Acetaminophen, Serum

Related Information: Alanine Aminotransferase, Serum
Aspartate Aminotransferase, Serum

Synonyms: Anacin-3®; Datril®; Liquiprin®; Paracetamol; Tempra®; Tylenol®
also acetophenetidin and phenacetin

Background: Acetaminophen is available in combination with codeine, acetylsalicylic acid, and coffeine or single and is seen frequently in overdose situations.

A metabolite, N-acetyl-p-benzoqinoneimine is inactivated by cysteine and mercapturic acid conjugation, glutathione is required for theses conjugation reactions. Standard therapy of poisoning is a 72h protocol of oral N-acetylcysteine (Mucomyst®), or an IV. administration for 20h to prevent hepatotoxicity by N-acetyl-p-benzoqinoneimine, which can not be detoxified due to depletion of glutathione stores caused by overdosing.

Rapid absorption, peak plasma levels within 30-60 min after therapeutic dose, in overdose situation, peak may be reached after 4h.

Bioavailability 75%-95%; urinary excretion 1-4%; plasma binding 20%-50%; volume of distribution 0.8-1.1 L/kg; half life time adults: 1-3h, neonates: 2-5h; peak time 0.5 -1.5h, peak concentration 20 µg/mL after 20 mg/kg orally.

Sampling: 1 mL heparin plasma

Reference Interval:

Therapeutic: 10-30 µg/ mL

Toxic: > 150 µg/mL within 4h post ingestion, > 50 µg /mL within 12h post ingestion

A good indicator for toxicity and to calculate half life: Assess post ingestion 4h blood level and post ingestion 8h: Half life exceeding 4h are consistent with hepatic dysfunction.

Acetylcholine Receptor Antibody, Binding

Related Information: Thyreoglobulin Antibody
Thyroperoxidase Autoantibody

Synonyms: Acetylcholine Receptor Blocking Antibody

Background: Two types of antibodies are known in Myasthenia Gravis (MG): Autoantibodies binding to sites of the acetylcholine receptor which are not involved in acetylcholine binding and autoantibodies blocking the binding of alpha bungarotoxin.

Sensitivity: overall, up to 35% of myasthenia Gravis patients have false negative test results, up to 50% in cases of ocular MG, up to 25% in patients with generalized MG. A higher number of false negatives are seen within the first year after onset of the disease.

False positive results occur in patients with Eaton Lambert syndrome and rarely in first degree relatives of MG patients, in patients with amyotrophic lateral sclerosis, primary biliary cirrhosis, carcinomas, autoimmune diseases and thymomas.

Specificity: Overall high, up to 99%.

Useful marker in the diagnosis of MG, monitor MG therapy while levels correlate with clinical improvement. Assessment of patients with thymomas: up to 50% of patients with thymomas have myasthenia gravis disease.

Sampling: 1 mL serum

Reference Interval: < 0.4 nmol/L

Acetylcholine Receptor Blocking Antibody see Acetylcholine Receptor Antibody, Binding

Acetylsalicylic Acid (ASA), Serum see Salicylate, Serum

Acid Phosphatase Total, Plasma

Related information: Prostatic Acid Phosphatase, Serum
Prostate Specific Antigen, Free, Serum
Prostate Specific Antigen, Serum

Synonyms: Phosphatase, Acid

Test includes: Prostatic Acid Phosphatase (will be determined if elevated in males only)

Background: Please see: Prostatic Acid Phosphatase, Serum

The family of acid phosphatases consists of isoenzymes derived from the prostate (characterized as tartrate sensitive) and from erythrocytes, macrophages and of other origin (tartrate resistant). Acid phosphatase may be increased in diseases of the prostate such as carcinoma, prostatitis, benign hyperplasia, urine retention, and in non-prostatic diseases such as bone metastasis of non prostatic origin and in myelocytic leukemias, Gaucher disease, and Niemann-Pick disease. The tartrate resistant form is not of prostatic origin and is a bone resorption marker.

False negative results may occur in adenocarcinoma confined within the prostate or extensive large forms of prostatic carcinomas.

Sampling: 2 mL serum, transport to laboratory immediately or separate plasma and freeze. Do not sample immediately after rectal examination of the prostate or TUR to avoid false positive results. Due to diurnal variation, morning collection is recommended. Serum bilirubin > 2 mg/dL interferes to a high degree with measurement, giving unreliable results.

