

Tumour markers

Tumour markers are substances that are made by cancer cells or by normal cells in response to cancer. Most people have these substances at a low level in their blood, but the amount of each marker can increase, sometimes a lot, when there is cancer in the body. Some tumour markers are specific to one type of cancer, while others may be present in many different types of cancer.

Why tumour marker tests are done

Tumour marker tests are done to:

- look for cancer in people who have a strong family history of a particular cancer but don't have symptoms (screening)
- diagnose cancer
- see how far the cancer has spread (staging)
- predict how aggressive the cancer is likely to be
- predict what treatment the cancer is likely to respond to
- predict how likely it is that the cancer will come back (recur) after treatment
- find out if cancer treatment is working or see if cancer has come back after treatment

What the results mean

A tumour marker test on its own is not enough to screen for or diagnose cancer. Tumour marker test results should be combined with:

- a thorough medical history
- a physical exam
- other lab tests
- imaging tests

If a tumour marker test is being used to monitor how treatment is working, your test results may be compared to results from before the start of treatment.

If tumour marker levels decrease or return to normal, it may mean that treatment is working, especially if levels were increased before treatment.

An increase in tumour marker levels may mean the cancer is not responding to treatment, is growing or has come back (recurred). A slight increase may not be significant. The doctor looks at trends in the increase over time.

Chemotherapy treatment can cause a temporary increase in tumour marker levels. This happens because chemotherapy causes cancer cells to die quickly and release large amounts of the tumour marker.

What happens if the results are abnormal?

Your doctor may recommend more tests, procedures, follow-up care or treatment.

Limitations of tumour markers

There are limitations to tumour markers. Other tests are usually needed to diagnose cancer or find out if cancer has come back after treatment. Some limitations of tumour markers include:

- A non-cancerous disease or condition can increase tumour marker levels. Some tumour markers can be high in people who do not have cancer.
- Some tumour markers are specific to a particular type of cancer, while others may be elevated in many types of cancer.
- Tumour marker levels may not rise until the cancer worsens. This is not helpful for finding cancer early or finding out if cancer has come back after treatment.
- Some cancers do not have known tumour markers.
- Some people do not have higher tumour marker levels even if the type of cancer they have usually makes tumour markers.

There are many different types of tumour markers, including:

Alpha-fetoprotein (AFP) (normal 0-6 KIU/L, 1-day turnaround, blood test)

AFP is an ancient but excellent tumour marker, whose specificity in primary liver cancer is very high, with the positive rate of 70%. If a patient has a history of hepatitis B, and has liver mass, with AFP > 400ng / ml and for 1 month, he can be diagnosed as liver cancer. In addition to liver cancer, AFP will also be elevated in endodermal sinus cancer, teratoma, testicular cancer, ovarian cancer, gastric cancer with liver metastases. The vast majority of viral hepatitis/cirrhosis patients will also see AFP increase, but it will not over 400ng / ml. Women AFP begin to rise after pregnancy for 3 months and reach the peak during 7 to 8 months, and 3 weeks after delivery it'll return to normal level.

Alpha-fetoprotein (AFP) is a protein normally made by the liver and yolk sac of a developing baby. AFP levels go down soon after birth. It is not normally found in healthy adults.

Why an AFP test is done

Your doctor may order an AFP test to help diagnose, monitor response to treatment and check for recurrence of the following cancers:

- a type of testicular cancer called non-seminoma germ cell tumour
- a type of ovarian cancer called germ cell tumour

In rare cases an AFP test may be used to help diagnose the following cancers:

- bile duct
- liver
- colon
- stomach
- lung
- breast
- lymphoma
- pancreas

Carbohydrate antigen 125 (CA125) (normal 0-35 U/mL, 1-day turnaround, blood test)

The most important clinical significance of CA125 is to reflect the ovarian cancer, with positive rate of 61.4%, and CA125 is a good indicator of the treatment efficacy and recurrence of ovarian cancer. If the treatment is effective, the CA125 will decline, and once recurrence occurs, CA125 will be elevated before the symptoms.

