Cancer Association of South Africa (CANSA)

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Fact Sheet on Tumour Markers

Introduction

A tumour marker is any cellular, molecular, chemical or physical change that can be measured and used to study a normal or abnormal process in the body. It can be found in the blood, urine, or body tissues and can be elevated in cancer. There are many different tumour markers, each indicative of a particular disease process, and they are used in oncology to help detect the presence of cancer.

[Picture Credit: Tumour Marker Test]

An elevated level of a tumour marker can indicate the presence of cancer, however, there can also be other causes of the elevation.

Tumour markers are assuming a growing role in all aspects of cancer care, starting from screening to follow-up after treatment, and their judicious application in clinical practice needs a thorough understanding of the basics of pathophysiology, techniques of identification or testing, reasons for out-of-range levels of tumour markers, as well as the knowledge of evidence of their role in any given malignancy. Tumour markers are, at the most, just an adjunct to diagnosis, and establishing a diagnosis on the basis of tumour markers alone (especially a single result) is fraught with associated pitfalls because of the problem of non-specificity. In reality an ideal tumour marker does not exist.

Some tumour markers are specific to one type of cancer, while others are related to several different types of cancer. Tumour markers may also become elevated with non-cancerous conditions. Tumour markers can be produced directly by the tumour or by non-tumour cells as a response to the presence of a tumour. Most tumour markers are tumour antigens, but not all tumour antigens can be used as tumour markers.

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There are some limitations to the use of tumour markers. Sometimes, non-cancerous conditions can cause the levels of certain tumour markers to increase. In addition, not everyone with a particular type of cancer will have a higher level of a tumour marker associated with that cancer. Moreover, tumour markers have not been identified for every type of cancer. Multiple Tumour marker tests will give a more exact result to find the origin of confirmed carcinoma of unknown primary (CUP) or to track the evolution of a confirmed tumour. Many different tumour associated antigens have been described and investigated.

Tumour markers include a variety of substances like cell surface antigens, cytoplasmic proteins, enzymes, hormones, onco-foetal antigens, receptors, oncogenes and their products. There have been numerous attempts to broaden the definition to accommodate the rapidly expanding set of identified tumour markers and include the following:

- Substances present in, or produced by, a tumour itself or produced by a host in response to a tumour that can be used to differentiate a tumour from normal tissue or to determine the presence of a tumour based on measurements in blood or secretions

- A molecule, a process or a substance that is altered quantitatively or qualitatively in precancerous or cancerous conditions, the alteration being detectable by an assay

- Biochemical indicators of the presence of a tumour. However, in common clinical practice, the term usually refers to a molecule that can be detected in plasma or other body fluids.

Although mammography, ultrasonography, computed tomography, magnetic resonance imaging scans, and tumour marker assays help in the staging and treatment of cancer, they are usually not definitive diagnostic. Diagnosis is usually confirmed by biopsy.
(Canadian Cancer Society; Wikipedia; National Cancer Institute; Sharma [2009]).

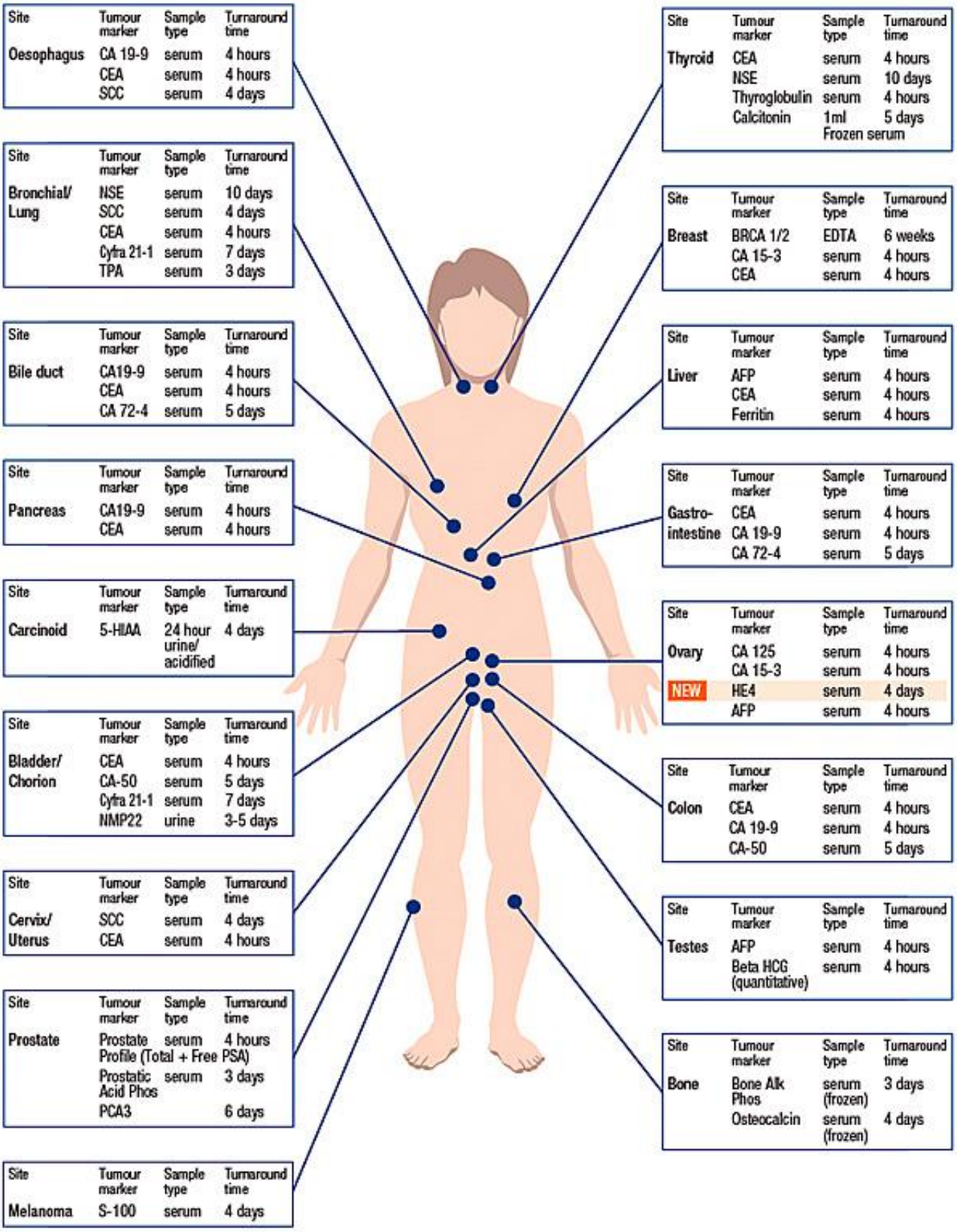
Limitations of Tumour Markers
Tumour markers are not fool proof. Other tests are usually needed to learn more about a possible cancer or recurrence.

Some of the limitations of tumour markers are listed below:

- A condition or disease, other than cancer, can elevate tumour marker levels
- Some tumour marker levels may be high in people without cancer
- Tumour marker levels may vary over time, making it hard to get consistent results
- The level of a tumour marker may not rise until a person's cancer worsens. This is not helpful for early detection, screening, or watching for recurrence
- Some cancers do not make tumour markers that are found in the blood. This includes cancers with no known tumour markers. Also, some patients do not have higher tumour maker levels even if the type of cancer they have usually makes tumour markers

(Cancer.Net).

Tumour Markers at a Glance



(The Doctors Laboratory).

Tumour Markers in General Use
Tumour markers alone are not diagnostic for cancer; for some types of cancer, they provide additional information that can be considered in conjunction with a patient's medical history and physical examination as well as other laboratory and/or imaging tests.

Tumour markers that are generally used in oncology are dealt with in this Fact Sheet. They are listed in no particular order.

This Fact Sheet may not contain a comprehensive list of all tumour markers, however, the most used tumour markers are included.

Tumour Marker CA 19-9
CA 19-9 was initially discovered among patients suffering from colorectal cancer, CA 19-9 was then noticed in pancreas cancer (very high levels), biliary tract cancers, stomach cancer. One should watch out for very high levels found in inflammatory diseases of the gastrointestinal tract, or biliary retention: when inflammation is treated, or the obstacle relieved, the CA 19-9 level normalizes very fast.

Usual sample: blood.