Reference Interval:

Male	< 7.2 U/L
Female	< 6 U/L
Children	< 8 U/L

Activated Partial Thromboplastin Time

Related Information: Fibrinogen, Functional
Prothrombin Time
Thrombin Time

Synonyms: Partial Thromboplastin Time;
Thromboplastin Time, Partial; PTT; APTT; aPTT

Background: PTT measures the clotting time from the activation of factor XII down to the final fibrin clot, thus covering the intrinsic and common pathway function, whereas the prothrombin time measures the function of the extrinsic and common pathways. PTT prolongations are caused by factor VIII, IX, XI, XII, prekallikrein and HMWK dysfunction and to a lesser extent to fibrinogen, factors II, V, and X of the common pathway (but not factor VII). Inhibitors such as lupus anticoagulants may or may not prolong PTT. Useful in monitoring therapeutic anticoagulants (heparin, hirudin, argatroban). PTT becomes prolonged for single factor deficiency if the factor is below 20%-40%, for multiple factor deficiency less severe functional impairment is indicated by PTT. Increase of factor VIII during acute phase reaction decreases PTT. To make sure that PTT prolongation by heparin therapy is not due to lupus anticoagulant factor, it is recommended to perform a Heparin Antifactor Xa assay in the first testing.

Causes of PTT prolongation:

Hereditary:

PT normal: deficiency of factor VIII, IX, XI, XII, prekallikrein, HMWK

PT prolonged: deficiency of fibrinogen, factor II, V, X

Acquired:

Lupus anticoagulant: (binding to phospholipids and interfere with their role as a cofactor, but usually associated with thrombosis) PT normal

Heparin: PT normal or abnormal

Hirudin or argatroban: PT more affected

Vitamin K deficiency, Coumadin® and liver dysfunction: PT more affected

DIC: PT more affected

Sampling: 2 mL citrate plasma. Plasma should be separated within 1h if PTT is used for monitoring heparin therapy, since PF4 released from platelets neutralize heparin.

Reference Interval: 25-40 seconds in adults, in newborns up to 55 seconds, decreasing at the age of 6 month to adult values.

Activated Protein C Resistance

Related Information: Activated Partial Thromboplastin Time
Antithrombin III
Protein C
Protein S , Total

Synonyms: APC Resistance, Factor V Leiden Screening Test

Background: Resistance to activated protein C (APC) leads to a hypercoagulable state. The test includes: APTT with $CaCl_2$, APTT with activated protein C and $CaCl_2$. Both assays are run in a 1:5 dilution in factor V deficient plasma. Ratio of APTT run with activated protein C over APTT run with $CaCl_2$ is reported.

Protein C is vitamin K dependant, produced in the liver, and requires thrombin and thrombomodulin for activation. Protein C in the presence of protein S inactivates factors Va and VIIIa .
Patients heterozygous for protein C or protein S may exhibit recurrent venous thrombosis. Patients homozygous in deficiency for protein C may present with general microvascular thrombosis in the neonatal period. Young patients have been reported with resistance to the action of APC with normal levels of protein C, protein S, antithrombin III and a point mutation in factor V gene and can be diagnosed by calculation of the ratio PTT in the presence of APA divided by PTT in absence of APC (see above).

Sampling: 2 mL citrate plasma. To avoid contamination with tissue factors, draw 1-3 mL (6-10 mL if blood is drawn from an indwelling catheter) into another container, discard, and draw the coagulation sample. Immediately invert sample 5-10 times gently to mix thoroughly. Tube must be filled at least 90% of requested tube volume. Separate the plasma from the cells within 30 min. Store at 2-8° C for maximum of 4h. Or freeze rapidly on dry ice and store at –70° C. Storage at –70° C up to 6 month.

Test results are not affected by oral anticoagulants or heparin, at less than 1 u/mL.

Reference Interval:

Normal: ratio > 2

Suspicious on hereditary protein C resistance: ratio 1.4-1.9

Acute Phase Proteins see Acute Phase Reactants, Serum

Acute Phase Reactants, Serum

Synonyms: Acute Phase Proteins

Overview: please see individual parameter

- Alpha 1 Antitrypsin, Serum
- Alpha 1 Microglobulin, Serum or Urine
- C Reactive protein, Serum
- C3 Complement (ß1C / §1A-Globulin), Serum
- C4-Complement (ß1-E), Serum
- Haptoglobin (Hp), Serum
- Ceruloplasmin (Cp) , Serum, Plasma

Sampling: 1 mL serum each test

Adenovirus, Serology and Antigen

Background: Adenoviruses are non-enveloped viruses with icosahedral nucleocapsids and linear double stranded DNA named on the isolation from adenoids.

