Tumor Markers

What are tumor markers?

Tumor markers are substances that can be found in the body when cancer is present. Ideally, a tumor marker would always be found in the blood in higher-than-normal amounts, but only when a certain type of cancer is present. In reality, tumor markers are rarely like that.

Some tumor markers are found in blood, but others are found in urine or other body fluids. Still others are found in tumors and other tissues. They may be made by the cancer cells themselves, or by the body in response to cancer or other conditions. Most tumor markers are proteins, but some newer markers are genes or other substances.

There are many different tumor markers. Some are linked only to one type of cancer, while others can be found in many cancers.

To test for a tumor marker, the doctor most often sends a sample of the patient's blood or urine to a lab. Sometimes a piece of the tumor itself is tested for tumor markers.

Tumor markers alone are rarely enough to show that cancer is present; they have many limitations (see the section, "The drawbacks of tumor markers"). Because of this, most doctors use only a few tumor markers. When a doctor looks at the level of a tumor marker, he or she will consider it along with the patient's medical history, physical exam, and other lab tests or imaging tests.

Recently, 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. It's been hard to identify single substances that provide useful information, but doctors are now beginning to look at patterns of genes or proteins in the blood. These new fields of genomics and proteomics are discussed in the section called "What's new in tumor marker research?"

How are tumor markers used?

Tumor markers can be helpful in a number of ways.

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's less likely to have spread and is easier to

treat. The first goal of tumor marker testing was to screen for cancer – to look for cancer in people without symptoms – but very few markers have been shown to be helpful in this way.

A perfect tumor marker would be one that could be used as a cancer screening blood test for all people. The tumor marker would only be found in people with cancer. It would tell doctors the type of cancer, how much cancer there is, and which treatment would work best. At this time no tumor marker tests work like this.

Today, the most widely used tumor marker is the prostate-specific antigen (PSA) blood test. The PSA test is used to screen men for prostate cancer. Men with prostate cancer usually have high PSA levels. But it's not always clear what the test results mean — men without cancer can have high PSA levels, and a normal PSA level does not always mean that no cancer is present. PSA is not a perfect tumor marker. And now, many doctors agree that PSA screening is not right for all men.

Right now, no other tumor marker is used to help screen for cancer in the general population. Some of the markers used now can help find cancer at an early stage, but because of their limitations, they are only checked in people who are known to be at high risk for certain types of cancer.

Diagnosing cancer

Usually, tumor markers can't be used alone to diagnose cancer. In most cases, cancer can only be diagnosed by a biopsy. (This means taking out a piece of the tumor so it can be checked for cancer by looking at the cells under a microscope.) Still, tumor markers can help figure out if cancer is a possibility. And if a cancer is already widespread when it's found, tumor markers can sometimes help figure out where it started.

For instance, let's say a woman has cancer throughout her pelvis and belly (abdomen). A high level of the tumor marker CA 125 will strongly suggest ovarian cancer, even if it isn't clear after surgery that the cancer started in the ovary. This can be important because treatment can then be aimed at ovarian cancer.

Alpha fetoprotein (AFP) is another example of a tumor marker that may be used to help diagnose cancer. The level of AFP can go up with some liver diseases, but when it reaches a certain high level in someone with a liver tumor, doctors can be fairly sure that the tumor is liver cancer (a biopsy will still be needed, though).

Determining the outlook (prognosis) for certain cancers

Some types of cancer grow and spread faster than others. But even within a cancer type, for instance testicular cancer, some cancers grow and spread more quickly or may be more or less responsive to certain treatments. Sometimes the level of a tumor marker can help predict the behavior and outlook for certain cancers. In testicular cancer, very high levels of the tumor markers HCG (human chorionic gonadotropin) or AFP are signs of a more aggressive cancer and a worse outlook for survival. Patients with high levels of these markers may be given more aggressive cancer treatments.

Seeing if certain treatments are likely to work

Certain markers found on cancer cells can be used to help predict if a certain treatment is likely to work. For example, in breast and stomach cancers, if the cells have too much of HER2 protein, drugs such as trastuzumab (Herceptin®) can be helpful in treatment. In cases like these, tumor tissue is checked for HER2 before treatment is started. If the cancer cells have normal amounts of HER2, the drugs won't help.