CA125 is a protein found on most ovarian cancer cells that is secreted into the blood stream and can be measured. CA125 can also be found on other normal and cancerous cells in the body.

What the results mean

An increased CA125 value can occur in both cancers and non-cancerous conditions.

Cancers

The CA125 blood levels can be increased in ovarian cancer and other cancers including:

- uterine
- fallopian tube
- pancreatic
- breast
- colorectal
- lung
- stomach

CA125 is, to date, the best-known test for ovarian cancer diagnosis. It is the serum marker most widely used to monitor therapeutic response, and to detect disease or disease recurrence in patients treated for epithelial ovarian cancer. However, only about 85% of all women with ovarian cancer have raised CA125, only 50% of women with early stage ovarian cancer have raised CA125, approximately 20% of ovarian cancers lack expression of CA125, and women with other, or benign, conditions can also have raised CA125 levels.

Human epididymis protein 4 (HE4) (normal <150pM, 1-day turnaround, blood test)

HE4 is a new marker for ovarian carcinoma, which is over-expressed in patients with ovarian, and some other cancers. Normal ovarian tissue has minimal production of HE4. When combined with CA125, HE4 significantly raises the level of sensitivity for the detection of ovarian cancer. HE4 is consistently expressed in patients with ovarian cancer and has demonstrated an increased sensitivity and specificity over that of CA125 alone.

A Risk of Ovarian Malignancy Algorithm (ROMA) classifies patients as being at low or high risk for malignant disease using both the CA125 and HE4 results and a woman's menopausal status. This risk is given as an adjunct to the test results for both CA125 and HE4. ROMA calculates a risk of finding ovarian cancer during surgery. ROMA classifies patients as being at low or high risk for malignant disease.

HE4 complements CA125 measurement in patients with ovarian cancer by providing improved sensitivity at fixed levels of specificity. This enhancement in sensitivity has been used to develop the ROMA algorithm that helps triage of women with adnexal mass to appropriate clinical/surgical management.

Pre-menopausal	ROMA* %	High Risk > 13.1% for pre-menopausal
Post-menopausal	ROMA %	High Risk > 27.7% for post-menopausal

Carbohydrate antigen 15-3 (CA153) test (normal <30 U/mL, 1-day turnaround, blood test)

CA15-3 has great clinical significance in the diagnosis of breast cancer. In the early stage of breast cancer, the sensitivity is low, 30%, but in the late stage, the sensitivity is up to 80%, which has important value in the efficacy, prognosis, recurrence and metastasis diagnosis of breast cancer. Other malignant tumours also have a certain positive rate, and in the liver, gastrointestinal tract, lung, breast, ovarian and other non-malignant tumour disease, the positive rate of less than 10%.

Cancer antigen 15-3 (CA15-3) is a protein made by a variety of cells, particularly breast cancer cells. The protein moves into the blood, where it can be measured.

CA15-3 levels are higher than normal in most women with breast cancer that has spread to other parts of the body (called metastatic breast cancer). Not all types of breast cancer will cause CA 15-3 levels to rise, as some types of cancer cells don't over-produce the antigen.

Why a CA15-3 test is done

CA15-3 is a tumour marker. It is used to check how breast cancer treatment is working and look for cancer that has come back, or recurred, after treatment.

If you are diagnosed with breast cancer that has spread to other parts of the body, or metastasized, you may have this test, along with other tests such as hormone receptor testing and HER2 status testing.

CA15-3 is not measured for early stage breast cancer because the levels of this protein are rarely higher than normal at this stage.

CA15-3 may be higher than normal in cancer of the lung, pancreas, ovary and prostate, but these levels are not as high as with breast cancer.

Non-cancerous conditions that increase CA 15-3 include endometriosis, pelvic inflammatory disease and liver disease. It can also be increased during pregnancy. With these conditions, CA15-3 levels usually only go so high. They don't usually keep climbing over time.