Adenoviruses are known to cause an exudative pharyngitis similar to group A Streptococcus

pharyngitis, pneumonia, epidemic keratoconjunctivitis or acute hemorrhagic conjunctivitis as well as hemorrhagic cystitis. Type 40 and 41 are causes of diarrhea in children. Transmission occurs by the fecal-oral route or infectious aerosols, predisposing schools, nursing facilities and hospitals. Severe adenovirus infections with fatal outcome have been reported in children and immunocompromised adults. Sarcomas are only induced in laboratory rodents, no evidence that adenoviruses cause cancer in humans has been found.
Serotypes 3,4,7,27 cause respiratory diseases, types 8 and 19 cause epidemic kerato-conjunctivitis, types 11 and 21 cystitis, type 40 and 41 gastroenteritis in children.

Sampling:

Serum:	2 mL citrate plasma.
Feces:	approx. 2 g of stool
Bronchial secret:	1-2 mL

Reference Interval:

Serology

Expected value of a single specimen for IgA:	negative < 0.7 COI
	borderline 0.7-1.0 COI
	positive >1 COI
IgG antibody negative	< 20 RE/mL

Feces	antigen detection: negative
Bronchial secret	antigen detection: negative

Adrenal Corticotropin see Adrenocorticotropic Hormone, ACTH

Adrenaline, Plasma see Catecholamines Fractionation, Plasma

Adrenaline, Urine see Catecholamines Fractionation, Urine

Adrenocorticotropic Hormone (ACTH), Plasma

Related Information: Cortisol, Free, Urine
Cortisol, Serum or Plasma
Growth Hormone, Serum
Testosterone total, free, Serum or Plasma

Synonyms: ACTH, Adrenal Corticotropin,

Background: ACTH is regulated via hypothalamic corticotropin releasing hormone (CRH) and ACTH provoke release of cortisol, androgens and mineral corticoids from the adrenal cortex.
Useful to distinguish ACTH dependent from ACTH independent Cushing syndrome; evaluate ectopic ACTH production; monitoring patients with adrenalectomy; diagnosis of Nelson´s syndrome; evaluation of secondary hypopituitarism.

ACTH in Pituitary Cushing s syndrome may be high normal or elevated. In ectopic ACTH syndrome ACTH usually high. Elevated in Nelson's syndrome, Addison's disease and adrenogenital syndrome. Cushing s due to adrenal adenoma or carcinoma usually very low.

Sampling: 1 mL heparin or EDTA plasma. Pre cool collection tube on ice, store on ice for immediate transport to the laboratory, or separate plasma and freeze at -70° C immediately. ACTH levels may be elevated by stress. Diurnal variation: Peak in the morning. Late PM levels up to 50% of morning levels. Specimens should be drawn between 6 and 10 AM or between 9 and 12 PM and always at the same time in case of follow up. Glucuronide therapy depresses ACTH.

Reference Interval:

Adults	at 8 AM	< 10-52 pg/mL
	at midnight	< 10 pg/mL

Higher values in cord blood and newborns

Al, Serum see Aluminium, Serum or Urine

Alanine Aminotransferase (ALT), Serum

Related information:
Acetaminophen, Serum
Alkaline Phosphatase, Serum
Antimitochondrial Antibody
Antinuclear Antibody
Aspartate Aminotransferase, Serum
Bilirubin, Fractionated, Serum
Ceruloplasmin (Cp), Serum or Plasma
Copper (Cu), Serum or Urine
Ethanol, Blood, Serum or Urine
Ferritin, Serum or Plasma
Gamma-Glutamyl Transferase, Serum
Glutamate Dehydrogenase (GLDH), Serum
Hepatitis B (HBV) Serology and Antigen Detection
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis C Antibody (Anti-HCV)
Hepatitis E Antibody (Anti-HEV)
Lactate Dehydrogenase (LDH), Serum

Synonyms: ALT; Glutamic Pyruvate Transaminase; GPT; SGPT

Background: ALT is a liver specific enzyme, values > 15 fold of the upper limit of the reference interval indicates acute hepatic necrosis of viral toxic or ischemic cause.

For diseases of the liver/biliary system ALT as a single parameter has a diagnostic sensitivity of 71%-83%. In combination of ALT, GGT, ChE the diagnostic sensitivity and specificity is nearly 100%.