Seeing how well treatment is working

One of the most important uses for tumor markers is to monitor (watch) patients being treated for cancer, especially advanced cancer. If a certain type of cancer has a tumor marker, the level of the marker may be able to be used to see if the treatment is working, instead of doing other tests like x-rays, CT scans, or bone scans.

If levels of the tumor marker in the blood go down, it's almost always a sign that the treatment is working. On the other hand, if the marker level goes up, this could mean the cancer is not responding and the treatment may need to be changed. (One exception is if the cancer is very sensitive to a certain chemotherapy treatment. In this case, the chemo can cause many cancer cells to die and release large amounts of the marker into the blood, which will raise the level of the tumor marker for a short time.)

Looking for recurrent cancer

Tumor markers are also used to look for cancer that might have come back (recurred) after treatment. Certain tumor markers may be useful once treatment is done and there is no sign of cancer in the body.

For instance, people who have been treated for colorectal cancer often have their blood tested for levels of the tumor marker CEA. This tumor marker is often checked before any treatment (including surgery) is done. If it's high, it will be checked again during and after treatment. It should go down as treatment progresses, and be at a normal level after treatment. Then, the level may be checked as part of follow-up, and if it starts going up again, it may be a sign that the cancer has come back (recurred), even when the person has no symptoms. Often, when a patient's CEA level goes up, their doctor will order imaging tests to see if a new tumor can be found early.

When are tumor markers checked?

Whether or not tumor markers are checked regularly depends on the type of cancer a person has and what kind of tumor marker is being measured.

Tumor markers that are measured **in the blood or other body fluids** may be tested at diagnosis; before, during, and after treatment; and then regularly for many years to see if the cancer has come back. During treatment, changes in tumor marker levels can be a sign of whether treatment is working.

Tumor marker levels of this type can change over time. The changes are important, which is why results of a series of level tests often mean more than a single result. If at all possible it's best to

compare results from tests done at the same lab, and always be sure that the results are of the same value, such as ng/mL (nanograms per milliliter) or U/mL (units/milliliter).

Testing of the tumor markers **on the cancer itself** is often done only at diagnosis. Unless the cancer comes back or doesn't go away, there may nothing left to measure after treatment.

The drawbacks of tumor markers

Early on in the search for tumor markers, the hope was that someday all cancers could be detected early with a blood test. A simple blood test that could find cancers in their earliest stages could prevent the deaths of millions of people. But very few tumor markers are useful for finding cancer at an early stage. There are a few reasons for this:

- Almost everyone has a small amount of these markers in their blood, so it's very hard to spot early cancers by using these tests.
- The levels of these markers tend to get higher than normal only when there's a large amount of cancer present.
- Some people with cancer never have high tumor marker levels.
- Even when levels of these markers are high, it doesn't always mean cancer is present. For example, the level of the tumor marker CA 125 can be high in women with gynecologic conditions other than ovarian cancer.
- Because cancer is many different diseases, no single tumor marker can be used to look for all types of cancer.

These are the reasons why, today, tumor markers are used mainly in patients who have already been diagnosed with cancer to watch their response to treatment or look for the return of cancer after treatment.

Specific tumor markers

The tumor markers listed here are available to most doctors and have reliable scientific information showing that they are useful.

This section lists 2 kinds of tumor marker tests:

- Tumor markers found in blood or urine
- Tumor markers found on the cancer itself (in tissue samples or biopsies of the cancer)

The cancers described in these brief summaries are those for which the marker is usually tested. These marker levels may be increased in other kinds of cancer, too. And though we may list the less common cancer types that may affect certain tumor marker levels, in many cases it's not yet clear how helpful those tumor markers may be for those cancers.

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 done. The values listed here are average values.

Most labs will list their own “reference ranges” along with any test results you get. If you are tested for a tumor marker, be sure to ask the doctor what your test results mean.

If you would like information on a specific type of cancer mentioned in connection with a tumor marker, go to our website and choose the cancer type from the drop-down menu Select a Cancer Type. You can also call us and ask for the cancer document.

Tumor markers found in blood or urine

These are markers that are often watched over time after a person is found to have a particular type of cancer linked to that marker. Sometimes, they might be used on a one-time basis to confirm a diagnosis.

