

Tumor Markers

• CA 125

General:

The CA 125 (carbohydrate antigen 12-5) is a glycolipoprotein with a high molecular weight of 1000 kD. CA 125 is found in fetal and adult normal tracheal, bronchial, bronchiolar and terminal bronchiolar epithelium, in tracheal, bronchial glands as well as in pleural mesothelium in addition to its occurrence in malignant lung tumors.

Indication: Therapy monitoring in ovarian carcinoma, suspicion of pancreas carcinoma (second marker after the CA 19-9).

Material: 1 ml serum, dialysate, aspirate, puncture specimen

Stability: 5 days at 2 to 8°C

TAT: same day, FML

Method: ECLIA

Units: U/ml

Ref.- range: <35.0

• CA 153

General:

CA 15-3 (cancer antigen 15-3) is a high-molecular mucin-carbohydrate, which is formed in mucosal cells and can be detected as secretion product. In healthy subjects CA 15-3 is detectable in traces. CA 15-3 is used for treatment monitoring (progression or remission).

Material: 1 ml serum, dialysate, aspirate, puncture specimen

Stability: 5 days at 2 to 8°C

TAT: same day, FML

Method: ECLIA

Units: U/ml

Ref.- range: <25.0

• CA 19-9

General:

CA 19-9 is a glycolipid antigen with a molecular weight of 36 kD and is also considered as the hapten of the Lewis blood group determinant. The main significance is early diagnosis (cut-off at 100 U/ml) as well as therapy monitoring of patients with pancreas carcinoma, hepatobiliary and stomach carcinoma (in combination with a second marker, e.g. CEA).

Indication: Suspicion of pancreas carcinoma, hepatobiliary carcinoma (liver carcinoma, biliary tract CA), stomach carcinoma.

Material: 1 ml serum, aspirate, puncture specimen

Stability: 14 days at 2 to 8°C

TAT: same day, FML

Method: ECLIA

Units: U/ml

Ref.- range: <39.0

Note: Undetectable CA 19-9 can be expected in patients and healthy persons with the rare blood group constellation: Lewis A/B negative (3-10 % of the population), as no CA 19-9 epitopes are expressed.

Increased: Cholestasis, cholecystitis, hepatitis, PBC, cirrhosis, CF, tumors of the gastrointestinal tract such as pancreatic tumor, pancreatitis, tumor of the liver, gall bladder, stomach and colorectal system, more rarely in ovarian carcinoma (mucous type) and uterine carcinoma.

• CA-50

General:

CA-50 is a carbohydrate antigen found on the surface of epithelial tumors and it seems to represent a general tumor-associated antigen. Its occurrence is not organ or tissue specific. The test is not useful as a screening test but it is of additional help, e.g. for CA 19-9 confirmation.

Material: 1 ml serum

TAT: 7-10 days*

Method: RIA

Units: U/ml

Ref.- range: <25.0

- **CA 72-4**

General:

CA 72-4 is a tumor associated mucin-like glycoprotein (TAG 72) with a molecular weight of 400 kD. The main indication is therapy monitoring of stomach carcinoma as the primary marker together with a second marker (CEA or CA 19-9).

CA 72-4 is used as a second marker in mucous ovarian carcinoma. Its clinical significance is the relatively high specificity in stomach carcinoma (> 95%). The serum concentration correlates with tumor mass, tumor stages and formation of metastases. The test is less suitable for screening or primary diagnosis.

Indication: Therapy monitoring of stomach carcinoma, second marker in mucous ovarian carcinoma.

Material: 1 ml serum

TAT: 7-10 days*

Method: ECL

Units: U/ml

Ref.- range: <6.9 borderline: 7.0 - 8.2

- **CA 242**

General:

The epitope of CA 242 antibody is a sialysed carbohydrate coexpressed with sialylated Lewis(a) antigen (CA 19-9) and CA 50 on the same macromolecular complex. CA 242 is considered as a tumor marker for pancreatic cancer and does not improve the sensitivities reached with CA 19.9 and CA 50, but the combination does achieve both a higher sensitivity and specificity.

Material: 1 ml serum

TAT: 7-10 days*

Method: EIA

Units: U/ml

Ref.- range: upto 25.0

- **CEA (Carcinogenic embryonic antigen)**

General:

CEA is a glycoprotein (MW 180 kD) and is normally detected only in the embryonic endodermal epithelium. The glycoprotein can appear in different malignant cells and is considered a tumor marker, but particularly a parameter used for monitoring. As tumor marker CEA is relatively unspecific and moderately sensitive.