In alcoholic liver disease, ALT is less sensitive than AST; AST to ALT ratio typically is 2 to 1 or higher. Low increased ALT (50 U/L to 400 U/L) indicates liver metastasis, cirrhosis, occlusion of biliary tract.

Moderate increased ALT (50 U/L to 1000 U/L): Toxic liver damage, chronic hepatitis, primary biliary cirrhosis, cholangitis.

High ALT (>1000 U/L) : acute viral hepatitis, hepatic ischemia

Limitations: In typhoid fever AST to ALT ratio increase > 1. In viral hepatitis, AST to ALT decrease to 0.5-0.8. Increase of ALT is observed in obesity. Thyroid disease can cause a slight elevation.

Sampling: 1mL serum or plasma. Avoid hemolysis. Activity in red cells is 6 times of that in serum.

Reference Interval:

		(U/L)
Adults	male	10-41
	female	10-31
Children	1-30days	1-25
	2-12 month	4-35
	1-3 years	5-30
	4-9 years	5-25
	10-18 years	5-30

Albumin, Liquor see Cerebrospinal Fluid (CSF), Liquor

Albumin, Serum

Related Information: C Reactive Protein, Serum
Protein Electrophoresis, Serum
Protein, Quantitative, Urine
Protein, Total, Serum

Background: Albumin accounts for approx 60% of total protein. Albumin is synthesized in the liver. Half life is 15-19 days.

High albumin indicates dehydration.

Decreased albumin occurs in liver disease, malabsorption, malnutrition, renal loss through nephrotic syndrome, loss through gastrointestinal diseases, 3rd degree burns, exfoliative dermatitis, loss through third spacing and dilution by IV. fluids.

Genetic variation: congenital analbuminemia, bis albuminemia.

Albumin, prealbumin and transferrin decrease with acute phase inflammatory or infectious processes (negative acute phase reactants).

Limitations: Albumin levels may decrease (< 0.5 g/dL) in patients in supine position. Drugs such as acetaminophen, amiodarone, estrogen/progestin, interleukin-2, oral contraceptives, phenytoin, prednisone, and valproic acid may decrease albumin. Increase may be related to anticonvulsants, furosemide, phenobarbital, prednisolone.

Sampling: 1 mL serum

Reference Interval:	(g/dL)	
	Children	Newborn	3.5-4.9
		1 year	3.6-5.0
		2-20 years	3.7-5.1
	Adults	21-60 years	3.5-5.3
		61-70	3.4-4.8
		71-80	3.3-4.7
		81-90	3.1-4.5
		>90	3.0-4.5
Critical value:	Less than 1.5 g/dL		

Albumin, Urine

Related Information: Protein, Quantitative, Urine

Background: Useful in diagnosis of hypoalbuminemia. Please see: Albumin, Serum also Protein, Quantitative, Urine.

Sampling: 5 mL aliquot of 24 h collected urine, please note total quantity.

Reference Interval: < 50 mg/24 h

Alcohol see Ethanol

Aldolase, Serum or Plasma

Related Information: Creatinine Kinase (CK, ANC-activated), Serum
Creatinine Kinase Isoenzymes, Serum
Myoglobin, Blood, Serum or Plasma
Myoglobin, Qualitative, Urine

Synonyms: ALD, Fructose Biphosphate Aldolase

Background: A marker enzyme in diseases of the skeletal muscles e.g. muscular dystrophy and dermatomyositis. Not elevated in neurogenic muscular atrophies (poliomyelitis, multiple sclerosis). Serum aldolase may also be elevated in hepatitis, myocardial infarction, hemorrhagic pancreatitis, gangrene, some neoplasias. Used in therapy monitoring of inflammatory myopathies.

Limitations:

Levels may be elevated up to 20 U/L by desoxycorticosterone, cortisone, ACTH injections.

Sampling: 2 mL blood, 1 mL serum or preferred, due to lacking platelet enzyme: 1 mL heparin plasma or 1 mL EDTA plasma. Avoid hemolysis. Transport to laboratory immediately or separate serum or plasma immediately and freeze.

Reference Interval:

Adults	male	2.1-8.0 U/L
	female	1.4-6.0 U/L
Children	0-2 years	2.0-12-0 U/L
	3-16 years	1.0-6.2 U/L

Normal range for inactive patients or at bed rest may be up to 50% lower.

Aldosterone, Serum or Plasma

Related Information: Aldosterone, Urine
Potassium, Serum or Plasma
Renin Activity, Plasma

Background: Aldosterone is produced under feed back loops of the renin angiotensin system in the zona glomerulosa of the adrenal cortex. Aldosterone and renin determination are key diagnostic tools in the diagnosis of primary hyperaldosteronism (PH) characterized by hypocalcemia, hyperaldosteronemia, and hypertension and suppressed renin activity.