Alpha-fetoprotein (AFP)

AFP can help diagnose and guide the treatment of liver cancer (hepatocellular carcinoma). Normal levels of AFP are usually less than 10 ng/mL (nanograms per milliliter). AFP levels are higher in most patients with liver cancer. AFP is also high in acute and chronic hepatitis, but it seldom gets above 100 ng/mL in these diseases.

In someone with a liver tumor, an AFP level over a certain value can mean that the person has liver cancer. In people without liver problems, that value is 400 ng/mL. But a person with chronic hepatitis often has high AFP levels. For them, AFP levels over 4,000 ng/mL are a sign of liver cancer.

AFP is also useful in following the response to treatment for liver cancer. If the cancer is completely removed with surgery, the AFP level should go down to normal. If the level goes up again, it often means that the cancer has come back.

AFP is also higher in certain germ cell tumors. Germ cells are cells that give rise to sperm and eggs (ova). Most are in the ovaries or testicles, but germ cells often remain in other parts of the body. Germ cell tumors with high AFP levels include some testicular cancers (those containing embryonal cell and endodermal sinus types), certain rare types of ovarian cancer (yolk sac tumor or mixed germ cell cancer), and some germ cell tumors that start in the middle of the chest (mediastinal germ cell tumors). AFP is used to monitor the response to treatment, since high levels should go down when treatment works. If the cancer has gone away with treatment, the level should go back to normal. After that, any increase can be a sign that the cancer has come back.BCR-ABL

Chronic myeloid leukemia (CML) cancer cells contain an abnormal gene called *BCR-ABL*. A test called *PCR* can find this gene in very small amounts in blood or bone marrow. In someone with blood and bone marrow changes that look like those seen with CML, finding the gene confirms the diagnosis. Also, the level of the gene can be measured and used to guide treatment.

Beta-2-microglobulin (B2M)

B2M blood levels are high in multiple myeloma, chronic lymphocytic leukemia (CLL), and some lymphomas (including Waldenstrom macroglobulinemia). Levels may also be higher in some non-cancerous conditions, such as kidney disease and hepatitis. Normal levels are usually below 2.5 mg/L (milligrams per liter). B2M is useful in helping predict the long-term outlook (prognosis) in

some of these cancers. Patients with higher levels of B2M usually have poorer outcomes. B2M is also checked during treatment of multiple myeloma and Waldenstrom macroglobulinemia to see how well the treatment is working.

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 can be a sign of some non-cancerous conditions, too, such as kidney stones or urinary tract infections.

The results of the test are reported as either positive (BTA is present) or negative (BTA is not present). It's sometimes used along with NMP22 (see below) to test patients for the return (recurrence) of bladder cancer.

This test is not used often. It's not as good as cystoscopy (looking into the bladder through a thin, lighted tube) for finding bladder cancer, but it may let doctors do fewer cystoscopies during bladder cancer follow-up. At this time, most experts still consider cystoscopy the best way to diagnose and follow-up bladder cancer.

CA 15-3

CA 15-3 is mainly used to watch patients with breast cancer. High 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 if treatment is working, but they may go up in the first few weeks after treatment is started. (This rise is caused when dying cancer cells spill their contents into the bloodstream.)

The normal level is usually less than 30 U/mL (units/milliliter), depending on the lab. But levels as high as 100 U/mL can be seen in women who do not have cancer. Levels of this marker can also be higher in other cancers, like lung, colon, pancreas, and ovarian, and in some non-cancerous conditions, like benign breast conditions, ovarian disease, endometriosis, and hepatitis.

CA 19-9

The CA 19-9 test was first developed to detect colorectal cancer, but it's most often used in people with pancreatic cancer. In very early cancer the level is often normal, so it's not a good screening test. Still, it's the best tumor marker for following patients who have 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 be used to watch bladder cancer and see how aggressive it is. It may also be used to watch colorectal cancer, but the CEA test is preferred for this type of cancer.

CA 19-9 can be high in other forms of digestive tract cancer, especially cancers of the stomach and bile ducts. It can also be high in some non-cancerous conditions such as thyroid disease, rheumatoid arthritis, inflammatory bowel disease, and pancreatitis (inflammation of the pancreas).