Indication: Therapy monitoring

Material: 1 ml serum

Stability: 14 days at 2 to 8°C

TAT: same day, FML

Method: ng/ml

Ref. -range: <3.4

- **HE4**

General:

The gene encoding HE4 is amplified in ovarian carcinomas, whereas its expression in normal tissues, including ovary, is low. The function of the HE4 protein (human epididymis protein 4) is currently unknown, but compared to CA 125 its specificity for malignant disease is higher. As a biochemical marker, HE4 has a higher potential than CA 125 in detecting early tumor stages and is found in 93% of serous and 100% of endometrioid epithelial ovarian cancers, also in the early stages. HE4 expression is highly restricted to the reproductive tracts and a low expression is found in normal tissue and benign tumors as well as in mucinous ovarian carcinomas; however, it is not found in the majority of non-ovarian cancers.

The combination of testing for HE4 and CA 125 significantly increases the diagnostic sensitivity and specificity for epithelial ovarian carcinomas. However, for detection in the early stage (I) HE4 is the best single marker with no increase in sensitivity when combined with CA 125 or any other marker (according to the study by Moore et al.)

Another advantage of HE4 is that it only shows higher concentrations in women with endometrial and ovarian cancer, however not with ovarian endometriomas or other types of endometriosis. Measuring the combination of both markers can be used to classify women with tumors into high and low risk groups and to estimate the risk of epithelial ovarian cancer in premenopausal and

postmenopausal women presenting with pelvic mass (using the ROMA™ - Risk of Ovarian Malignancy Algorithm), see **ROMA**.

Indication: Monitoring of therapy, recurrence and progressive disease in patients with epithelial ovarian carcinoma (not as primary screening test).

Material: 1 ml serum

TAT: 5-7 days*

Method: CMIA

Units: pmol/L

Ref.- range: <70 premenopausal < 140 postmenopausal

Note: Results should be interpreted only in conjunction with other investigations and procedures in the diagnosis of disease and management of patients and the HE4 test should not replace any established clinical examination.

- **Prostate specific antigen, PSA**

General:

The prostate specific antigen is a glycoprotein and a tissue specific secretion product of the prostate gland cells, similarly as prostate specific acidic phosphatase (PSP). It is used as an organ specific tumor marker. The concentration in the prostate gland secretion is 1 million times higher than in plasma, its half-life is 2.2 days.

In healthy men PSA supports the liquefaction of the seminal plasma. Under cell stress (manipulation, inflammation, necrosis, tumor) PSA penetrates through the basal cell membrane and enters into the blood stream (increased values).

Indication: Screening of prostate gland carcinoma, course monitoring after prostate gland resection, radiotherapy, monitoring of hormonal therapy of the prostate gland carcinoma, prostatitis

Material: 1 ml serum

Stability: 5 days at 2 to 8°C

TAT: same day, FML

Method: ECL

Units: ng/ml

Ref.-range: <4.00

Note: In routine diagnostics a PSA value of 10 ng/ml is considered to be the approximate limiting value for the differentiation between benign prostatic hyperplasia (BPH) and prostate gland carcinoma. See also Tumor marker. The combination of complexed (CPSA) or free PSA offers a better differential diagnosis in the range under 10 ng/ml.

Comments: **Increased:** prostatitis, infarction of the prostate gland, compression of the prostate gland (digital examination, catheterization of the bladder, cystoscopy, obstruction of the bladder exit), benign prostatic hyperplasia (BPH), prostate gland carcinoma (at present PSA is the most sensitive parameter), metastasis after removal of the primary tumor.

Other: other malignant disorders (values rarely over 10 ng/ml): gastrointestinal and hypernephroid carcinomata, leucosis, hepatic cellular carcinoma.

- **Prostate specific free antigen, free PSA**

General: The part of free PSA in relation to total PSA is considerably lower in patients with prostate gland carcinoma than in benign prostate hyperplasia.

Indication: Differential diagnosis benign/malignant prostate gland disorders

Material: 1 ml serum

Stability: 5 days at 2 to 8°C

TAT: same day, FML

Method: ECL

Units: ng/ml

Ref. range: see report

- **Prostate specific antigen, complexed, cPSA**

General: In the PSA borderline range (between 4 and 10 ng/ml) it is sometimes difficult to differentiate correctly between prostate gland carcinoma and benign prostatic hyperplasia. Determination of PSA-isoforms can improve this situation. Free PSA (fPSA) or the ratio (fPSA/tPSA) is an additional decision criterion for a prostate gland biopsy. Complexed PSA has been described as a superior parameter compared to the ratio fPSA/tPSA.