Ca 19-9 is not sensitive or specific enough to use as a screening test for cancer, and it is not diagnostic of a specific type of cancer. Its main use is as a tumour marker:

- To help differentiate between cancer of the pancreas and other conditions, such as pancreatitis
- To monitor a person's response to pancreatic cancer treatment and/or cancer progression
- To watch for pancreatic cancer recurrence

CA 19-9 can only be used as a tumour marker if the cancer is producing elevated amounts of it. Since CA 19-9 is elevated in about 65% of those with bile duct (hepatobiliary) cancer, it may be ordered to help evaluate and monitor people with this type of cancer. It is also associated with gall bladder cancer, stomach cancer and cancer of the colon.

CA 19-9 may be ordered along with other tests, such as carcinoembryonic antigen (CEA), bilirubin, and/or a liver panel, when a person has symptoms that may indicate pancreatic cancer. These symptoms include abdominal pain, nausea, weight loss, and jaundice.

If CA 19-9 is initially elevated in pancreatic cancer, then it may be ordered several times during cancer treatment to monitor response and on a regular basis following treatment to help detect recurrence.

CA 19-9 may sometimes be ordered when a doctor suspects hepatobiliary cancer and/or bile duct obstruction. Non-cancerous causes of bile duct obstruction can cause very high CA 19-9 levels, which fall when the blockage is cleared. In these cases, it is a good idea to wait at least a week or two after the blockage is removed to re-check CA 19-9 levels.

Low amounts of CA 19-9 can be detected in healthy people, and many conditions that affect the liver or pancreas can cause temporary elevations.

Moderate to high levels are found in pancreatic cancer, other cancers, and in several other diseases and conditions. The highest levels of CA 19-9 are seen in cancer of the exocrine pancreas. This cancer arises in the tissues that produce food-digesting enzymes and in the ducts that carry those enzymes into the small intestine. About 95% of pancreatic cancers are of this type.

Serial measurements of CA 19-9 may be useful during and following cancer treatment. Rising or falling levels may give the doctor important information about whether the treatment is working, whether all of the cancer was removed successfully during surgery, and whether the cancer is recurring.

Unfortunately, early pancreatic cancer gives few warning signs. By the time a person has symptoms and significantly elevated levels of CA 19-9, pancreatic cancer is usually at an advanced stage.

The reference range of serum CA 19-9 is less than 37 U/mL.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CA 19-9 for the diagnosis of pancreatic cancer is dependent on the cutoff level (see the table below). A normal level is less than 37 U/mL, which corresponds to a sensitivity of 81% (68%-93%), a specificity of 90% (76%-100%), a PPV of 72%, and a NPV of 96%.[1, 2] However, when CA 19-9 levels are greater than 1000 U/mL, sensitivity is 41%, specificity is 99.8%, PPV is 97%, and NPV is 89%.

Cut-off levels of CA 19-9 for the Diagnosis of Pancreatic Cancer

Cut-off (U/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
37	81	90	72	96
100	68	98	87	94
300	54	99	92	91
1000	41	99.8	97	89

Elevated levels of CA 19-9 can be seen in healthy individuals. Elevated levels can also be seen in benign conditions, such as the following:

- Biliary tract obstruction
- Cholangitis
- Inflammatory bowel disease
- Acute or chronic pancreatitis
- Liver cirrhosis
- Cystic fibrosis
- Thyroid disease

Elevated levels of CA 19-9 can be seen in the following malignant conditions as well:

- Bile duct cancers
- Colorectal cancers
- Gastric cancers
- Ovarian cancers
- Hepatocellular cancers
- Oesophageal cancers

- Pancreatic cancers

Additionally, at least 5% of the population is unable to produce the CA 19-9 antigen. The overall low specificity and sensitivity of this assay precludes its use as a screening tool for pancreatic cancer. An elevated tumour marker level needs to be interpreted within the context of the patient's history, physical examination, diagnostic imaging, and laboratory work-up findings.

High CA 19-9 levels (i.e. greater than 1000 U/mL) correlate with unresectable or more advanced tumours, although this preoperative evaluation of CA 19-9 has not been widely used to establish inoperability. High marker levels may also be used to predict patient outcomes. A decrease or normalisation of CA 19-9 levels postoperatively correlates with a longer duration of survival. Conversely, rising marker levels postoperatively have been correlated with shorter duration of survival and increased disease recurrence.

Finally, CA 19-9 levels can be used to monitor tumour response to active treatment with surgery, with or without chemotherapy, radiation therapy, and/or other targeted or biological therapies. A decrease in CA 19-9 levels confirms the effectiveness of the therapeutic regimen, while a stable or rising level may indicate the need to change therapies.
(LabTestsOnline; Medscape; CancerSafe).

Tumour Marker CEA

Carcinoembryonic antigen (CEA) is a protein found in many types of cells but associated with tumours and the developing foetus. It is the oldest tumour marker used: with no specificity, it remains largely used because, covering a large range of pathologies, it allows following several different cancers. It was primarily used in colorectal cancer monitoring. In colon cancer and rectum cancer, the CEA level is closely related to the tumoural differentiation and carcinoma stage.

Usual sample: Blood.

Uses: staging of applicable cancers, to determine prognosis, and to monitor success of treatment and detect recurrence.

Significant increase is observed in relapses, preceding clinical signs from 2 to 12 months. Apart from the digestive area, CEA is used in particular in lung cancer, thyroid cancer, and also ovary, liver, uterine.

Preferably it should be used with other tumour markers, such as CA 15-3, CA 19-9, CA 125, CA 72-4, NSE, Cyfra-21, depending upon the considered cancer.

CEA is tested in blood. The normal range is <2.5 ng/ml in an adult non-smoker and <5.0 ng/ml in a smoker.

Benign conditions that can increase CEA include smoking, infection, inflammatory bowel disease, pancreatitis, cirrhosis of the liver, and some benign tumours (in the same organs which have cancers with increased CEA). Benign disease does not usually cause a CEA increase over 10 ng/ml.

The main use of CEA is as a tumour marker, especially with intestinal cancer. The most common cancers that elevate CEA are in the colon and rectum.

Other cancers include: cancer of the pancreas, stomach, breast, lung, and certain types of thyroid and ovarian cancer. Levels over 20 ng/ml before therapy are associated with cancer which has already metastasised (spread).

CEA is useful in monitoring the treatment of CEA-rich tumours. If the CEA is high before treatment, it should fall to normal after successful therapy. A rising CEA level indicates progression or recurrence of the cancer. (Chemotherapy and radiation therapy can themselves cause a rise in CEA due to death of tumour cells and release of CEA into the blood stream but that rise is typically temporary).

"Carcinoembryonic" reflects the fact that CEA is made by some cancers ("carcino-") and by the developing foetus ("-embryonic").
(MedicineNet.Com; CancerSafe; LabTestsOnline).

Tumour Marker BR-ABL
This tumour marker is associated with the following cancers:

- Chronic myeloid leukaemia (CML)
- BCR-ABL-positive acute lymphocytic leukaemia (ALL)

Usual samples:

- Blood
- Bone marrow

It is used to help in diagnosing and to monitor success of treatment as well as detecting possible recurrence.
(LabTestsOnoline).

Tumour Marker SCC-Ag
Squamous cell carcinoma antigen (SCC-Ag) belongs to the serine protease inhibitor (Serpin) family of proteins. Elevated expression of SCC-Ag has been used as a biomarker for aggressive squamous cell carcinoma (SCC) in cancers of the:

- Cervix
- Lung
- Head and Neck
- Liver

Levels of SCC can also be used as an aid to stage the carcinoma and to determine the response to treatment.
(Plos.Org; Medical Dictionary).

Tumour Marker NSE
The NSE (neuroenzyme-specific-enolase) is an enzyme only found is nervous tissue or in neuroendocrine tissue. At present, it is used first in lung cancer, the “small cells” one. There

exists a correlation between the scattering of the small cells cancer and the NSE level : in limited forms, 50% show high levels; in disseminated cancers, 100% show high levels. Besides its interest in diagnostics, the NSE, during the first sessions of chemotherapy (when required), allows the appreciation of the quality of the response to the treatment : its level increases during the cells lyse, thus demonstrating the tumour's sensitivity to the treatment. Moreover, the NSE shows high levels in neuroblastomas, pheochromocytomas, and is also used in medullar thyroid cancer.

Tumour marker, NSE: Neuron-specific enolase (NSE) is a substance that has been detected in patients with certain tumours, namely:

- Neuroblastoma
- small cell lung cancer
- medullary thyroid cancer
- carcinoid tumours
- endocrine tumours of the pancreas
- melanoma.

Studies of NSE as a tumour marker have concentrated primarily on patients with neuroblastoma and small cell lung cancer. Measurement of NSE levels in patients with these two diseases can provide information about the extent of the disease and the patient's prognosis (outlook), as well as about the patient's response to treatment.
(MedicineNet.Com; CancerSafe).

