrhosis from various causes. This is a common type of cancer in Southeast Asia.

Liver cancers can cause elevated levels of *alpha fetoprotein (AFP)*. Higher AFP levels occur in about 2 of 3 patients with liver cancer. An elevated AFP in someone with chronic hepatitis may suggest the diagnosis of this cancer, although further testing must be done along with a biopsy to prove that there is cancer.

Because liver cancer is not very common in the United States, AFP testing is not used to test the general population for this type of cancer. Screening with AFP has been successful in parts of Asia where liver cancer is common. Sometimes the cancer is found early enough so that the patient can be cured with surgery. Because of this success, some doctors in the United States may screen their patients with cirrhosis of the liver due to hepatitis B or C. A rising AFP level might indicate cancer.

AFP can be used to help determine the most appropriate treatment for liver cancer and to follow patients after curative surgery or other treatment.

(For more information refer to the ACS document [Liver Cancer](#).)

Lung Cancer

No tumor markers have proven useful as screening tests for lung cancer.

Some of the tumor markers that may be elevated in lung cancer are the *carcinoembryonic antigen (CEA)* in non-small cell lung cancer and the *neuron-specific enolase (NSE)* in small cell lung cancer. Sometimes doctors will follow these markers to evaluate treatment results. There are many other markers that can also be followed. However, because lung cancer is fairly easily seen on chest x-rays or other imaging tests, tumor markers play a less important role.

(For more information refer to the ACS document [Lung Cancer \(Non-Small Cell\)](#) or [Lung Cancer \(Small Cell\)](#).)

Melanoma Skin Cancer

No tumor marker is of value in finding this disease early.

The markers *TA-90*, *S-100*, and some other markers can be used to test tissue samples to help diagnose melanoma in areas of concern.

Blood levels of TA-90 have been used to help find out if the melanoma has metastasized (spread). If the blood TA-90 level is high, there is a good chance the melanoma is metastatic. But TA-90 can sometimes be elevated in the absence of metastatic melanoma. Because of this, it has not yet been used to plan treatment or predict prognosis.

S-100 is also elevated in the blood when the disease is widespread. This marker can also be used to look for progression of the melanoma.

(For more information refer to the ACS document [Melanoma Skin Cancer](#).)

Multiple Myeloma

There are no tumor markers commonly used to screen for this disease, although tests for immunoglobulins can be used to help detect it or make a diagnosis. Protein electrophoresis and immunofixation can find these immune system proteins in the blood or urine of most patients with myeloma.

Pieces of immunoglobulins in the urine, called *Bence Jones* proteins, are found in some patients with multiple myeloma. Most people with myeloma also have detectable levels of immunoglobulins, called *monoclonal proteins* or *M-proteins*, in their blood. (These proteins lead to a monoclonal spike, or M spike, on the test readout.) These markers can help diagnose the disease, but a bone marrow biopsy may be needed to confirm the diagnosis. They are also helpful in tracking the course of the disease and its response to treatment.

Many patients with multiple myeloma also have higher blood levels of *beta-2-microglobulin*, which can also provide information on prognosis and the response to treatment.

(For more information refer to the ACS document [Multiple Myeloma](#).)

Ovarian Cancer

Epithelial ovarian cancer (the most common form of ovarian cancer) is linked with elevated levels of CA 125. Other markers that are sometimes measured are CA 72-4 and *LASA-P*. CA 125, which is elevated in most women with advanced disease, is the standard marker that most doctors use. Ovarian cancer, even when advanced, is often confined to the abdomen and pelvis and hard to find through x-ray testing. Because of this, the CA 125 is often the easiest and most effective way to measure the response to treatment or to find a cancer that has come back.

CA 125 is also being used by some doctors to screen for ovarian cancer in women with a strong family history of ovarian cancers. Such women usually get regular ultrasounds for early detection along with CA 125 measurements.