Carbohydrate antigen 19-9 (CA199) (normal 0-27 KIU/L, 1-day turnaround, blood test)

CA19-9 is an important indicator of digestive system tumours. In pancreatic cancer, gallbladder carcinoma and cholangiocarcinoma, CA19-9 is significantly increased, especially in pancreatic cancer the positive rate is 75%.

CA19-9 is the common term for carbohydrate antigen sialyl Lewis a. It is a protein found on the surface of certain cancer cells. It may be found in the blood when it is shed by cancer cells.

CA19-9 is commonly used as a tumour marker for some types of cancer of the pancreas. But this test cannot be used by itself to find pancreatic or other cancers because:

- CA19-9 is also found in healthy adults in small amounts in the pancreas, liver, gallbladder and lungs.
- About 5% of people do not produce CA19-9, so this test cannot be used for them.
- The blood levels of this antigen may also be at a higher than normal level in healthy people and in people with non-cancerous conditions such as pancreatitis or bile duct obstruction.

Non-cancerous conditions include:

- liver diseases, such as cirrhosis or hepatitis
- inflammation of the gallbladder (cholecystitis) or gallstones
- inflammation of the pancreas (pancreatitis)
- cystic fibrosis
- some disorders of the lung, kidney or gastrointestinal tract
-

Types of cancer include:

- some types of pancreatic cancer
- colorectal
- stomach
- liver
- bile duct
- lung
- breast
- uterine
- ovarian

The highest levels of this antigen are most commonly seen in people with advanced pancreatic cancer. CA19-9 is not usually high in people with very early stages of the disease.

If CA19-9 levels have been higher than normal, a decrease in CA19-9 or a return to normal values may mean that the cancer is responding well to treatment. An increase may mean that the cancer is not responding well to treatment, is still growing or is coming back. A slight increase may not be important. The doctor compares the levels over time.

Carbohydrate antigen 50 (CA50) (normal <25 u/mL, 7-day turnaround, blood test)

CA50 is also a very broad tumour marker, and in liver, lung, stomach, rectum, pancreas, gallbladder, kidney, uterus, ovary, breast, bladder, prostate cancer, lymphoma, melanoma pneumonia, nephritis, pancreatitis, colitis and other infectious diseases, it will also increase. In addition, some ulcerative disease, autoimmune diseases also make CA50 rise.

Carcinoembryonic antigen (CEA) (normal 0-5 ug/L, 1-day turnaround, blood test)

Found in 1965, CEA can be described as the most broad spectrum of indicators, as its rise can be seen in the colorectal cancer, stomach cancer, lung cancer, pancreatic cancer, breast cancer, ovarian cancer, uterus and cervical cancer, urinary tract tumours, and other malignant tumours with different degrees of positive rate. In short, CEA is most likely to rise in adenocarcinoma, followed by squamous cell carcinoma and poorly differentiated carcinoma. When there is a late tumour stage, loaded tumour, or tumour metastasis, there will be increased CEA.

Carcinoembryonic antigen (CEA) is a protein normally found in very low levels in the blood of adults. The CEA blood level may be increased in certain types of cancer and non-cancerous (benign) conditions. A CEA test is most commonly used for colorectal cancer.

Cancers

The CEA blood levels are often increased in colorectal cancer and may be increased in other cancers including:

- breast
- lung
- pancreatic
- stomach
- liver
- ovarian

Non-cancerous conditions

The CEA blood level may be increased in non-cancerous conditions including:

- a peptic ulcer
- ulcerative colitis
- rectal polyps
- emphysema
- benign breast disease
- an inflammation such as pancreatitis (inflammation of the pancreas) or cholecystitis (inflammation of the gallbladder)

Smokers who do not have cancer can also have an increased CEA value.

Human chorionic gonadotropin (hCG or b-hCG)

(Males: less than 2 IU/L, Serum hCG levels in healthy women: Non-pregnant premenopausal women: 97.5% of women have results \leq 1 IU/L, Postmenopausal women: 97.5% of women have results \leq 7 IU/L, (1-day turnaround, blood test)

hCG or b-hCG is a hormone that the placenta makes when a woman is pregnant. Certain cancer cells can also make it.