Tumour Marker Cyfra 21-1

CYFRA 21-1 - the "cytokeratin fragment" is the most stunning marker ever discovered. Very few laboratories monitor it at present. It is especially interesting for lung cancer, diagnostic and follow-up of epidermoidis forms.

Among all forms of lung cancer (lung cancer presents many different forms), the Cyfra 21-1 delivers an appreciated sensitivity of 65%, and an exceptional specificity of 95%. Its value is closely tied to the stage: levels increase progressively from limited stages to disseminated ones.
While surgery has long been the unique solution for these cancers ("non small cells" ones), the association radiotherapy-chemotherapy, even for locally advanced stages, is used at present: the regular evaluation of the Cyfra allows easier follow-up treatment, and even better when associated with other tumour markers.

The Cyfra is now used by top teams in breast cancer: its elevation in follow-up demonstrates, very early, the apparition of metastases.

Cyfra can also be used in uterine cancer, oesophageal cancer, and bladder cancer.
(CancerSafe).

Tumour Marker TPA

Tissue polypeptide antigen (TPA) is a differentiation and proliferation marker of non-squamous epithelium and derived neoplasms. No reliable tumour markers are available for bladder cancer. TPA is also a tumour marker in gastric and colorectal carcinoma.

Usual sample: tissue.
The normal cut off value was defined at 95 units per litre. Its monitoring proved to be a reliable predictor of tumour progression. Tissue polypeptide antigen is a useful marker not for the early detection of bladder cancer but for the monitoring of the efficacy of treatment.
(Wiley Online Library; Van Poppel, *et al*.).

Tumour Marker CA 72-4
Among the new tumour markers that have been recently proposed, CA 72-4 is of particular interest, not only for its capabilities in diagnosing and monitoring certain neoplastic diseases, but also for its excellent specificity. Several studies focused on the potential clinical usefulness of CA 72-4 in gastrointestinal (GI) and gynaecological cancer, showing a sensitivity of approximately 40% in colorectal and gastric cancer and 50% in ovarian cancer, with an overall specificity of more than 95%. Longitudinal evaluations of patients with either GI or gynaecological malignant diseases demonstrated that significant elevations of CA 72-4 serum levels may be predictive of recurrent disease. Moreover, the combination of CA 72-4 with other known serum markers, such as CEA and CA 19-9 for GI cancer or CA 125 for ovarian cancer, indicated that an increase in the sensitivity can be achieved without substantial changes in the overall specificity, improving the possibility of monitoring these patients. In conclusion, these results provide a strong argument for the use of CA 72-4 in the management of these neoplastic diseases.

Usual sample: blood.
(Guadagni, *et al.).*

Tumour Marker 5-HAA
Also known as: HIAA; Serotonin Metabolite
Formal name: 5-hydroxyindoleacetic Acid
Related tests: Serotonin; Chromogranin A.

The 5-hydroxyindoleacetic acid (5-HIAA) urine test is used to help diagnose and monitor carcinoid tumours. It may be ordered by itself or along with a blood serotonin and/or chromogranin A level. 5-HIAA is the primary metabolite of serotonin that is excreted in the urine. Concentrations of 5-HIAA may be significantly increased when a person has a carcinoid tumour that produces serotonin.

A 24-hour urine sample is preferred for the 5-HIAA test because the level of the metabolite can vary during the day. A random urine sample is sometimes tested, usually along with a urine creatinine level, when a 24-hour sample is not feasible. The random sample is not as accurate, however, and if excess 5-HIAA is released intermittently, then it may be missed.

This test is primarily ordered when a person has symptoms suggestive of a carcinoid tumour.

Examples of symptoms include:
- Flushing of the face and neck (appearance of deep red color, usually with sudden onset)
- Diarrhoea, nausea, vomiting
- Rapid heart rate
- Wheezing, coughing, difficulty breathing

This test may also be ordered at intervals to help monitor the effectiveness of treatment in people who have been diagnosed with and treated for a serotonin-secreting carcinoid tumour.

A significantly increased level of 5-HIAA in a 24-hour urine sample in a person with carcinoid syndrome symptoms is suggestive but not diagnostic of a carcinoid tumour. In order to diagnose the condition, the tumour itself must be located and a sample of it examined (biopsy). The health practitioner will frequently follow an abnormal test result with an order for an imaging scan to help locate any tumour(s) that may be present.

Someone with symptoms may still have a carcinoid tumour even if the concentration of 5-HIAA is normal. The person may have a tumour that does not secrete serotonin or one that secretes it intermittently.

A person with no symptoms and normal levels of 5-HIAA is unlikely to have a serotonin-secreting carcinoid tumour.

In those who are being monitored following treatment for carcinoid tumour, decreasing levels of 5-HIAA indicate a response to treatment, while increasing or continued excessive concentrations indicate that the treatment has not been successful.
(LabTetsOnline).

Tumour Marker CA-50

CA 50, a novel cancer-associated carbohydrate marker, is detected by the C 50 antibody that has been obtained by immunisation of mice with a human colorectal adenocarcinoma cell line. This antibody that defines CA 50 reacts with both the afucosyl form of sialylated Lewis(a) carbohydrate moiety and sialylated Lewis(a) moiety which is also the antigenic epitope in the CA 19-9 assay.

CA 50 is not organ-specific and its elevated levels in serum can be observed in a variety of malignancies, especially gastrointestinal cancers. In contrast to CA 19-9, high CA 50 levels can also be seen in malignant tumours outside the digestive tract.

The expectation, that CA 50 might be positive in the Lewis negative patients who cannot synthesize CA 19-9, is supported by the histoimmunologic study. However, in serum determination close correlation between CA 50 and CA 19-9 has been observed even in patients who have Lewis negative phenotype. In clinical application, CA 50 is marginally beneficial for the diagnosis, but very useful for the follow-up of patients with pancreatic cancers. It gives results rather similar to CA 19-9.

Moderately high serum levels of CA 50 can also be seen in benign hepatobiliary diseases, especially in jaundice cases. Therefore, this should be considered in order to obtain the most advantage of the marker. For other gastrointestinal cancers, CA 50 in combination with other previously defined markers may give additional information for the evaluation of some patients with colorectal, biliary, or gastric cancers.
(Bunworasate & Voravud).

Tumour Marker NMP 22
More than 30 urinary biomarkers have been reported for use in bladder cancer diagnosis, but only a few are commercially available; the remainder are still being tested. Commercially available tests include the following:

- Urine cytology
- Fluorescence in situ hybridization (FISH)
- Nuclear matrix protein (NMP-22)
- BTA *stat*
- BTA TRAK
- ImmunoCyt/uCyt+
- CertNDx
- CxBladder

Newer, voided urine assays (ie, bladder tumor antigen [BTA *stat*, BTA TRAK], NMP-22, fibrin/fibrinogen degradation products [FDP]) are being used for the detection and surveillance of urothelial carcinoma. These tests have high false-positive and false-negative rates. In the future, other newer assays based on telomerase and microsatellite analysis may prove to be a better detection method than urinary cytology.

Chromosomal alterations have been associated with urothelial carcinoma. One encouraging test is a multitarget interphase FISH assay called UroVysion that consists of probes to the centromeres of chromosomes 3, 7, 17, and 9p21. Aneuploidy of chromosomes 3, 7, and 17 and deletion of chromosome 9 have been associated with high sensitivity and specificity to detect bladder cancer. Often, this is an anticipatory positive result with a positive finding preceding visual evidence of bladder tumour.

The use of additional urine markers such as UroVysion (FISH), BTA, and NMP-22 in the initial diagnosis of bladder cancer is controversial. All of these assays may yield false-positive and false-negative results.
(Medscape).

Tumour Marker Chromogranin A (CgA)
This tumour marker is associated with Neuroendocrine tumours (carcinoid tumours, neuroblastoma). It is one of the most sensitive tumour markers for carcinoid tumours.

Usual sample: blood.

It is used to diagnose the listed neuroendocrine cancers as well as to monitor the success of treatment and to assist in detecting recurrence.
(LabTstsOnline).

Tumour Marker PSA
Tumour marker Prostate Specific Antigen (PSA) is a very good marker, very well known, because of its high specificity: found in normal prostatic epithelioma and secretions, but not in other tissues. It is a glycoprotein, whose function is to liquefy the seminal plasma.

PSA is normally present, in low concentrations, in every male adult's blood. Produced by

normal and abnormal cells of the prostate, it is highly sensitive to the presence of prostate cancer: its increasing is correlated to the tumour grade and its volume.

The PSA, as a sensitive test, is used for screening for all men over 50. Decreased mortality from the disease could be between 20 to 30%.