Secondary hyperaldosteronism is part of a response in patients with decreased renal plasma flow or reduced plasma volume observed in congestive heart failure, cirrhosis, nephritic syndrome, renal artery stenosis. Elevated renin and aldosterone levels are also seen in Bartter syndrome and Gitelman's syndrome. Patients on thiazide diuretics may have test results mimicking PH.

Sampling: 2 mL blood or 1 mL serum

Patient preparation: Antihypertensive drugs, cyclic progestogens, estrogens, heparin therapy, thermal stress, after starvation influence the value, best is discontinuation of medications at least 2 weeks before sample collection. Patient should be on normal sodium diet for 2 weeks (135 mmoL or 3 g sodium per day). Aldosterone peaks in the morning.

For collection, the patient should be in supine or upright position 4h before and during blood drawing. Please specify all information influencing the values on the request form.

After blood is drawn, please transport the specimen to the laboratory immediately or separate serum and freeze sample.

Reference Interval: (ng/dL)

Aldosterone			
	Newborn / Children	12h	34.3-125.3
		24h	21.7-105.4
		2 days	19.1-112.3
		3 days	9.0-91.3
		4 days	8.3-92.1
		5 days	7.2-83.0
		6-30 days	6.9-81.2
		1-12 month	6.9-55.2
		1-2 years	6.1-49.5
		2-6 years	4.0-27.1
		6-14 years	3.1-14.8
	Adults	Supine position	2.9-14.5
		Upright position	6.5-28.5
	Renin	in supine position	3-19
		after stimulation	5-40

Aldosterone, Urine

Related Information: Aldosterone, Serum or Plasma
Aldosterone, Urine
Potassium, Serum or Plasma
Potassium, Urine
Renin Activity, Plasma
Sodium, Urine

Background: see Aldosterone, Serum or Plasma

Sampling: Patients preparation and standardization: Please see Aldosterone, Serum or Plasma

Collect 24h urine in a container supplemented with 10 mL of 20% hydrochloric acid. Aliquot of 5 mL is used for the test. Keep cool during the collection period. Ship a 5 mL aliquot to the laboratory, note total quantity.

Reference Interval: 3.0-15.0 µg/24h

Alkaline Phosphatase, Serum

Related Information:
Alkaline Phosphatase, Liver- Intestine- Bone Isoenzymes, Serum
Alkaline Phosphatase, Placental Isoenzyme, Serum
Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Ethanol, Blood, Serum or Urine
Gamma-Glutamyl Transferase (Gamma-GT), Serum
Hepatitis B (HBV), Serology and Antigen Detection
Hydroxyproline,Total, Urine
Leucine Aminopeptidase (LAP), Serum
Osteocalcin, Serum or Plasma

Background: Sources for serum Alkaline Phosphatase (ALP) are intestine, kidney, placenta, but 80% originates from liver, where it is synthesized by the biliary epithelium and excreted by the bile. AP may be increased in obstructive biliary processes even with normal bilirubin values.
Use: Elevated in non-fasting specimens, bone growth, acromegaly, osteogenic sarcoma, liver-bone metastasis, leukemia, myelofibrosis, mastocytosis, myeloma, Paget's disease, thus use as a tumor marker, hyper-or hypovitaminosis of vitamin D may cause elevations. Other conditions are hyperthyroidism, hyperparathyroidism, chronic alcohol abuses. Especially useful in biliary obstructions caused by pancreas head tumors, choledocholithiasis, cholestasis, however usually normal in patients with cholecystitis or cholangitis without stone formation.
Elevated values also in cirrhosis, infiltrative liver diseases (sarcoid, TB, amyloidosis, abscess), autoimmune cholangiopathy, in viral hepatitis, diabetes mellitus, rheumatic diseases (30-50% of the patients).
In children very high, transient levels without signs of diseases have been reported.
Drugs: Many drugs cause an up to 10 fold increase of ALP.
Decrease may occur after blood transfusion, in hypophosphatasia or during zinc deficiency (needed as a cofactor).
Wilson's disease: high bilirubin and decreased ALP, Ratio <2 is distinctive.
Lower levels are seen during sepsis, viral diseases, such as infectious mononucleosis, CMV infections.