Why an hCG test is done

An hCG test may be done to:

- confirm that you are pregnant
- help diagnose some types of cancer and other conditions
- find out if cancer treatment is working
- watch for cancer coming back during follow-up care

What the results mean

Your hCG levels may be higher than normal for many different reasons.

The level of hCG in your blood may be higher than normal because you are pregnant or you have a certain kind of bowel disease, a stomach ulcer or cirrhosis of the liver. Your HCG level can also be high if you smoke cannabis (marijuana).

An increased level of hCG in the blood may help your doctor diagnose:

- gestational trophoblastic disease (GTD)
- germ cell tumours of the ovary and testicle (both cancerous and non-cancerous tumours)

If you have liver, stomach, pancreatic, lung, breast or skin cancer, the level of hCG in your blood may be higher than normal.

Prostate-specific antigen (PSA) test (normal Total 0-4.1 ug/L, Free 0-0.90 ug/L, Free: Total Ratio >0.19 is normal, 1-day turnaround, blood test)

A prostate-specific antigen (PSA) test measures the amount of PSA in the blood. PSA is a protein made by prostate cells. It is mostly found in semen, but small amounts of PSA can also be found in the blood of healthy men.

Why a PSA test is done

A PSA test may be done to:

- help find prostate cancer early in men who don't have any signs or symptoms of the disease
- check for cancer in men who have signs or symptoms of prostate cancer
- confirm a diagnosis when other tests suggest prostate cancer
- predict a prognosis (outcome) for prostate cancer
- predict if cancer has spread outside the prostate
- plan treatment for prostate cancer
- monitor men with prostate cancer who are being treated with active surveillance
- find out if cancer treatments are working
- find out if cancer has come back (recurred) after treatment

Who should have a PSA test?

Men older than 50 years should talk to their doctor about their personal risk of developing prostate cancer and the benefits and risks of having a PSA test. The Canadian Cancer Society recommends that you should also talk to your doctor about PSA testing if you:

- will soon be 50 years old
- have a family history of prostate cancer or are of African ancestry
- have symptoms of prostate cancer

Benefits and risks

The PSA test can help detect prostate cancer early, but it can also cause false alarms or can miss prostate cancer when it's really there. It's important that men talk to their doctor about their personal risk of developing prostate cancer as well as the benefits and risks of PSA testing.

Benefits

A PSA test can find prostate cancer early, before it grows large or spreads outside of the prostate. Finding cancer early can mean that treatments will be more successful.

Risks

PSA testing carries the following risks.

A false-positive result on a PSA test suggests that a man might have prostate cancer when he actually doesn't. This happens quite often with PSA testing and only about 1 in 4 abnormal results is due to cancer. A false-positive result can lead to unnecessary follow-up testing that is more invasive, such as repeated biopsies. It can also cause men and their families unnecessary anxiety and distress.

A false-negative result means that the test shows that the PSA level is normal even though prostate cancer is present. PSA testing misses about 15% of prostate cancers. Getting a false-negative result may mean that a man and his doctor ignore symptoms of prostate cancer.

Overdiagnosis means diagnosing prostate cancer that would never pose a serious threat to a man's health. Overdiagnosis can lead to giving treatments that aren't absolutely necessary (overtreatment). Research shows that 23%–42% of prostate cancers that are found with PSA testing may never need to be treated. But most men diagnosed with prostate cancer still choose to have treatment. Unnecessary follow-up testing and treatment put a man at risk for problems, including erectile dysfunction and loss of bladder control (called urinary incontinence).

How a PSA test is done

A PSA test is a blood test that is done in a lab or hospital. Ejaculation can affect PSA levels in the body, so you may be told not to ejaculate for a few days before the test.

Tell your doctor if you are taking drugs to treat benign prostatic hyperplasia, prostatitis, urinary problems or baldness. These drugs can lower PSA levels.