CA 125 is being studied as a screening tool in women who have no family history of ovarian cancer. At the present time, most medical groups do not recommend CA 125 testing for ovarian cancer screening because it is not clear whether it will detect the cancer early enough to increase the cure rate. Another problem with this test is that ovarian cancer is not common, and the CA 125 level can be elevated in other cancers and other conditions. Therefore, an elevated CA 125 is more likely to be due to some other cause, even though a lot testing might be needed to rule out ovarian cancer.

The second most common group of ovarian cancers is the germ cell tumors. Patients with these cancers often have elevated levels of *HCG* and/or *AFP*, which are useful in diagnosis and follow-up.

(For more information refer to the ACS document [Ovarian Cancer](#).)

Pancreatic Cancer

No markers have been found to be helpful in screening for pancreatic cancer.

The CA 19-9 marker is the most useful marker for pancreatic cancer. Most people with pancreatic cancer have elevated levels of this marker in their blood. The higher the level, the more likely the disease has spread.

It is also useful in patient follow-up. Patients whose CA 19-9 levels drop to normal after surgery have a much better outlook than those people whose CA 19-9 remains elevated after surgery. This marker can also be used to follow the effects of treatment on more advanced disease.

Some doctors also follow the level of CEA in the blood, but it may not be as helpful as the CA 19-9 level.

(For more information refer to the ACS document [Pancreatic Cancer](#).)

Prostate Cancer

The most commonly used marker to detect prostate cancer is the *prostate-specific antigen (PSA)*. Prostate cancer can often be detected in its early stages by

measuring blood levels of PSA. Levels above 4 ng/mL suggest cancer may be present, while levels above 10 ng/mL strongly suggest cancer. Doctors usually advise that men with elevated PSA levels have their prostate gland biopsied to find out if there is cancer.

Prostate cancer is often a slow growing cancer that is found in older men. For this reason, it is not clear if screening with PSA actually saves lives. Some doctors believe that screening may cause more harm than good. It may lead some men to get treated for cancers that would never have caused them problems, and the treatment itself can have major side effects.

PSA is very useful in monitoring recurrent disease. After surgery, the PSA level should be undetectable or near undetectable (0 or very close to 0). Those treated with radiation therapy should also have a significant drop in PSA after treatment. A rise in PSA after treatment could mean the disease is coming back and that more treatment should be considered. The PSA can also be used to follow the response to treatment for more advanced disease.

Another marker being studied for following prostate cancer is the *prostate-specific membrane antigen (PSMA)*. It's not yet clear how useful it will be.

In rare cases, prostate cancers that do not cause abnormal blood PSA levels and do not respond well to hormone therapy turn out to have neuroendocrine features. Men with these cancers may have higher than normal levels of *chromogranin A*. These cancers are more likely to respond to certain chemotherapy drugs.

Prostatic acid phosphatase (PAP) is an older, less sensitive marker which is no longer used very much.

(For more information refer to the ACS document [Prostate Cancer](#).)

Stomach (Gastric) Cancer

No marker has been developed specifically for this cancer. Some other digestive cancer markers may be elevated, such as *CEA*, *CA 72-4*, and/or *CA 19-9*. If the levels of these markers are elevated at the time of diagnosis, the levels can be followed while the cancer is being treated.

(For more information refer to the ACS document [Stomach Cancer](#).)

Testicular Cancer

Tumor markers are very important in this cancer and are used by doctors to follow its course. The markers usually elevated in the blood of men with testicular cancer are *human chorionic gonadotropin (HCG)* and *alpha fetoprotein (AFP)*. There are different kinds of testicular cancers, and they differ in the level and kind of marker that is elevated.

Seminoma: About 10% of men with seminoma, a type of testicular cancer, will have elevated HCG. None will have elevated AFP.

Non-seminoma: More than half of men with early stage disease will have elevated HCG or AFP or both. The amount of the marker found in the blood does not

necessarily help in predicting outcome. The markers will be elevated in most men with more advanced disease.