CA 27-29

CA 27-29 is another marker that can be used to follow patients with breast cancer during or after treatment. This test measures the same marker in the blood as the CA 15-3 test, but in a different way. Although it's a newer test than CA 15-3, it's not any better in detecting either early or advanced disease. And it's not high in all people with breast cancer.

The normal level is usually less than 40 U/mL (units/milliliter), depending on the testing lab. This marker can be high in other cancers, too, such as cancers in the colon, stomach, kidney, lung, ovary, pancreas, uterus, and liver. It may also be higher than normal in some non-cancerous conditions, for instance, in women in the first trimester of pregnancy; and in people with endometriosis, ovarian cysts, non-cancerous breast disease, kidney stones, and liver disease.

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), as well as fallopian tube cancer and primary peritoneal cancer.

Normal blood levels are usually less than 35 U/mL (units/milliliter). More than 90% of women with advanced ovarian cancer have high levels of CA 125. If the CA-125 level is high when the woman is first diagnosed, changes in the CA-125 level can be used during treatment to get an idea of how well it's working.

Levels are also high in about half of women whose cancer has not spread outside the ovary. Because of this, CA 125 has been studied as a screening test. But the trouble with using it as a screening test is that it would still miss many early cancers, and problems other than ovarian cancer can cause a high CA-125 level. For example, it's often higher in women with uterine fibroids or endometriosis. It can also be higher in men and women with lung, pancreatic, breast, liver, and colon cancer, and in people who have had cancer before. Because ovarian cancer is a rather rare disease, a high level of CA-125 is more likely to be caused by something other than ovarian cancer.

Some women with uterine (endometrial) cancer also have high levels of CA-125. If CA-125 levels are increased, it can be used to see how well the treatment is working.

Calcitonin

Calcitonin is a hormone produced by cells called *parafollicular C cells* in the thyroid gland. It normally helps regulate blood calcium levels. Normal calcitonin levels are below 5 to 12 pg/ml (picograms per milliliter). In medullary thyroid carcinoma (MTC), a rare cancer that starts in the parafollicular C cells, blood levels of this hormone are often greater than 100 pg/ml.

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 known to be at risk.

Other cancers, like lung cancers and leukemias, can also raise calcitonin levels, but usually calcitonin blood tests are not used for detecting these cancers.

Carcinoembryonic antigen (CEA)

CEA is not used to diagnose or screen for colorectal cancer, but it's the preferred tumor marker to help predict outlook in patients with colorectal cancer.

The normal range of blood levels varies from lab to lab, and smokers often have higher levels. But even in smokers, levels higher than 5.5 ng/mL (nanograms per milliliter) are not normal. The higher the CEA level at the time colorectal cancer is detected, the more likely it is that the cancer is advanced.

CEA is also the standard marker used to follow patients with colorectal cancer during and after treatment. In this way CEA levels are used to see if the cancer is responding to treatment or if it has come back (recurred) after treatment.

CEA also may be used for lung and breast cancer patients. This marker can be high in some other cancers, too, like melanoma, lymphoma, thyroid, pancreas, liver, stomach, kidney, prostate, ovary, cervix, and bladder cancer. If the CEA level is high at diagnosis, it can be used to follow the response to treatment. CEA levels can also be high in some non-cancerous diseases, like hepatitis, chronic obstructive pulmonary disease (COPD), colitis, rheumatoid arthritis, and pancreatitis, and in smokers who are otherwise healthy.

Chromogranin A

Chromogranin A (CgA) is made by neuroendocrine tumors. These are tumors which come from cells that release hormones into the blood when they get certain nerve signals. These include carcinoid tumors, neuroblastoma, and small cell lung cancer. The blood level of CgA is often high in people with these diseases.

It's probably the most sensitive tumor marker for carcinoid tumors. But still, it's only abnormal in 1 out of 3 people with localized disease and 2 out of 3 of those with cancer that has spread (metastatic cancer). Levels can also be high in some advanced forms of prostate cancer. It's hard to define the normal level for CgA because there are different ways to test for this marker and each has its own normal value.