As an ultra sensitive PSA is available, enabling to track 0,001 ng/ml, one can find every elevation of the value, after treatment. When serious follow-up is needed, one can discriminate: early increases mean a metastatic disease evolution, while late increases rather mean local relapse.
But there does exist a major benign condition of PSA increasing: inflammation or trauma of the prostate, benign hypertrophy of the prostate are frequently involved: to clear the matter, without invasive biopsy, the FPSA/PSA ratio level is now available.
(CancerSafe).

Prostate Serum Profile (Total + Free PSA)
Free PSA is a newer evaluation for prostate health. Most PSA in the blood is bound to serum proteins, but a small amount is not protein-bound and is called free PSA. In men with prostate cancer, the ratio of free (unbound) PSA to total PSA is decreased.

The free PSA test measures the percentage of free PSA relative to the total amount. The lower the ratio, the greater the probability of prostate cancer.

Measuring free PSA may help eliminate unnecessary biopsies. Free PSA readings increase immediately after ejaculation, returning slowly to baseline levels within about 24 hours. Although not used as an initial screening test, a lower percentage of free PSA might mean your doctor needs to do a further workup.

Below are the percentage of PSA ranges and what they represent as far as prostate cancer risk. Note that when the percentage of free PSA is high (over 20**%**), this means the risk of prostate cancer is low, whereas a low percentage of free PSA (under 11**%** indicates high risk).

PROSTATE CANCER RISK

Free PSA%	**50-64 Years**	**65-75 Years**
0.00-10.00%	56%	55%
10.01-15.00%	24%	35%
15.01-20.00%	17%	23%
20.01-25.00%	10%	20%
Over 25%	5%	9%

FPSA - the PSA is in fact considered from six different ways. Very often, it is interesting to couple the freePSA with the PSA. The known “PSA” (for prostate specific antigen) is, in fact, blood circulating under 2 forms: a free one, the FPSA, and an attached one (to alpha1antitrypsin); the FPSA represents 10 to 40% of the TPSA (total PSA).

Patients with a prostate cancer show a FPSA/TPSA ratio lower than people with benign hypertrophy: when ratio is lower than 0.25, be careful, there is risk of cancer; the lower the ratio, higher the risk. When the range is between 0 to 0,25, it covers 95% of cancers.

Using the PSA and FPSA dosages significantly reduces the number of unnecessary biopsies. Using the ratio avoids the need for biopsy in about 20% of patients who would undergo this procedure (not risk free) based upon the PSA dosage alone.
(LifeExtension; CancerSafe).

Prostatic Serum Acid Phos (PCA3)
PCA3 is a molecular diagnostic test performed on urine rather than blood and detects mRNA that is excreted into the urethra via the epithelial cells that line the prostatic ducts. Prostate cancer cells tend to produce this compound far more than normal cells do.

The PCA3 urine test has to be done in a urologist’s, or other doctor’s, office, because it requires a digital rectal massage just prior to collection of the urine.

PCA3 testing is most useful when repeated over a period of time to monitor for changes in the observed value. In general, a PCA3 score of 35 is considered the optimal cut-off. A score of greater than 35 reflects an increased probability of a positive biopsy. A score of less than 35 reflects a decreased probability of a positive biopsy.
(LifeExtension).

Tumour Marker S-100
A heterogeneous group of 159 tumours was studied for the presence of S-100 protein by the immunoperoxidase technique in order to determine whether this marker may be of value in facilitating immunocytochemical diagnosis.

Among cases of melanocytic and pigmented lesions, S-100 was widely distributed and demonstrated the strongest degrees of reactivity. S-100 protein was identified in virtually all nerve sheath tumours such as schwannomas, neurofibromas, myxoid sheath nerve tumour and also in some tumours of controversial histogenesis such as granular cell tumours.

The great majority of carcinomas did not express S-100, with only two cases of breast carcinoma displaying focal S-100 staining. In a miscellaneous group of tumours S-100 was demonstrated in chordomas, myoepitheliomas and Wilms' tumour with Schwann cell differentiation.

Despite its presence in a wide array of cell types, S-100 protein continues to be an extremely useful marker especially for soft tissue and peripheral nervous system tumours.
(Schmitt & Bacchi).

Tumour Marker Thyroglobulin

The measurement of the protein Thyroglobulin (abbreviated Tg) in blood, is an important laboratory test for checking whether a patient still has some thyroid present. The power of a serum Tg measurement lies in the fact that Tg can only be made by the thyroid gland (either the remaining normal part or the tumourous part). This means that when a patient has had their thyroid completely removed, the measurement of Tg in a blood sample can be used to check whether there is any tumour left behind.

Detectable Tg Levels: When patients have had cancerous growths that make Tg, the absence of Tg in a blood sample is usually good news for a patient who has had thyroid surgery to remove their thyroid gland containing a cancerous growth. However, many patients still have measurable levels of Tg in their blood after surgery. Often this Tg is coming from a small amount of normal thyroid left behind. This means that a measurable level of Tg does not necessarily indicate the presence of tumour. Often physicians will give a small dose of radioiodine to get rid of the last remaining part of the normal thyroid gland in order to make later Tg measurements a better marker for any tumour left behind.

TSH & Tg: Thyroid Stimulating Hormone (TSH) is the pituitary (master gland at the base of the brain) hormone that drives the thyroid gland to produce thyroid hormones and as a by-product, release Tg into the blood. TSH is believed to cause the growth of most thyroid tumours. This is why it is important to take thyroxine medicine (e.g.: synthroid, levoxyl, unithroid) to keep TSH levels low. When TSH is high (before scanning) Tg is increased about ten times. You should not compare the Tg level measured while taking thyroxine medicine (when TSH is low) with the Tg level measured when TSH is high.

Tg Measurements before Surgery: Many physicians still do not recognize the value of a pre-operative Tg measurement. A high Tg level before surgery does not indicate that a tumour is present. However, when a biopsy suggests that the growth is cancerous, the finding of a high Tg level before surgery is a good sign, because it suggests that the tumour makes Tg, and that after surgery Tg can be used as a sensitive tumour marker test. In fact, Tg will be a more sensitive post-operative tumour marker test when the cancerous growth is small and the pre-operative Tg is high! When a patient has a low Tg pre-operatively, the cancerous growth might be unable to efficiently make Tg. In such patients, an undetectable Tg level after surgery is less reassuring than if the patient had had a high pre-operative Tg value. Conversely, when Tg is detected post-operatively in such patients despite ablation of all normal thyroid, this could indicate that a large amount of tumour is still present.

Tg Measurements after Surgery: Changes in the Tg level over time (six months or yearly intervals) are more important than any one Tg result. After surgery, blood samples are usually taken for Tg measurement while the patient is taking their daily dose of thyroxine medication (TSH low).

Tg Method-to Method Differences: Unfortunately, Tg measurement is technically difficult and different Tg methods produce different results. Tg measurements made by different laboratories on the same blood specimen from a patient can vary as much as two-times! It is important to compare Tg measurements made by the same method, if possible performed by the same laboratory. This is because method-to-method differences makes it impossible to tell whether a change in the Tg level means there is a change in the amount of tumour, or is just a problem with the way the test is done.

Concurrent Tg Re-measurement: Some laboratories save all the unused blood left after a Tg test has been completed, so that the spare blood can be re-measured side-by-side with a future blood sample. This "concurrent remeasurement" approach is the best way to tell

whether a change in the Tg level means that there has been a change in the amount of tumour, or is just due to the way the test was done. The concurrent remeasurement approach helps the physician check for tumour re-growth at an earlier stage. Additionally, laboratories that bank patient specimens will have them available for any new tumour-marker tests that may be developed in the future.

Tg Antibodies (TgAb): Approximately 15 to 20 percent of thyroid cancer patients have antibodies to Tg that circulate in their blood. These antibodies are abbreviated as TgAb on laboratory reports. Unfortunately, TgAb interferes with the measurement of Tg by most methods. Whether these antibodies cause incorrectly high or low values depends on the type of Tg method used by the laboratory.

Most clinical labs use the more modern type of Tg method (called immunometric assays (IMAs) or "sandwich" methods). These methods typically report falsely low Tg values when TgAb is present in a patient's blood. Falsely low values may lead to a delay in necessary treatment. Alternatively, an inappropriately high Tg level, which can be a problem with some of the older type of Tg method (called radioimmunoassays, RIAs) can cause patient anxiety and lead to unnecessary scans or treatment.

There is currently disagreement between professionals regarding the best type of method to use (IMA or RIA) for patients with antibodies. Some laboratories in the United States believe that RIA methods have less TgAb interference and provide more clinically reliable values than IMA methods. In fact, these laboratories believe that IMA methods should not be used at all when TgAb is present, because an falsely low Tg value is more of a problem than a falsely high Tg one. For example, an inappropriately low Tg value reported because of TgAb interference can lead to a delay in treatment. In contrast, an inappropriately high Tg value reported because of TgAb interference usually increases vigilance on the part of the physician.