Indication: Differential diagnosis benign/malignant prostate gland disorders

TAT: 7-10 days*

Method: CLIA

Units: ng/ml

Ref. range: < 3.2

• ROMA Risk of Ovarian Malignancy Algorithm (Index)

General:

To better assess the risk of epithelial ovarian cancer in both pre- and post-menopausal women with pelvic mass the combination of two markers can be used in an algorithm (ROMA) to give a predictive value. These results must be interpreted in conjunction with other methods in accordance with standard clinical management guidelines. The combination of all of this information can help in determining the most appropriate course of care.

The first marker is HE4 (human epididymal protein 4), which is an early stage marker used to monitor response to therapy in patients with epithelial ovarian cancer. In conjunction with the second marker, CA 125, a tumor marker, the diagnostic sensitivity and specificity for epithelial ovarian carcinoma significantly increases. HE4 is more sensitive as a single marker; however, the combination of both markers is more sensitive than either marker alone.

The ROMA calculation for risk prediction and stratification using serum levels of CA125 + HE4 is a new differential diagnostic tool for women presenting with pelvic mass to successfully classify them into high- and low-risk groups.

Indication: pre- and post-menopausal women presenting with a pelvic mass to estimate their risk of epithelial ovarian cancer

Material: 1 ml serum

TAT: 7-10 days*

Method: RECH

Units: %

Ref.- range: pre-menopausal:

ROMA value $\geq 11.4\%$, high risk of finding epithelial ovarian cancer

ROMA value $\leq 7.4\%$, low risk of finding epithelial ovarian cancer

post-menopausal:

ROMA value $\geq 29.9\%$, high risk of finding epithelial ovarian cancer

ROMA value $\leq 25.3\%$, low risk of finding epithelial ovarian cancer

Literature: Moore, R.G., McMeekin, D.S., Brown, A.K., et al. (2009). A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with pelvic mass. *Gynecol Oncol.* 112(1): 40-46.

Index by organs

Tumor	Marker
Bladder	CEA, TPA , SCCA
Hydatidiform mole	β -HCG (up to 1 Mio. U/l, frequency 1:20,000), SP1
Bronchial /lungs	CEA, TPA, M2PK
Squamous epithel. ca.	SCCA , CEA , Cyfra 21.1
Small-celled ca.	NSE, TPA , CEA
Adeno/others:	CA 72-4 , CEA, TPA, ACTH, ADH, ferritin, PTH, calcitonin
Cervix	SCCA, Cyfra 21.1, CEA, TPA
Chorion	β -HCG
Bladder	NMP 22
Colon	CEA, CA 19-9, CA 72-4 , M2PK
Endometrium/uterus	SCCA, CEA, CA 125
Bile duct	CA 19-9 , CA 125, CEA, (CA 50)
Testicular	AFP , β -HCG, SP 1, NSE, SCCA, M2PK

Tumor	Marker
Hypophysis	Prolactin (prolactinoma), GH (gigantism, acromegaly), ACTH (Cushing syndrome)
Intestine	CEA, CA 19-9 , serotonin (5-HIAA/carcinoid syndrome)
Germinal	AFP, β -HCG, SP1
Liver	Primary hepatocellular carcinoma: AFP, CA 19-9
Lungs	(see bronchial /lungs)
Stomach	CA 72-4, CEA , gastrin, (CA 50)
Mamma	CA 15-3, CEA, TPA
Mouth/tongue	SCCA , CEA, TPA, CA 19-9
Suprarenal (medulla)	Metanephrines, catecholamines, VMS (pheochromocytoma)
Suprarenal (cortex)	Cortisol (Cushing), DHEA, aldosterone (hypertension), testosterone (virilization)
Kidneys	CEA, renin
Esophagus	SCCA, CEA, CA 19-9, CA 125, Cyfra 21.1
Ovary	CA 125, CASA, CA 72-4, AFP, CEA, TPA, β -HCG, testosterone (virilization)

Pancreas	CA 19-9, CEA + u-PA*, CA 125, TPA, α -amylase;
	Insulin, C-peptide (insulinoma); gastrin (gastrinoma)
Paraneoplastic syndrome	ACTH, cortisol, calcitonin, serotonin (5-HIAA)
Prostate gland	PSA**, prostate acidic phosphatase (PSP)
Rectum	see under colon (CRC, rectum approx.)
Thyroid gland	Papill. /fol. thyroglobulin (hTG) medullar calcitonin, (CEA)

* u-PA = "Plasminogen activator", tumor marker for pancreas carcinoma which shows high specificity and sensitivity in combination with CEA.