Taking drugs called *proton-pump inhibitors* (such as omeprazole and lansoprazole) to reduce stomach acid can raise CgA levels in healthy people. Be sure your doctor knows what drugs you are taking before this lab test is done. HE-4

Some ovarian cancers have too much of a gene called *HE-4*, and make more of a protein called *HE-4* (or *HE4*). Levels of this protein can be measured in the blood and can be used like CA 125 to guide ovarian cancer treatment. This test is most often used in patients who have normal CA 125 levels. HE-4 levels can go up in some benign conditions as well as with some other cancers, so it's not used as a screening test.

Human chorionic gonadotropin (HCG)

HCG (also known as *beta-HCG* or *β-HCG*) blood levels are high in patients with some types of germ cell tumors. (Germ cells give rise to sperm and ova. Most are in the ovaries or testicles, but germ cells often appear in other parts of the body.) HCG is high in some testicular and ovarian cancers and in gestational trophoblastic disease, mainly choriocarcinoma. It's also higher in some people with mediastinal germ cell tumors — cancers in the middle of the chest (the mediastinum)

that start in the same cells as germ cell tumors of the testicles and ovaries. Levels of HCG can be used to help diagnose these conditions and can be watched over time to see how well treatment is working. They can also be used to look for cancer that has come back after treatment has ended (recurrence).

A high blood level of HCG will also raise suspicions of cancer in certain situations. For example, in a woman who still has a large uterus after pregnancy has ended, a high blood level of HCG might be a sign of a cancer. This is also true of men with an enlarged testicle or anyone with a tumor in their chest.

It's hard to define the HCG normal level because there are different ways to test for this marker and each has its own normal value.

Immunoglobulins

Immunoglobulins are not classic tumor markers but instead are antibodies, which are blood proteins normally made by immune system cells to help fight germs. There are many types of immunoglobulins, with names like IgA, IgG, IgD, and IgM. One test that can be done called *quantitative immunoglobulins* measures the amount of each type of immunoglobulin (like IgA, IgG, etc). This test can tell if you have too much or too little of one type of immunoglobulin. Bone marrow cancers such as multiple myeloma and Waldenstrom macroglobulinemia often cause a person to have too much of one type of immunoglobulin in the blood. Sometimes having a high level of one type of immunoglobulin (from one of these diseases) leads to a high level of immunoglobulin overall. The blood test that measures the overall level of immunoglobulin is just called the *globulin level*.

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 just one certain immunoglobulin (called a *monoclonal* immunoglobulin). This can be seen on a serum protein electrophoresis (also called SPEP) test. In this test, the blood proteins are separated by an electrical current. With myeloma or macroglobulinemia, the high amount of the one immunoglobulin forms a "spike" on the SPEP. This is often called the *M spike*, *monoclonal protein*, or *M protein*. The level of the spike is important because some people may show low levels of a spike without having myeloma or macroglobulinemia. The diagnosis of multiple myeloma or Waldenstrom macroglobulinemia must be confirmed by a biopsy of the bone marrow.

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

Free light chains

Immunoglobulins are made up of protein chains: 2 long (heavy) chains and 2 shorter (light) chains. Sometimes in multiple myeloma an M protein can't be found, but the level of the *light chain* part in the blood is high, instead. This level can be measured with a blood test called *free light chains*, and can be used to help guide treatment.

When light chains are found in the urine, it's called *Bence Jones protein*. To test for this, the patient must collect all urine for a full 24 hours to send to the lab. These results can be followed over time to help guide treatment.

Inhibin

A rare type of ovarian cancer, called an ovarian stromal cancer, can raise the blood levels of a substance called *inhibin*. The doctor can check for inhibin in the blood to help make the diagnosis of stromal cancer and to keep an eye on the cancer in case it comes back.

Lactate dehydrogenase (LDH)

LDH is used as a tumor marker for testicular cancer and other germ cell tumors. (Germ cells give rise to sperm cells or ova, but they are found in a number of places in the body beyond ovaries and testicles.) It's not as useful as AFP and HCG for diagnosis because the blood level goes up with many other things besides cancer, including blood and liver problems. LDH is mainly used to detect tissue damage in the body such as muscle injury, heart attack, stroke, and other conditions.

Still, high levels of LDH predict a poorer outlook for survival. LDH levels are also used to monitor the effect of germ cell cancer treatment and to watch for recurrent disease. LDH may be used for other cancers, too, including lymphoma, melanoma, and neuroblastoma.