Some laboratories now restrict the use of the IMA methods to patients without antibodies and continue to use the older RIA-type methods for patients with antibodies, although the RIA test result takes longer to report.

TgAb Methods: Since interference by Tg Antibodies has serious effects on the reliability of the Tg value reported, it is important to use a precise and sensitive Tg antibody test method to detect TgAb. Unfortunately, TgAb methods differ even more than Tg methods! Some patients are judged to be antibody-positive by some methods and antibody-negative by others. It is therefore important to compare TgAb measurements made by the same method, if possible performed by the same laboratory. It is also important for the laboratory to use a modern sensitive immunoassay test to check for TgAb.

One can tell if one’s TgAb was measured by one of these tests by the units that are reported. If the antibody result is followed by U/mL or IU/mL it is a modern immunoassay test. If the antibody is reported in titers (1:100, 1:400, 1:1600 etc) this is an insensitive old-style agglutination test.

Serial TgAb Measurements: It is important for the laboratory to measure TgAb in every specimen sent for Tg measurement. This is both because a patient's TgAb status may change from positive to negative or vice versa, and also because the trend in TgAb values over time (i.e. 6 to 12 months) gives additional information on how well the tumour is responding to treatment. A trend down in TgAb levels overtime (years) is a good sign that treatment is effective. In contrast, an increase over time may be an early sign of a recurrence. When a patient has TgAb detected, it is not unusual to see a temporary rise in

the TgAb level during the first six months following radioiodine therapy. This may even be a sign of the effectiveness of the treatment. Usually, TgAb values return to the original value or below after six months.

Usual Samples: blood and tissue.
(Thyca.Org; LabTestsOnline).

Tumour Marker AFP

Tumour marker AFP - the developing foetus normally produces the alpha-foetoprotein. Its level decreases fast after birth, and normally is not detectable in safe adult's blood (except during pregnancy). Elevated results of the AFP strongly suggest the presence of primitive liver cancer, or a germinal ovarian or testicular cancer.

The AFP's interest lies in cancers of the liver, then ovary and testicle.

Alpha-foetoprotein is a tumour marker that is associated with certain cancers:

- Germ cell cancers of ovaries & testes (Non-seminomatous, particularly embryonal and yolk sac, testicular cancers)
- Some primary liver cancers (hepatocellular)

Usual sample: blood.

It is used to help in diagnosing certain cancers. It is also used to monitor success of treatment and to detect recurrence.

Non-Cancerous Reasons for Elevated Levels - Pregnancy (clears after birth), liver disease (hepatitis, cirrhosis, toxic liver injury), inflammatory bowel disease.

Low levels are present in both men & non-pregnant women (0-15 IU/ml). Generally results >400 are caused by cancer (Half-life 4-6 days).
(Oncolink.Org; LabTestsOnline; CancerSafe).

Calcitonin Tumour Marker

Also known as: Human Calcitonin; Thyrocalcitonin
Formal name: Calcitonin
Related tests**:** RET Oncogene; Calcium, TSH, T3, T4, Thyroglobin, CEA

The calcitonin test is primarily used to help diagnose C-cell hyperplasia and medullary thyroid cancer, to evaluate the effectiveness of treatment, and to monitor those affected for recurrence. It is also ordered to screen for medullary thyroid cancer in family members of people with multiple endocrine neoplasia type 2 (MEN 2).

Stimulation tests are more sensitive than calcitonin measurements alone. This involves collecting a baseline sample, then giving a person an injection of intravenous calcium or pentagastrin to stimulate calcitonin production. Several more blood samples are then collected over the next few minutes to measure the effect of the stimulation. People with early C-cell hyperplasia and/or medullary thyroid cancer will usually have very significant increases in their levels of calcitonin during this test.

Calcitonin levels may be ordered when someone is suspected of having C-cell hyperplasia or medullary thyroid cancer. A person may experience signs and symptoms, such as:

- A lump or swelling at the front of the neck
- Pain at the throat or front of the neck
- A change in the voice, hoarseness
- Difficulty swallowing or breathing
- Persistent cough not associated with a cold

A recent study also recommended measuring calcitonin before surgery in all people with thyroid nodules, but not all clinicians agree. Stimulation tests may be ordered when someone has indeterminate or normal calcitonin results but clinical suspicions remain. Calcitonin tests may be periodically performed on family members of those who have MEN 2, starting at an early age, in order to detect medullary thyroid cancer or C-cell hyperplasia as early as possible. When someone has been treated for medullary thyroid cancer, calcitonin testing will usually be ordered at regular intervals to monitor treatment effectiveness and recurrence.

A low level of calcitonin means that it is unlikely that symptoms are due to C-cell hyperplasia or medullary thyroid cancer. An elevated concentration of calcitonin means that excessive amounts are being produced. Significantly elevated levels of calcitonin are a good indicator of C-cell hyperplasia or medullary thyroid cancer; however, the doctor will use other procedures, such as a thyroid biopsy, scan, and ultrasound, to establish the diagnosis.

With successful treatment for medullary thyroid cancer, which may involve removal of the thyroid gland and often some surrounding tissues, calcitonin levels will usually fall to very low levels. If the values stay low over time, then it is likely that the treatment was effective. In some cases, calcitonin levels will fall but remain moderately elevated after treatment. This means that some calcitonin-producing tissue remains. Doctors will monitor calcitonin and watch for increases over time. If calcitonin levels begin to rise, then it is likely that there is a recurrence of medullary thyroid cancer.
(LabTestsOnline).

Tumour Marker DCP
Its full name is Des-gamma-carboxy prothrombin. It is associated with hepatocellular carcinoma (HCC).

Usual sample: blood.

It is used to monitor the success of treatment of HCC as well as to detect possible recurrence. It is a new test: often used along with an imaging study plust AFP and/or AFP-L3%. The latter is useful for:

Distinguishing between hepatocellular carcinoma and chronic liver disease

- Monitoring individuals with hepatic cirrhosis from any aetiology for progression to hepatocellular carcinoma

- Surveillance for development of hepatocellular carcinoma in individuals with a positive family history of hepatic cancer

o Surveillance for development of hepatocellular carcinoma in individuals within specific ethnic and gender groups who do not have hepatic cirrhosis, but have a confirmed diagnosis of chronic infection by hepatitis B acquired early in life including:

- African males above the age of 20
- Asian males above the age of 40
- Asian females above the age of 50

(Mayo Clinic).

ALK Gene Rearrangements

Transforming rearrangements of the ALK (anaplastic lymphoma kinase) gene have recently been described in non-small cell lung cancer (NSCLC).
The most common rearrangement arises from an inversion in the short arm of chromosome 2 that creates a fusion between the 5' portion of the EML4 (echinoderm microtubule-associated protein-like 4) gene and the 3' portion of the ALK gene. At least seven ALK gene rearrangement variants have been described involving different EML4-ALK breakpoints or rarely other non-EML4 fusion partners.

ALK rearrangements may be readily identified in tumour tissue by reverse transcription-polymerase chain reaction or fluorescent in situ hybridization. Although ALK gene rearrangements affect only about 4% of all lung cancers, they are more frequent in adenocarcinomas, in never or light smokers, and seem almost mutually exclusive with activating EGFR or KRAS mutations.

Promising results seen in patients with NSCLC containing fluorescent in situ hybridization-detected ALK rearrangements treated on a phase I study with PF02341066, an oral ALK inhibitor, indicate that ALK represents a new therapeutic target in this molecularly defined subset of NSCLC.
(Solomon, *et al*.).

BRCA 1 / 2 Tumour Marker

Also known as: BRCA; Breast Cancer Susceptibility Genes 1 and 2

Formal name: Breast Cancer Gene 1 and Breast Cancer Gene 2

Related tests: CA-125; Gene Expression Test for Breast Cancer; CA 15-3; Her2/neu:Eostrogen/Progesterone Receptor Status

Standard *BRCA1* and *BRCA2* tests are used to detect mutations that are known to increase the risk of breast and ovarian cancer development. If a *BRCA1* or *BRCA2* mutation has been identified in a family member with breast and/or ovarian cancer, then that specific mutation can be tested in other family members to assess their risk.

Specific *BRCA1* and *BRCA2*mutations are associated with some ethnic groups, such as those of Ashkenazi Jewish descent, and can be used to evaluate the risk of individuals in this group.