** PSA (prostate gland specific antigen) is part of the small group of suitable tumor markers.

Index by markers

Tumor Marker	Tumor and/or disease	Non-malignant increase
ACTH	HVL, lungs	M. Addison, AGS
AFP	Liver, germ cells	Liver, pregnancy
Bence Jones	Plasmocytoma	
CA 125	Ovary, bile ducts , gastrointestinal tract, mamma, pleural mesothelioma	
CA 15-3	Mamma, ovary, cervix, endometrium	
CA 19-9	Pancreas, CRC, esophagus, GIT, liver, mucous membrane of mouth/tongue	
CA 72-4 (TAG 72)	Stomach , ovary	Acute pancreatitis, hepatic cirrhosis, lung diseases, connective tissue diseases
Calcitonin	Medullar thyroid gland carcinoma	
CASA	Ovary	

CEA	CRC, pancreas (CEA+u-Pa), intestinal tract, stomach, lungs, kidney, mamma, ovary, bladder	Smokers (precancerosis), hepatic cirrhosis, inflammatory diseases of the lungs and the intestine
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Tumor Marker	Tumor and/or disease	Non-malignant increase
Chromogranin	Endocrine tumors (neuroblastoma, carcinoid, pheo-chromocytoma, small-celled lung carcinoma)	in restricted kidney function, distinctive GIT absorption defect (malabsorption syndrome), M. Whipple and local sprue
Cortisol	Pituitary gland/ adrenal cortex	
Cyfra 21.1	carcinoma of the lungs, cervix, esophagus	
DHEA sulfate	Pituitary gland/ adrenal cortex	
Dopamine	Sympathetic cell row	
Ferritin	M. Hodgkin, leukemia, lymphoma, kidney, (pancreas, mamma	Iron overloading, infections, hepatopathies, Still syndrome,
Gastrin	Gastrinoma	
GH (HGH)	HVL (acromegaly)	
β-HCG	Chorionepithelioma, hydatidiform mole,	

	pregnancy, testicular tumor	
5-HIAA	Carcinoid syndrome	
Catecholamines	Suprarenal gland medulla	
M2 pyruvate kinase	Proliferation activity of different tumors of the gastrointes-tinal section, lungs, mamma and renal cell carcinoma,	
Metanephrines	Suprarenal gland medulla	
β 2-microglobulin	Lymphoma, multiple myeloma, lymphatic leukemia, HIV	Viral diseases
Tumor Marker	Tumor and/or disease	Non-malignant increase
Neopterin	Lymphoma, leukemia, HIV	Viral diseases
NMP 22	Carcinoma of the bladder	Interstitial cystitis, infections of the urine tract, invasive operations (cysto-scopy, catheterization, OP)
NSE	Small-celled bronchial carcinoma, neuroblastoma, melanoma	
u-PA	Pancreas (particularly in combination with CEA)	
Prolactin	Pituitary gland	Hypothyroidism
PSA	Prostate gland	Prostate gland which has been examined manu-ally or with instruments 12 h before blood collection (also catheterization as well as cystoscopy etc.), benign hypertrophy
SCC	Cervix, esophagus, mouth	Lungs, squamous epithelium
Serotonin	Carcinoid syndrome	

Testosterone	Ovary/adrenal cortex	Hyperplasia of adrenal cortex
Thyroglobulin	Papill. /foll.-thyroid gland carcinoma	
TPA (TPS)	Small-celled bronchial carcinoma, bladder, cervix, ovary, mamma	Diseases of the lungs and GIT
VMA	Adrenal medulla	

Tumor markers, clinical value:

Marker	Screening	Diagnosis	Prognosis	Therapy success	Growth (Relapse)
AFP (hepatoma, seminoma and chorion-epithelioma)	++	++	+	+	+
β-HCG	++	++	+	+	+
CEA					+
Calcitonin	+				
PSA	++	++		+	+
CA 125		+ (Ovary)	+	+	
CA 153				+	
CA 19-9		+ (Pancreas)	+	+	+
CA 72-4		+			+



CASA		(+) (Ovary)	+		
NSE		(+)	(+) (small cell)		+

For complete list of laboratory test offered at Freiburg Medical Laboratory, please visit <http://www.fml-dubai.com/parameter-listings/>