Neuron-specific enolase (NSE)

NSE, like chromogranin A, is a marker for neuroendocrine tumors such as small cell lung cancer, neuroblastomas, and carcinoid tumors. (Neuroendocrine tumors grow from cells that release hormones into the blood when they get certain nerve signals.) NSE is not used as a screening test.

This blood test is most useful in following up patients with small cell lung cancer or neuroblastoma. (Chromogranin A seems to be a better marker for carcinoid tumors.) High levels of NSE may also be found in medullary thyroid cancer, melanoma, and pancreatic endocrine tumors. Levels higher than 9 ug/L (micrograms per milliliter) are usually considered abnormal, but this varies with the lab doing the test.

NMP22

NMP22 is a protein found in the nucleus (control center) of cells. Levels of NMP22 are often high (more than 10 U/mL or units/milliliter) in the urine of people with bladder cancer.

This test is not widely used at this time. So far it hasn't been found to be sensitive enough to be used as a screening tool. It's most often used to look for bladder cancer that has come back after treatment. It's a less invasive way to look for cancer than cystoscopy (looking into the bladder with a thin, lighted tube), but it's not always as accurate. NMP22 testing can't take the place of cystoscopy completely, but it might allow doctors to do cystoscopies less often. NMP22 levels can also be high in some non-cancerous conditions or in people who have had recent chemo treatment.

Prostate-specific antigen (PSA)

PSA is a tumor marker for prostate cancer. PSA is a protein made by cells of the prostate gland, which is found only in men. It's the only marker used to screen for a common type of cancer, but most medical groups do not recommend using it routinely to screen all men. (The American Cancer Society recommends that men talk to a doctor and make informed decisions about testing.)

The PSA blood level can be high in prostate cancer, but PSA levels can be affected by other things, 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 infected or inflamed prostates. It can also be high for a day or 2 after ejaculation.

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. Levels higher than 10 ng/mL mean cancer is likely. The area between 4 and 10 is a gray zone. Men with PSA levels in this borderline range have about a 1 in 4 chance of having prostate cancer. A doctor may recommend a prostate biopsy (getting samples of prostate tissue to look for cancer) for a man whose PSA level is above 4 ng/mL.

Not all doctors agree with these cutoff points. This is because some men with prostate cancer do not have a high PSA, while some others with a borderline or high level will not have cancer.

Some doctors believe it's more useful to follow the PSA level over time because an increase from one year to the next might 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 in the borderline range (between 4 and 10 ng/mL) is measurement of the *free PSA* (also *percent-free PSA* or fPSA). PSA is in the blood in 2 forms—some is bound to a protein and some is not (free). The fPSA is the ratio of how much PSA circulates free compared to the total PSA level. A lower fPSA means that the likelihood of having prostate cancer is higher and a biopsy should probably be done. Many doctors recommend biopsies for men whose fPSA is 10% or less, and advise men to think about a biopsy if it's between 10% and 25%. Using these cutoffs detects most cancers and helps some men avoid unnecessary prostate biopsies. This test is widely used, but not all doctors agree that 25% is the best cutoff point to decide on a biopsy, and the cutoff may change depending on PSA level.

The PSA test is very valuable in monitoring the response to treatment and in the follow-up of men with prostate cancer. In men who have been treated with surgery meant to cure the disease, the PSA should fall to an undetectable level. The PSA should also go down after treatment with radiation therapy (although it doesn't go away completely). A rise in the PSA level may be a sign the cancer is coming back.

Prostatic acid phosphatase (PAP)

PAP (not to be confused with the Pap test for women) is another blood test for prostate cancer. It was used before the PSA test was developed but is seldom used now because the PSA test is better. It may also be used to help diagnose multiple myeloma and lung cancer.

S-100

S-100 is a protein found in most melanoma cells. Some studies have shown that blood levels of S-100 are high in most patients with melanoma that has spread to other parts of the body. So, this test is sometimes used to look for melanoma spread before, during, or after treatment. Tissue samples (biopsies) of suspected melanomas also may be tested for this marker to help in diagnosis.

Soluble mesothelin-related peptides (SMRP)

This blood test is sometimes used along with imaging tests to watch a rare type of lung cancer called *mesothelioma*. It may also be used to see if mesothelioma has come back (recurred) after treatment.