Only about 2% of the US population carries a BRCA1 or BRCA2 mutation. Because of this, genetic testing is not recommended for the general population. BRCA1 and BRACA2 testing

should be considered for individuals with a family history of a *BRCA1*/*BRCA2* mutation or a personal history of, for example:

- Breast cancer diagnosed at or before age 50 or ovarian cancer at any age
- Breast cancer diagnosed at or before age 50 with 1 or more close relatives with either breast cancer under age 50 or ovarian cancer, fallopian tube, primary peritoneal cancer at any age, or a limited family history
- Two primary breast cancers, one occurring before age 50
- Breast cancer diagnosed before age 60 that is negative for oestrogen receptors and progesterone receptors and for HER2/neu (triple negative)
- Breast cancer at any age with the presence of a family history of 2 or more relatives with breast or ovarian cancer, or one male relative with breast cancer, or in the setting of Ashkenazi Jewish ancestry

It is recommended that people be counselled by a genetic counsellor both before and after *BRCA* testing.

BRCA1 and *BRCA2* testing is not recommended as a screening tool for the general population. When a person has a strong family history of breast cancer or ovarian cancer or has a relative with a *BCRA1* or *BCRA2* mutation, they may choose to undergo testing. Someone who is considering testing should talk to their doctor and seek counselling by a genetic counsellor prior to and after testing.

The presence of a *BRCA1* or *BRCA2* mutation means that the person tested is at an increased risk for developing hereditary breast and/or ovarian cancer syndrome. However, even within a family with the same *BRCA* mutation, not everyone will develop cancer and those that do may develop it at different times during their life. According to the National Cancer Institute (NCI), estimates of lifetime risk for breast cancer in women with *BRCA1* or *BRCA2* mutations is about 85%, and estimates of risk for ovarian cancer range from 30% to 50%.

The absence of a *BRCA1* or *BRCA2* mutation means that the person tested is not in the high risk group for breast and/or ovarian cancer related to the *BRCA* gene. The person's risk of developing either of these cancers is the same as that of the general population.

For additional discussion of other things to consider when assessing one's risk, see below.

The degree of risk conferred with a positive result is difficult to quantify for a specific person. Results must be interpreted in conjunction with the tested person's personal and family history. A genetic counsellor should explain the meaning of the results, treatment options for the individual that are intended to decrease risk, and testing options for other family members.

Genetic testing for *BRCA1* and *BRCA2* mutations cannot occur with a 100% mutation detection rate; thus even with a negative result there is very small chance that there is a *BRCA1*/*BRCA2* gene mutation present that was not identified by the testing method utilized. In addition, there are other genes that may have mutations that can contribute to a family's risk for cancer.

Genetic testing for just *BRCA1* or *BRCA2* will only detect mutations in these two genes; therefore, if a mutation is present in another gene known to cause an increased risk for breast cancer, *BRAC1*/*BRCA2* testing will not detect it.

In addition, sometimes a personal or family history of cancer may suggest a factor or combination of other factors that contribute to a person's risk. In these families, it is likely that common risk factors such as shared genes that only sometimes cause cancer (low penetrance), shared environment and exposures, and shared lifestyle habits are increasing the risk for cancer above that of the general population. While individuals in these families typically do not have increased risks anywhere near as high as those seen in individuals with *BRCA1* or *BRCA2* mutations, they often will have increased risks for cancer slightly above those of the general population and sometimes increased cancer surveillance is recommended.

Positive test results may have implications for other family members. When one member of a family is tested for *BRCA* mutations, issues often arise about how to share this information with other family members. It may be helpful to seek advice from a genetic counsellor about how to communicate results with other family members.
Pre- and post-test consultation with a genetic counsellor about genetic testing cannot be overemphasized. There are many issues to be considered when preparing for a genetic test and upon learning the results, and a genetic counsellor has the knowledge and expertise to help sort through them.
(LabTestsOnline).

Tumour Marker CA 15-3
Its full name is Cancer Antigen 15-3 or Carbohydrate Antigen 15-3.

CA 15-3 is not sensitive or specific enough to be considered useful as a tool for cancer screening. Its main use is to monitor a person's response to breast cancer treatment and to help watch for breast cancer recurrence. CA 15-3 is sometimes ordered to give a doctor a general sense of how much cancer may be present (the tumour burden). CA 15-3 can only be used as a marker if the cancer is producing elevated amounts of it, so this test will not be useful for all people with breast cancer.

This tumour marker is raised in:

- Breast Cancer (often not elevated in the early stages of breast cancer)
- Lung cancer
- Ovarian cancer
- Endometrial cancer
- Bladder cancer
- Gastrointestinal cancer

Non-cancerous conditions when it may also be elevated include:

- Liver disease (cirrhosis, hepatitis)
- Lupus
- Sarcoid
- Tuberculosis
- Non-cancerous breast lesions

Values of importance:
< 31 U/ml (30% of patients have an elevated CA 15-3 for 30-90 days after treatment, so one should wait 2-3 months after starting new treatment before doing a check).
(Oncolink.Org; LabTestsOnline).

Ferritin Tumour Marker

Ferritin is a globular protein found mainly in the liver, which can store about 2'250 iron (Fe3+)ions. The ferritin molecule consists of a protein shell (apoferritin) composed of heavy and light subunits, which surrounds a crystalline core containing iron oxide and phosphate.

Ferritin is synthesized in the liver, spleen and numerous other body tissues, with major concentrations found in the liver, spleen, bone marrow, and intestinal mucosa.

The ferritin levels measured have a direct correlation with the total amount of iron stored in the body. If ferritin is high there is iron in excess, which would be excreted in the stool. If ferritin is low there is a risk for lack in iron, which sooner or later could lead to anaemia.

In the setting of anaemia, serum ferritin is the most sensitive lab test for iron deficiency anaemia. In contrast, serum ferritin levels are normal or increased in anaemia associated with chronic disease. Elevated serum ferritin levels have been observed in acute and chronic liver disease and lymphoid malignancy (leukaemia and Hodgkin lymphoma).

High serum ferritin levels have also been associated with an elevated risk for myocardial infarction in men. Ferritin is also used as a marker for iron overload disorders, such as haemochromatosis in which the ferritin level may be abnormally raised.

Ferritin is an acute-phase reactant, it is often elevated in the course of disease.

Free iron is toxic to cells, and the body has an elaborate set of protective mechanisms to bind iron in various tissue compartments. Within cells, iron is stored complexed to protein as ferritin or hemosiderin.

Apoferritin binds to free ferrous iron and stores it in the ferric state. Under steady state conditions, the serum ferritin level correlates with total body iron stores; thus, the serum ferritin level is the most convenient laboratory test to estimate iron stores.

Ferritin ELISA - Immunoenzymatic colorimetric method (ELISA) for quantitative determination of Ferritin in serum or plasma.

Principle of the Assay - The Ferritin assay is based on simultaneous binding of human Ferritin to two monoclonal antibodies; one is immobilized on the microplate, the other is soluble and conjugated with horseradish peroxidase (HRP). Microtiter strip wells are pre-coated with anti- Ferritin IgG antibodies.

Ferritin in samples and standards binds to the immobilised antibodies on the surface of the microtiter wells and the second, soluble anti-Ferritin antibody conjugated with HRP binds to the immobile antibody-Ferritin-complex during the first incubation. Afterwards a bound/free separation is performed by solid-phase washing. The immune complex is visualised by adding Tetramethylbenzidine (TMB) substrate, which gives a blue reaction product.

The intensity of this product is proportional to the amount of Ferritin in samples and standards. Sulphuric acid is added to stop the reaction. This produces a yellow endpoint colour. Absorption at 450 nm is read using an ELISA microwell plate reader.

Specific performance characteristics:

	Intra-assay	Inter-assay	Analytical Sensitvity	Accuracy
	CV%	CV%	ng/ml	± SD
Ferritin	4	4.8	1.0	98.4% ± 4.7%

Correlation with another available Ferritin assay performed on 54 samples is r = 0.99 (NovaTec).

Tumour Marker 72-4

Tumour marker CA 72-4 - diagnosing gastric carcinoma is often complicated and can be extremely difficult due to presentation with vague, non-specific symptoms that are sometimes associated with non-malignant disease.

Although endoscopy, coupled with histologic evaluation of biopsy specimens, is most often used to make definitive diagnosis, the search for additional non-invasive diagnostic procedures has longed continued. Strong new clinical evidence has recently emphasised the clinical value of the CA 72-4 serum tumour marker assay in diagnosis and monitoring of gastric cancer. CA 72-4 is THE stomach cancer tumour marker.

It is used together with tumour markers CEA and CA 19-9.
(CancerSafe)

Tumour Marker CA 125

Tumour marker CA 125 is a very interesting marker for ovarian cancer : the CA 125 is the essential marker for this cancer. It's THE marker in serous adenocarcinomas. The cut-off at 35 UI/l allows distinguishing women free of cancer from patients suffering this cancer, with a specificity between 82-100%.