What the results mean

PSA levels depend on a man's age. As men get older, their PSA levels naturally go up, but PSA can go up and down for many reasons. Doctors have a hard time agreeing on what is a normal PSA level. But some researchers use a cut-off PSA level of around 3 ng/mL to help them decide which men have the greatest risk of developing prostate cancer. It's important for you to discuss your PSA level result and what it means for your risk of prostate cancer with your doctor. Your doctor will help you determine your risk of prostate cancer in relation to your age, family history and other personal information.

A higher than normal PSA level doesn't always mean that a man has prostate cancer. High PSA levels can also be caused by:

- an enlarged prostate due to benign prostatic hyperplasia
- an inflamed or infected prostate (called prostatitis)
- a urinary tract infection
- a recent medical test or procedure on the prostate, such as a transrectal ultrasound (TRUS) or biopsy
- a urinary catheter
- a bladder exam
- sexual activity that includes ejaculation
- bike riding often or a recent long bike ride
- warmer climates

Sometimes the PSA level goes up temporarily after a couple of years of receiving radiation therapy to treat prostate cancer. This is called a PSA bounce. In most cases, the PSA level will fall the next time it is checked. Treatment isn't needed unless the PSA level continues to rise.

There is no limit to how high a PSA level may rise. But some men with prostate cancer will have a normal PSA level. For these reasons, researchers are still trying to find out the best way to use the PSA test to find prostate cancer. They are also looking for other ways to find prostate cancer early.

Free and bound PSA

In the blood, PSA is either bound or free (unbound). Bound PSA means that it is attached to other proteins. PSA that is not attached to other proteins is called free PSA because it circulates freely in the blood. Percent-free PSA is a ratio that compares the amount of free PSA to the total PSA level. The total PSA level includes the amount of both free and bound PSA in the blood.

Free PSA levels are often higher in men with non-cancerous conditions of the prostate and lower in men with prostate cancer. If a man has a total PSA level between 4 and 10, doctors may test his blood for free PSA. A percent-free PSA above 25% is considered normal. Some doctors recommend that men with a percent-free PSA of 18% or less should have a prostate biopsy. Other doctors recommend having a biopsy if the percent-free PSA is around 12% or less.

Early CDT Lung (10-day turnaround, USA, blood test)

7 Autoantibodies are reported as one of the following levels:	
• High Level	<i>meaning one or more is above the high cut-off value</i>
• Moderate Level	<i>meaning one or more is above the low cut-off value but all are below the high cut-off value</i>
• Low Level	<i>meaning all are below the low cut-off value</i>

How many people survive lung cancer?

- The earlier diagnosed the better – the five-year survival rate for early stage is 43-73%, while for later stage disease it is 2-13%
- The five-year survival rates for men and women diagnosed with lung cancer are 7.3% and 8.7% respectively

EarlyCDT-Lung is a blood test developed to measure a panel of 7 autoantibodies, associated specifically with lung cancer. In the early stages of solid tumour cancer, autoantibodies are produced in response to tumour antigens. Autoantibodies are present, and remain measurable, in all stages.

The *EarlyCDT-Lung* test can also be used in conjunction with diagnostic imaging such as X-Ray or CT scan, to further assess the risk of lung cancer being present where indeterminate lung nodules have been detected, but which may or may not be a sign of cancer.

This is not a genetic test for predisposition – a positive test may indicate the presence of the disease and an increased risk of malignancy.

Results of an *EarlyCDT-Lung* test

There are three possible test results; **High Level**, **Moderate Level** and **Low Level**, depending on the level of autoantibodies in the blood compared to low and high cut-off values for each autoantibody. A High or Moderate Level test result means there is increased risk for lung cancer. Follow-up, which may include CT imaging, would be indicated and should take into account risk factors, symptoms and other relevant patient history, if available. A High or Moderate Level test result does not definitively mean that lung cancer is present. A Low Level test result indicates a lower likelihood of lung cancer than a Moderate or High Level result, however it does not mean that the patient does not have, or will not develop, lung cancer. Continued monitoring is recommended consistent with the patient's history, overall risk profile and other clinical findings.