Researchers are looking at whether SMRP can be used as a screening tool in people at high risk for mesothelioma.

Thyroglobulin

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

Thyroglobulin levels in the blood should fall to undetectable levels after treatment for thyroid cancer, unless part of thyroid gland was left after surgery. A rise in the thyroglobulin level after treatment can mean the cancer has come back (recurred). In people with thyroid cancer that has spread, thyroglobulin levels can be followed over time to watch the results of treatment.

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

Tumor markers found on the cancer itself

These tumor markers are usually checked at diagnosis, or shortly after a biopsy confirms cancer. This type of test requires a tissue sample that includes cancer cells, which is usually harder to get than blood or urine. Since cancer cells themselves are being tested, it's typically a one-time test result. The information is often used to further identify the cancer or to help choose a treatment.

Anaplastic lymphoma kinase (ALK)

Some lung cancers have changes in the *ALK* gene that cause the cancer cell to make a protein that leads to out-of-control growth. Tumor tissues can be tested for this gene change. If it's found, the patient can be treated with a drug that targets the abnormal protein, like crizotinib (Xalkori®).

BRAF

Defects (mutations) in the *BRAF* gene can be found in melanoma, thyroid cancer, and colorectal cancer. About half of melanomas have a *BRAF* mutation, most often the one called *BRAF* V600. This mutation causes the gene to make an altered BRAF protein that signals melanoma cells to grow and divide. This mutation can be tested for in tumor tissue. If it's found, the patient can be treated with a drug that targets the altered BRAF protein, such as vemurafenib (Zelboraf®).

Colorectal cancers that have BRAF mutations aren't helped by drugs that target the epidermal growth factor receptors (see below). Doctors typically check tumor tissue to be sure it doesn't have BRAF mutations before starting patients on these drugs.

Some melanomas have different *BRAF* mutations. These melanomas can be treated with a different targeted drug.

BRAF mutations have also been found in some other cancers, including thyroid cancer and lung cancer. So far, though, drugs targeting *BRAF* mutations are not used to treat these diseases.

Epidermal growth factor receptor (EGFR)

This protein, also known as *HER1*, is a receptor found on cells that helps them grow. Tests done on a piece of the cancer tissue can look for increased amounts of these receptors, which is a sign that the cancer may grow fast, spread quickly, and be harder to treat. Patients with elevated EGFR may have poorer outcomes and need more aggressive treatment, particularly with drugs that block (or inhibit) the EGFR receptors.

EGFR may be used to guide treatment and predict outcomes of non-small cell lung, head and neck, colon, pancreas, or breast cancers. The results are reported as a percentage based on the number of cells tested.

Some lung cancers have certain defects (mutations) in the *EGFR* gene that make it more likely that certain drugs will work against the cancer. These gene changes are more common in lung cancer patients who are women, non-smokers, or Asian.

HER2 (or HER2/neu, erbB-2, or EGFR2)

HER2 is a protein that tells some cancer cells to grow. It's present in larger than normal amounts on the surface of breast cancer cells in about 1 out of 5 people with breast cancer. Higher-than-normal levels can be found in some other cancers, too, such as some stomach and esophageal cancers. HER2 is usually found by testing a sample of the cancer tissue itself. Cancers that are HER2-positive tend to grow and spread faster than other cancers.

All newly diagnosed breast cancers and advanced stomach cancers should be tested for HER2. HER2-positive cancers are more likely to respond to drugs that work against the HER2 receptor on cancer cells.

Hormone receptors

Breast tumor samples from all people with breast cancer are tested for estrogen and progesterone receptors. These 2 hormones often fuel the growth of breast cancer cells. Breast cancers that contain estrogen receptors are often called *ER-positive*; those with progesterone receptors are *PR-positive*. About 2 out of 3 breast cancers test positive for at least one of these markers. Hormone receptor-positive breast cancers tend to grow more slowly and may have a better outlook than cancers without these receptors. Cancers that have these receptors can be treated with hormone therapy such as tamoxifen or aromatase inhibitors.

Some gynecologic tumors, such as endometrial cancers and endometrial stromal sarcomas, are also checked for hormone receptors to see if they can be treated with hormone therapy drugs.