HCG is almost always elevated and AFP is never elevated in choriocarcinoma, a subtype of non-seminoma. As with the other non-seminomas, the amount of the marker found in the blood does not necessarily help in predicting outcome. In contrast AFP, but not HCG, is elevated in another subtype known as yolk sac tumor or endodermal sinus tumor.

(For more information refer to the ACS document [Testicular Cancer](#).)

What Should You Ask Your Doctor About Tumor Markers?

It is important to talk openly with your cancer care team. Don't be afraid to ask any question that's on your mind, no matter how small or silly it might seem to you. Here are some questions you might ask. Be sure and add your own.

- Do I have any elevated tumor markers?
- Which tumor markers are elevated?
- What does this mean for me?
- Does the elevation in my tumor marker(s) change my treatment?
- Will you use these markers to evaluate my treatment?
- How often will I be tested?

What's New in Tumor Marker Research?

Because it's important to detect cancer early and to be able to follow it during or after treatment, researchers are looking for new and better tumor markers. But as doctors have learned more about cancer, they've found that the level of a single protein or other substance in the blood may not be the best marker for the disease.

Genomics

Researchers are starting to focus their attention on genetic markers to detect cancer. We know that most cancers have changes in their DNA, the molecules that direct the functions of all cells. By looking for DNA changes in blood, stool, or urine, scientists may be able to find cancers very early. The study of patterns of DNA changes (known as *genomics*) is likely to prove more useful than looking for single DNA changes.

Proteomics

Another newer approach is called *proteomics*. This technique looks at the pattern of all the proteins in the blood (instead of looking at individual protein levels). New testing equipment allows doctors to look at thousands of proteins at one time. It's unlikely that such a test would be used in a doctor's office, but it may help researchers narrow down which protein levels are important in a particular type of cancer. This information could then be used to develop a blood test that might look only at these important proteins.

These new testing methods are still in the early stages of development. Very few are in routine use at this time.

New Developments and Areas of Research for Some Common Cancers

Bladder cancer: Doctors have been looking for ways to detect recurrences of bladder cancer by testing the urine. Looking at DNA in the urine has been very successful so far. In fact, the urine tests can find cancer recurrence before doctors can see it by looking directly into the bladder with cystoscopy.

Breast cancer: Breast cancer cells probably spill into the blood, even in early stages of the disease. Researchers have found abnormal DNA from these cells in the blood of patients with breast cancer. About half of patients with even early stage breast cancer have cancer cells detectable in their blood. Researchers are still trying to determine if the presence of these cells can help predict a person's outlook.

New genetic tests may help determine if women are likely to have a recurrence after initial treatment, and whether they might benefit from additional (adjuvant) hormone therapy or chemotherapy. Tests such as Oncotype DX™ and MammaPrint®, which look at a number of specific genes in a breast tumor sample, are now being used by some doctors for this purpose, and other tests are being studied.

Colorectal cancer: Most colorectal cancers contain changes in genes such as APC, k-ras, and p53. New studies have found abnormal DNA molecules in the stools of people with early colorectal cancer. Testing stool samples for these DNA changes may prove to be an effective way to screen for this disease.

Other studies have found changes in DNA in the blood of patients with early colorectal cancer. Looking at the number of repeated sequences in DNA (known as microsatellite instability) may give doctors clues as to how well treatment might work.

Lung cancer: Studies have found elevated levels of DNA in the blood of patients with lung cancer, while more sensitive tests have been able to detect abnormal DNA in their blood. These abnormal DNA changes have also been found in the sputum of patients with early lung cancer. Doctors think that this may some day be a good way of finding lung cancer early in patients who have a high risk of developing the disease.

Liver cancer: The gene called p53 is often abnormal in liver cancers. Blood tests can find this abnormality in circulating DNA of some patients with this cancer. It's not yet clear how useful this will be.