Squamous cell carcinoma antigen (SCCA) (normal <1.5ng/mL, 5-day turnaround, blood test)

Specific marker for Squamous cell carcinoma. It is used for the diagnosis of squamous cell carcinoma, cervical cancer, lung cancer, head and neck cancer, as its concentration increased with the condition increased. Its increase can also be seen in hepatitis, cirrhosis, pneumonia, tuberculosis and other benign diseases, including inflammatory skin conditions.

Neuroson-specific enolase (NSE) (5-day turnaround, blood test)

is associated with several cancers, but it is used most often to monitor treatment in patients with neuroblastoma or small cell lung cancer.

Small cell lung cancer is a form of neuroendocrine cancer that often grows rapidly and quickly spreads to other organs. It often responds to chemotherapy and radiation more impressively than does non-small cell cancer

Types of small cell lung cancer

There are two stages of small cell lung cancer:

- Limited stage: Cancer is generally found only in one lung. There may also be cancer in nearby lymph nodes on the same side of the chest.
- Extensive stage: Cancer has spread beyond the primary tumour in the chest to other parts of the body.

Urinary Bladder Cancer Antigen (UBC) (5-day turnaround, urine test) NEW from TDL 2023

A mid-stream urine sample (not first morning urine)

CYFRA 21–1 (4-days turnaround, blood test)

This assay is an automated immunochemiluminometric assay performed on serum. The assay utilizes KS19.1 and BM19.21 monoclonal antibodies in a standard sandwich format. Validation studies revealed favorable performance characteristics including limit of blank of 0.01 ng/mL, linearity from 0.1 to 100 ng/mL, and overall imprecision of < 4%. The upper 95th percentile reference limit was 1.5 ng/mL for healthy adult subjects.

Our data show that CYFRA 21–1 is complimentary to CEA and SCC in a stage-dependent manner. While none of the markers performed well when used alone, a panel consisting of these three markers has high sensitivity and should be considered in the evaluation of non-small cell lung cancer (NSCLC) patients.

Squamous Cell Carcinoma SCC (4-days turnaround, blood test)

The SCC antigen, a tumour marker for squamous cell carcinoma, is already used for the diagnosis and follow-up of carcinoma of the cervix, head and neck and the lungs.