In mucinous carcinomas, it has to be associated with CEA and CA 19-9.

In germinal tumours, we associate it with AFP and BHCG. CA 125 is also used in lung cancer - in the "small cells" form, it is used with the NSE
(CancerSafe).

Tumour Marker B2M (Beta-2 microglobulin)

Serum and plasma $beta_2$ microglobulin values have emerged as markers for the activation of the cellular immune system, as well as a tumour marker in certain hematologic malignancies. Urine $beta_2$ microglobulin values indicate renal filtration disorders.

Measurement of values in both serum and urine can help distinguish a problem of cellular activation from a renal disorder.

The reference range of $beta_2$ microglobulin in urine samples is 0-0.3 µg/mL. In serum or plasma samples, the reference range is 0-3 µg/mL.

Beta-2 microglobulin tumour marker is used to determine the prognosis and to monitor the success of treatment and to detect recurrence in:

- Multiple myeloma
- Chronic lymphocytic leukaemia (CLL
- Some lymphomas

Usual sample:

- Blood
- Urine
- Cerebrospinal Fluid

It may be elevated in other conditions such as certain kidney diseases.
(Medscape; LabTestsOnline).

Tumour Marker hCG

Its full name is Human chorionic gonadotropin, also called Beta-hCG.

It is associated with:

- Testicular cancer
- Trophoblastic disease
- Germ cell tumours
- Choriocarcinoma

Usual samples:

- Blood
- Urine

It is used to help diagnose the specific cancers as well as to monitor the success of treatment and to detect possible recurrence.

It is usually elevated in pregnancy.
(LabTestsOnline).

Tumour Marker JAK2 Mutation

It is associated with certain types of leukaemia.

Usual samples:

- Blood
- Bone marrow

It is used to help diagnose leukaemias. It is also used to diagnose bone marrow disorders characterised by overproduction of one or more types of blood cells known as myelo-proliferativbe neoplasms (MPNs), especially Polycythaemia Vera (PV).
(LabTestsOnline).

KRAS Mutation Tumour Marker
It is associated with the following cancers:

- Colorectal cancer
- Non-small cell lung cancer

Usual sample: tissue.

It is used to:

- Determine prognosis
- Guide the choice of treatment

It helps determine whether treatment with targeted therapy is appropriate.
(LabTestsOnline).

Tumour Marker Lactate Dehydrogenase (LDH)
A lactate dehydrogenase (LD or LDH) test is a non-specific test that may be used in the evaluation of a number of diseases and conditions. LD is an enzyme that is found in almost all of the body's cells (as well as in bacteria) and is released from cells into the fluid portion of blood (serum or plasma) when cells are damaged or destroyed. Thus, the blood level of LD is a general indicator of tissue and cellular damage. The level of LD may also rise in other types of body fluids (e.g. cerebrospinal fluid, pleural fluid, etc.) in the presence of certain diseases.

An LD *blood* test may be used:

- As a general indicator of the existence and severity of acute or chronic tissue damage
- To detect and monitor progressive conditions such as anaemia, including haemolytic anaemia and megaloblastic anaemia, or severe infections
- To help stage, determine prognosis, and/or monitor treatment (i.e., chemotherapy) of cancers, such as germ cell tumours (e.g., some types of testicular cancer and ovarian cancer), lymphoma, leukaemia, melanoma, and neuroblastoma

An LD test is performed on *body fluids* for a few different reasons:

- To help evaluate cerebrospinal fluid and distinguish between bacterial or viral meningitis
- To evaluate other body fluids such as pleural, peritoneal or pericardial fluid and help determine whether the accumulation of fluid is due to injury and inflammation (exudate) or due to an imbalance of pressure within blood vessels and the amount of protein in the blood (transudate). This information is helpful in guiding treatment.

An LD level may be ordered, along with other tests such as a comprehensive metabolic panel (CMP), when a health practitioner suspects that a disease or condition is causing some degree of cellular or tissue damage. If LD is elevated, then more specific tests, such as ALT, AST or ALP, may help diagnose the condition and help determine which organs are involved. Once the acute or chronic problem is diagnosed, total LD levels may be ordered at regular intervals to monitor its progress and/or resolution.

LD levels may also occasionally be ordered when an individual has experienced muscle trauma or injury or when a person has signs and symptoms of haemolytic anaemia.
LD testing may be ordered on a regular basis when an individual has been diagnosed with cancer.

Body fluid test - this test may be ordered, for example, when a person has signs and symptoms of meningitis or when someone has a build-up of fluid around the heart, lungs or in the abdomen.

Some related tests include:

- Comprehensive metabolic panel
- Haptoglobin
- Liver panel
- CSF analysis
- Body fluid analysis
- Pleural fluid analysis
- Pericardial fluid analysis
- Peritoneal fluid analysis

It is associated with:

- Testicular cancer
- Other germ cell tumours

Usual sample: blood.

It is used to:

- Stage the cancer
- Determine prognosis
- Monitor the success of treatment
- Detect recurrence

(LabTestsOnline).

Tumour Marker SMRP

It full name is Soluble Mesothelin-related Peptides. It is associated with mesothelioma (a rare type of cancer associated with asbestos exposure).

Usual sample: blood.

It is used to monitor the success of treatment and to detect recurrence.

It is often used in conjunction with imaging tests.
(LabTestsOnline).

T-cell Receptor Gene Rearrangement

This tumour marker is associated with T-cell lymphoma. It is used to detect characteristic changes (rearrangements) in specific genesis T-cells.

Usual samples:

- Bone marrow
- Tissue
- Body fluid
- Blood

(LabTestsOnline).

Tumour Marker HE 4

Human epididymis protein 4 (HE4) belongs to the family of whey acidic four-disulfide core proteins. Currently, the biologic function of HE4 is unknown.

HE4 has been shown to be overexpressed in 93% of serous, 100% of endometrioid, and 50% of clear cell ovarian carcinomas. In a study of 233 patients with a pelvic mass, including 67 with epithelial ovarian cancer, HE4 had a higher sensitivity for ovarian cancer detection than cancer antigen 125 (CA 125), 72.9% versus 43.3%, respectively, at a specificity of 95%. Researchers also found HE4 to be elevated in more than half of the ovarian cancer patients who did not have elevated CA 125 levels; therefore, the combination of markers provided slightly improved cancer diagnostic sensitivity for the detection of ovarian cancer.

The main established application of HE4 is in post-therapy monitoring of ovarian cancer patients, who had elevated pre-treatment levels. In this setting, it complements CA 125 measurement and facilitates follow-up of patients with little or no CA 125 pre-treatment elevations.

Certain histological types of ovarian cancer (mucinous or germ cell tumours) rarely express HE4, therefore the use of HE4 is not recommended for monitoring of patients with these types of ovarian cancer.

Reference Values:

- Females: < or =140 pmol/L
- Males: Not applicable

Interpretation - increase in human epididymis protein 4 (HE4) suggests recurrence or disease progression, while a decrease suggests therapeutic response. A change in serum HE4 concentration of > or =20% is considered significant.

Cautions - results cannot be interpreted as absolute evidence of the presence or absence of malignant ovarian disease, because mild elevations of human epididymis protein 4 (HE4) might also be present in individuals with benign gynaecologic conditions (ovarian cysts, cystadenomas, leiomyomas, myomas, fibromas, and endometriosis), hypertension, congestive heart failure, renal and liver disease.

Serial testing for patient HE4 results should be used in conjunction with other clinical methods for monitoring ovarian cancer.

HE4 should not be used as a screening test for ovarian cancer.

The use of this test in disease states other than ovarian cancer has not been clinically validated.

Ovarian cancer (OC) is a relatively manageable malignancy when diagnosed at an early stage, but late-stage detection almost always translates into a poor prognosis. Researchers

have been vigorously working on the identification of a more reliable biomarker to assist in early detection, as well as treatment - and general disease-monitoring. HE4 is among the most frequently upregulated genes in epithelial ovarian carcinomas based on gene expression profiles.

Several publications have demonstrated HE4's superiority over CA-125 as an OC biomarker. Specifically, HE4's ability to distinguish benign diseases from malignancies (i.e., its sensitivity) affords it with an advantage over CA-125 alone in OC detection. The use of CA-125 for detection of OC in premenopausal women is associated with a sensitivity and specificity so low that it is almost exclusively reserved for application in postmenopausal cases.
(Mayo Clinic; Medscape).

Beta HCG (Quantitiative) Tumour Marker
Tumour marker BHCG is normally produced by placenta during pregnancy. In fact, it's used as pregnancy test, since its level grows fast in first three months.