Melanoma: In patients with advanced melanoma, small numbers of melanoma cells are found circulating in the blood. This may prove to be a good way of finding out how advanced a person's melanoma is and whether it is responding to treatment. Further study is needed.

Oral cavity cancers: Abnormal DNA can be found in saliva samples of people with these cancers. It may be a good way to detect them early in people at high risk or who have been treated for these cancers. Research on this approach is under way.

Ovarian cancer: Several different blood tests are being studied for early detection of this cancer. The most successful appears to be the use of protein patterns in patients' blood. This method, called proteomics, has shown some promising early results in detecting cancer in women with the earliest stages of the disease. Larger studies confirming these results are still needed before it becomes a widely accepted

screening test.

The use of CA 125, combined with imaging tests such as ultrasound, as a screening test for ovarian cancer is still being studied.

Prostate cancer: There is a major clinical trial in progress to determine the value of PSA screening for prostate cancer. There are also newer versions of this test that look specifically at certain fractions of PSA, such as free PSA or complexed PSA, which may give more useful information. Doctors are also studying the usefulness of watching the change in PSA levels over time, as opposed to focusing on a single test result.

There are also attempts to look at protein patterns within the blood as a way of detecting the disease in the early stages. Other new tests are looking at particular proteins or genes to try to determine which prostate cancers are likely to be aggressive (and therefore require treatment) and which are likely to grow more slowly (and therefore can probably just be watched carefully).

Most of these new methods of detecting cancer are still in the experimental stage. Many studies are in progress to try to determine how useful they will be.

Additional Resources

More Information From Your American Cancer Society

The following related information may also be helpful to you. These materials may be ordered from our toll-free number, 1-800-ACS-2345.

After Diagnosis: A Guide for Patients and Families (also available in Spanish)

[American Cancer Society Guidelines for the Early Detection of Cancer](#) (also available in Spanish)

Questions that People Ask About Cancer (also available in Spanish)

[Signs and Symptoms of Cancer](#) (also available in Spanish)

[Talking With Your Doctor](#) (also available in Spanish)

[Testing Biopsy and Cytology Specimens for Cancer](#)

Understanding Your Lab Test Results

What Is Cancer? (also available in Spanish)

The following information may also be helpful to you. These books may be ordered from our toll-free number, 1-800-ACS-2345 (1-800-227-2345).

American Cancer Society's Complete Guide to Colorectal Cancer
American Cancer Society's Complete Guide to Prostate Cancer
Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery. 2nd ed.

National Organizations and Web Sites*

In addition to the American Cancer Society, other sources of information include:

National Cancer Institute
Telephone: 1-800-4-CANCER
Internet Address: <http://www.cancer.gov>

*Inclusion on this list does not imply endorsement by the American Cancer Society.

No matter who you are, we can help. Contact us anytime, day or night, for information and support. Call us at 1-800-ACS-2345 or visit www.cancer.org.

References

Associated Regional and University Pathologists (ARUP) Laboratories. ARUP's Laboratory Test Directory. Available at: <http://www.aruplab.com/TestDirectory/testdirectory.jsp>. Accessed November 19, 2007.

Bigbee W, Herberman RB. Tumor markers and immunodiagnosis. In: Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Gansler TS, Holland JF, Frei E III, eds. *Cancer Medicine*. 6th ed. Hamilton, Ontario: BC Decker; 2003: 209-220.

Lab Tests Online. Tumor Markers. 2006. Available at: http://labtestsonline.org/understanding/analytes/tumor_markers/glance.html. Accessed November 19, 2007.

Lee P, Pincus MR, McPherson RA. Diagnosis and management of cancer using serologic tumor markers. In: McPherson RA, Pincus MR, eds. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 21st ed. Philadelphia, Pa: Saunders Elsevier; 2007: 1353-1366.

Taken from <http://www.cancer.org>