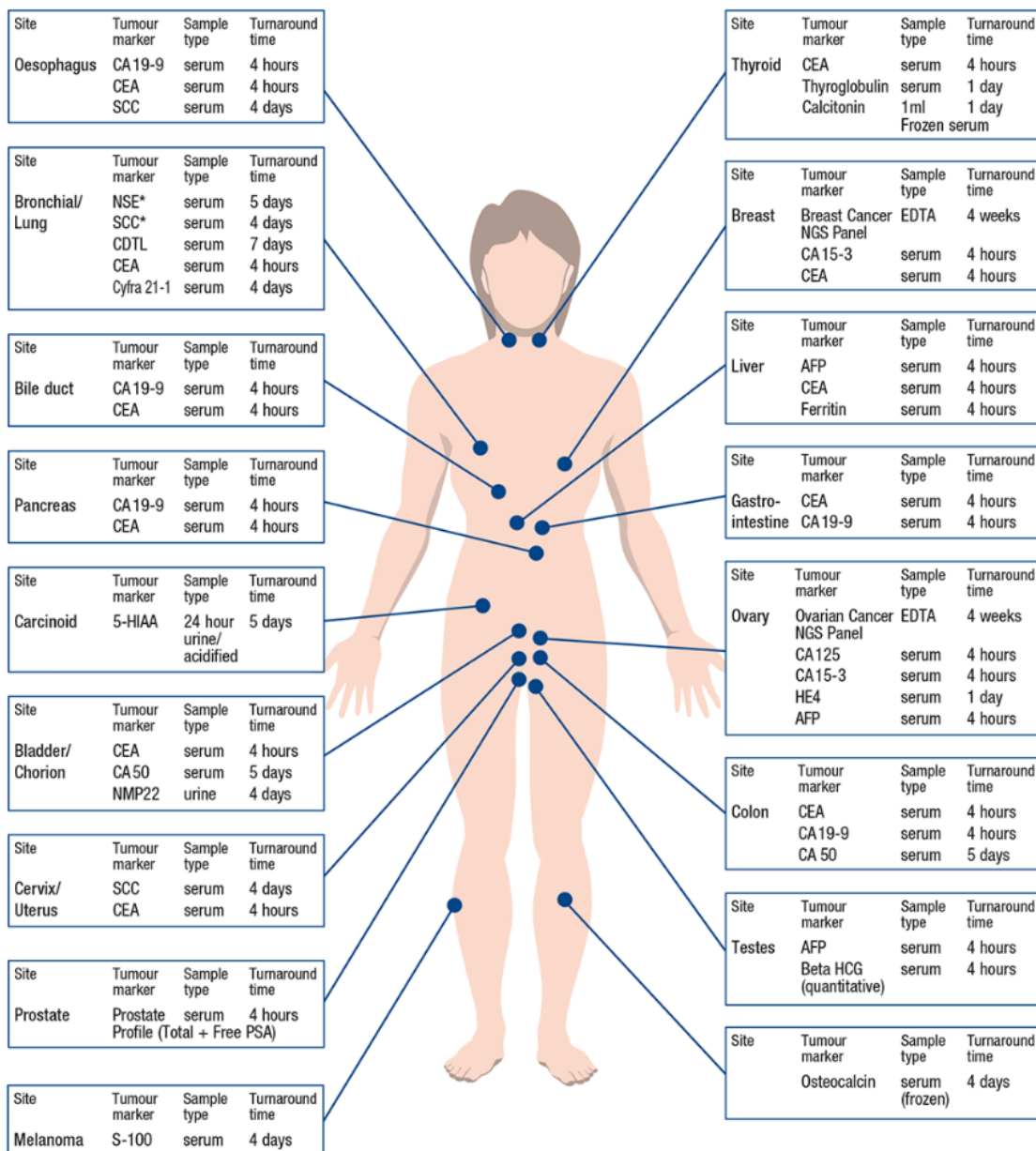
S100 (4-days turnaround, blood test)

S100 is an acidic-calcium-binding protein, composed as a heterodimer of two isomeric subunits alpha and beta and was first described in cells of neuroendocrine origin. It plays an important role in various cellular processes such as cell differentiation and proliferation and interacts with the tumour suppressor gene p53. S100 is also present in melanoma cells and its immunohistochemical detection is widely used in the histopathological diagnosis of malignant melanoma. S100 has been detected in the serum of patients with malignant melanoma and many clinical studies have been performed to establish this protein as a tumour marker in different stages of the disease. The data suggest that S-100 beta-protein in serum of patients with malignant melanoma could be an independent prognostic marker and an additional clinical parameter for progression of metastatic disease and serological monitoring during systemic therapy

Common tumour markers at specific sites (suggested by TDL)

Oesophagus	CA19-9, CEA, SCC
Bronchial/Lung	CDTL, CEA, SCC, Cyfra 21-1, NSE
Bile Duct	CA19-9, CEA
Pancreas	CA19-9, CEA
Bladder	CEA, CA50, UBC
Cervix/Uterus	SCC, CEA
Prostate	PSA (Total & Free)
Melanoma	S-100
Thyroid	CEA, Thyroglobulin, Calcitonin
Breast	CEA, CA15-3, Breast Cancer NGS Panel
Liver	AFP, CEA, Ferritin
GIT	CEA, CA19-9
Ovary	CA125, CA15-3, AFP, HE4, Ovarian Cancer NGS Panel
Colon	CEA, CA19-9, CA50
Testes	AFP, bHCG
Bone	Osteocalcin

Tumour marker sites diagram



* NSE: Neurone Specific Enolase
 SCC: Squamous Cell Carcinoma