Apart from this field, BHCG is used for testicular cancer, where high levels can be observed; less commonly, ovary, liver, and last, stomach, pancreas and lung.

Be aware that marijuana consumption leads to increased levels.
(CancerSafe).

Osteocalcin Tumour Marker
Serum osteocalcin (OC) is derived largely from new cellular synthesis. It is a marker for bone formation and a non-invasive specific marker of osteoblastic activity. The clinical significance of OC in monitoring prostatic cancer bone metastases was evaluated.

Pre-treatment serum OC levels were determined with a radioimmunoassay kit in a total of 63 patients with prostate cancer (8 with stage B, 12 with stage C, 12 with stage D1, and 31 with metastatic bone disease). The OC levels in patients with skeletal metastasis were significantly higher than those in patients without bony lesions (P less than 0.01).

The pattern of the initial changes in OC levels were analysed in patients with skeletal metastasis who received endocrine treatment. The pre-treatment OC value is of little use in predicting the response to treatment. The patients whose OC level initially increased and remained high tended to have a shorter interval to disease progression. On the other hand, the pattern of initial changes in OC varied according to the regimen of endocrine treatment.

Our study suggests that OC seem to reflect the response to treatment and might lead to the improvement in follow-up procedures. However, the clinical significance of OC as a marker of the response of bone metastasis should be carefully discussed with regard to the direct hormonal effect on bone metabolism.
(Arai, *et al*.).

Some Pathologies and Their Respective Tumour Markers

Breast	CA15-3, CEA, Cyfra 21-1.
Ovary	CEA, CA125, CA 19-9; AFP, BHCG.
Uterine	SCC, Cyfra 21-1 ; CEA, CA 19-9, CA 125.
Prostate	PSA, FPSA and ratio.
Testicle	BHCG, AFP.
Colorectal	CEA, CA 19-9, CA 125.
Pancreas	CEA, CA 19-9, CA 72-4.
Liver	AFP, CEA.
Stomach	CA 72-4, CEA, CA 19-9.
Oesophagus	CEA, Cyfra 21-1.
Thyroid	CEA, NSE.
Lung	NSE, CYFRA 21-1; CEA, CA 125, CA 19-9.
Bladder	TPA, CEA, Cyfra 21-1.

(CancerSafe).

Values of Some Tumour Markers

Range – moderate to high values:

CEA	ng/ml <5 5-10 10->100 000
AFP	ng/ml <15 15-200 200-10 000
PSA	ng/ml <4 4-10 10-1 000
FPSA/PSA	ratio : >0.25 . <0.25 <0.10
CA 15-3	U/ml <40 40-60 60-30 000
CA 19-9	U/ml <35 35-100 100-5 000 000
CA 125	U/ml <35 35-50 50- 50 000
CA 72-4	U/ml <6.7 7-30 30-10 000
BHCG	UI/ml <5 >5 5-500 000
B2M	mg/l <2 >2 2-10
NSE	ng/ml <21 22-40 40-10 000
CYFRA 21	ng/ml <3,5 >3,5 3,5-1000.

(CancerSafe).

Multiple Tumour Marker Tests

Tumour markers are not, by and large, useful diagnostic tests, but more often useful to find the origin of confirmed carcinoma of unknown primary (CUP) or to track the evolution of a confirmed tumour.

Multiple Tumour marker tests will give a more exact result; these are:

- Colorectal: M2-PK, if M2-PK is not available, so can test CEA, CA 19-9, CA 125
- Breast: CEA, CA 15-3, Cyfra 21-1
- Ovary: CEA, CA 19-9, CA 125, AFP, BHCG
- Uterine: CEA, CA 19-9, CA 125, Cyfra 21-1, SCC
- Prostate: PSA, FPSA and ratio
- Testicle: AFP, BHCG
- Pancreas/Stomach: CEA, CA 19-9, CA 72-4
- Liver: CEA, AFP
- Oesophagus: CEA, Cyfra 21-1

- Thyroid: CEA, NSE
- Lung: CEA, CA 19-9, CA 125, NSE, Cyfra 21-1 (Sensitivity at 95 percent percentile for Cyfra 21-1 is 79 percent, while for SCC and CEA are 41 and 31 percent respectively)
- Bladder: CEA, Cyfra 21-1, TPA

(Wikipedia).

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Sources and References

American Family Physician
http://www.aafp.org/afp/2003/0915/p1075.html

Arai, Y., Takeuchi, H., Oishi, K. & Yoshida, O. 1992. Osteocalcin: is it a useful marker of bone metastasis and response to treatment in advanced prostate cancer? *Prostate*. 1992; 20(3):169-77.

Bunworasate, U. & Voravud, N. 1995. CA 50: a tumor marker for gastrointestinal malignancies. *J Med Assoc Thai*. 1995 May;78(5):255-70.

Canadian Cancer Society
http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/tests-and-procedures/tumour-markers/?region=on

Cancer.Net
http://www.cancer.net/navigating-cancer-care/diagnosing-cancer/tests-and-procedures/tumor-marker-tests

CancerSafe
http://www.cancersafe.com/screening/index.asp

Guadagni,F., Roselli, M., Cosimelli, M., Ferroni, P., Spila, A., Cavaliere, F., Casaldi, V., Wappner, G., Abbolito, M.R. & Greiner, J.W. 1995. CA 72-4 serum marker: a new tool in the management of carcinoma patients. Cancer Invest. 1995. 13(2):227-38.

Lab Tests Online
https://labtestsonline.org/understanding/analytes/ca19-9/tab/test/
https://labtestsonline.org/understanding/analytes/tumor-markers/start/1
https://labtestsonline.org/understanding/analytes/tumor-markers/start/2
https://labtestsonline.org/understanding/analytes/5hiaa/tab/test/
https://labtestsonline.org/understanding/analytes/calcitonin/tab/test/
https://labtestsonline.org/understanding/analytes/brca/tab/test/
https://labtestsonline.org/understanding/analytes/ca15-3/tab/test/
https://labtestsonline.org/understanding/analytes/ldh/tab/test/

LifeExtension
http://www.lifeextension.com/magazine/2013/12/prostate-diagnostic-and-assessment-tests/page-01

Mayo Clinic
http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/62137
http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/88878

Medical Dictionary
http://medical-dictionary.thefreedictionary.com/Tumor+Markers

MedicineNet.Com
http://www.medicinenet.com/script/main/art.asp?articlekey=8722
http://www.medicinenet.com/script/main/art.asp?articlekey=8732

Medscape
http://emedicine.medscape.com/article/2087513-overview#a2
http://emedicine.medscape.com/article/1953022-overview
http://emedicine.medscape.com/article/2086864-overview
http://www.medscape.com/viewarticle/711023_5

National Cancer Institute
http://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-markers-fact-sheet

NovaTec
http://www.novatec-id.com/products/tumor-markers/ferritin/

OncoLink.Org
http://www.oncolink.org/treatment/article.cfm?id=296
http://www.oncolink.org/treatment/article.cfm?id=296

Plos.Org
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0019096

Sharma, S. 2009. Tumor markers in clinical practice: general principles and guidelines. *Indian J Med Paediatr Oncol*. 2009 Jan-Mar, 30(1):1-8. Doi: 10.41009756328.13

Schmitt, F.C. & Bacchi, C.E. 1989. S-100 protein: is it useful as a tumour marker in diagnostic immunocytochemistry? Histopathology, 1989. Sep: 15(3):281-8.

Solomon, B., Varella-Garcia, M. & Camidge, D.R. 2009. ALK gene rearrangements: a new therapeutic target in a molecularly defined subset of non-small cell lung cancer. *J Thorac Oncol.* 2009 Dec;4(12):1450-4. doi: 10.1097/JTO.0b013e3181c4dedb.

The Doctors Laboratory
http://www.tdlpathology.com/about-tdl/publications/lab-report-newsletter/spring-2010/tumour-markers

Thyca.Org
http://www.thyca.org/pap-fol/more/thyroglobulin/

Tumour Marker Test
http://www.thesilverpen.com/breast-cancer-information-facts/breast-cancer-diagnosis/tumor-markers/

van Poppel, H., Billen, J., Goethuys, H., Elgamal, A.A., Gerits, M., Mortelmans, L., Blanckaert, N. & Baert, L. 1996. Serum tissue popypeptide antigen (TPA) as tumor marker for bladder cancer. *Anticancer Res*. 1996. Jul-Aug. 16(4B):2205-7.

Wikipedia
https://en.wikipedia.org/wiki/Tumor_marker

Wiley Online Library
http://onlinelibrary.wiley.com/doi/10.1111/j.1445-2197.1982.tb05282.x/abstract