KRAS

Cetuximab (Erbitux®) and panitumumab (Vectibix®) are two drugs that target the EGFR protein and can be useful in the treatment of advanced colorectal cancer. But these drugs don't work in

colorectal cancers that have mutations (defects) in the *KRAS* gene. Doctors now commonly test the tumor for this gene change and only use these drugs in people whose cancers do not have the mutation.

KRAS mutations can also help guide treatment for some types of lung cancer. For instance, tumors with the mutations do not respond to treatment with drugs erlotinib (Tarceva®) or gefitinib (Iressa®). Doctors are looking at how KRAS may be used in many other types of cancer, too.

S-100

S-100 is a protein found in most melanoma cells. Tissue samples (biopsies) of suspected melanomas may be tested for this marker to help in diagnosis. Sometimes, a blood test that detects S-100 is used to look for melanoma spread before, during, or after treatment.

Other tumor marker tests: commercial labs and research studies

Tests for many other tumor markers are available through commercial testing labs, but these are seldom used.

Some of these tests may even be advertised as being better than the more common markers, but this hasn't yet been shown in scientific studies. In some of these cases, the tests have been taken off the market at the request of the Food and Drug Administration (FDA). Still, there are tests available for many types of cancer that have not yet been proven to work.

Researchers use other tumor markers that 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.

What should you ask your doctor about tumor markers?

It's 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 minor it might seem to you. Here are some questions you might ask. Be sure and add your own.

- Have you checked for any tumor markers, or do you plan to do so?
- Do I have any tumor markers that are higher than normal?
- Which tumor marker levels are high?
- What does this mean for me?
- Are there other health problems or medicines that could affect my tumor marker levels?
- Will my tumor marker level change my treatment?
- Will you use these markers to evaluate my treatment? If so, what will you watch for?
- How often will the tumor markers be checked?

Please contact us if you'd like to learn more about a certain type of cancer or the tumor markers linked to a certain type of cancer.

What's new in tumor marker research?

Because it's important to find cancer early and 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 is often not the best marker for the disease. They're still looking for better ways to find and follow people with different types of cancer.

Genomics

The study of patterns of DNA changes (or mutations) is called *genomics*. We know that most cancers have changes in their DNA, the molecules that direct the functions of all cells. It's these changes that turn a normal cell into a cancer cell. By looking for DNA changes in blood, stool, or urine, scientists may be able to find cancers very early. Looking at the patterns of changes is likely to prove more useful than looking for single DNA changes.

Proteomics

Another newer approach is called *proteomics*. This technology looks at the patterns of all the proteins in the blood instead of looking at individual protein levels. With new testing equipment doctors can 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 certain type of cancer. This information could then be used to develop a blood test that might look only at these important proteins. Then, blood or a tissue sample could be checked for the protein pattern as a way to find cancer.

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

To learn more

More information from your American Cancer Society

Here is more information you might find helpful. You also can order free copies of our documents from our toll-free number, 1-800-227-2345, or read them on our website, www.cancer.org.

Early detection and cancer basics

What Is Cancer? (also in Spanish)

American Cancer Society Guidelines for the Early Detection of Cancer (also in Spanish)

Signs and Symptoms of Cancer (also in Spanish)

Finding out about cancer

Talking With Your Doctor (also in Spanish)

Testing Biopsy and Cytology Specimens for Cancer

Cancer Information on the Internet

Your American Cancer Society has detailed information on most types of cancer. Choose any cancer type under Select a Cancer Type to learn more about common cancers.

Your American Cancer Society also has books that you might find helpful. Call us at 1-800-227-2345 or visit our bookstore online at www.cancer.org/cancer/bookstore to find out about costs or to place an order.

National organizations and websites*

Along with the American Cancer Society, other sources of information include:

American Society of Clinical Oncology (ASCO)
Website: www.cancer.net

> Free oncologist-approved cancer information to help you make the best possible health care decisions.

National Cancer Institute
Toll-free number: 1-800-422-6237 (1-800-4-CANCER)
TTY: 1-800-332-8615
Website: www.cancer.gov

> Accurate, up-to-date information about cancer for patients, their families, and the general public.

**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 cancer-related information and support. Call us at **1-800-227-2345** or visit www.cancer.org.

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