Sampling: 2 mL blood or 1 mL serum, fasting sample

Reference Interval:

Children	< 300 U/L
Adults	35-120 U/L
Pregnancy, particularly third trimester	< 240 U/L

Values may increase in upright position. The higher range in children is due to bone growth.

Alkaline Phosphatase Liver- Intestine- Bone Isoenzymes, Serum

Related Information: Alkaline Phosphatase, Serum
Alkaline Phosphatase, Placental Isoenzyme, Serum
Calcium (Ca), Total, Serum
Hydroxyproline, Total, Urine
Osteocalcin, Serum
Pyridinolines

Background: Test is used to determine the fraction of liver-intestine isoenzyme or bone isoenzyme.
Bone fraction is cleared by the liver and may be elevated during liver diseases.
An increased bone fraction is associated with Paget disease, osteoblastic tumors, hyperparathyroidism, rickets, and osteomalacia. Useful in monitoring bone mineralization during hormone replacement therapy in postmenopausal women. Useful tool in detection of bone metastasis from prostate or breast carcinomas. 35% of patients with diabetes mellitus have an elevated bone fraction
Increase in intestinal fraction is observed in diabetes mellitus, renal failure, and cirrhosis.
Determination of isoenzymes is only of value if total alkaline phosphatase elevation is not explained by findings such as gamma glutamyl transferase activity, LDH, cirrhosis, bilirubin.

Sampling: 1 mL serum, fasting state.

Reference Interval:

liver, gall, intestine isoenzyme fraction	6-74 U/L
bone isoenzyme fraction	11-102 U/L

Remark: Intestine isoenzyme fraction lacking in 60% of the normal population.

Alkaline Phosphatase Placental Isoenzyme, Serum

Related Information: Alkaline Phosphatase, Serum
Alkaline Phosphatase, Liver-Intestine-Bone Isoenzymes, Serum
Calcium (Ca), Total, Serum
Hydroxyproline, Total, Urine
Pyridinolines

Background: The placental isoenzyme or placenta like isoenzymes such as Regan and Nagao are more stable than the liver or bone forms, especially they are insensitive to heat. Germ cells and placenta synthesize the enzymes.
Elevated levels are found in patients with malignancies, the highest frequency (80%) occurs in germ cell tumors, particularly seminoma, resp dysgerminoma in females. Other tumors are serous carcinomas of the ovary, non-seminomatous germ cell tumors, endometrial carcinomas, and leukemia.

Sampling: 1 mL serum, fasting.

Reference Interval: < 100 mU/L

Alpha$_1$ - Antitrypsin, Serum

Related Information: Alpha 1 Antitrypsin Phenotyping
Bilirubin, Fractionated, Serum
C-Reactive Protein, Serum
Protein Electrophoresis, Serum

Synonyms: A_1 Antitrypsin, AAT, Acute Phase Proteins, Alpha$_1$ Protease Inhibitor

Background: A_1 Antitrypsin deficiency is associated with chronic obstructive lung disease or liver cirrhosis. AAT is a protease inhibitor blocking the action of trypsin, elastase, chymotrypsin, collagenase, leukocytic protease, plasmin, thrombin, enzymes which are released as during inflammation of the lung. As a response AAT is a member of the Acute Phase Proteins.
Liver disease is caused by the toxic effect of the ATT mutant and starts to present in infancy with prolonged jaundice, neonatal hepatitis syndrome, mild aminotransferase elevation, portal hypertension, severe liver dysfunction in children, chronic hepatitis in adults and in carcinoma.
A screening in newborn revealed a prevalence of ATT deficiency of 0.064%.
Limitations: Difficult to interpret during elevation of CRP, often false normal results during pulmonary inflammation.

Sampling: 2 mL serum

Reference Interval: 90-200 mg/dL
however, as compared to a highly purified research standard, there is an overestimation by the tested values of 30% - 50%. Low at birth.

Alpha$_1$-Antitrypsin Phenotyping

Background:
The Z allele is associated with emphysema or cirrhosis. The frequency in England is:

Allele	Frequency (%)	serum level (mg/dl)	Emphysema risk
MN	86	150-350	base
MS	9		base
MZ	3	90-210	base
SS	0.25	100-140	base
SZ	0.2	75-120	mild
ZZ	0.029	20-45	high
Null-null		0	very high

Absence of homozygous ZZ, alpha 1 antitrypsin is usually associated with z state, but SS and SZ may be affected as well.

Sampling: 4 mL blood or 2mL serum, avoid hemolysis

Alpha $_1$-Fetoprotein (AFP), Serum

Related Information: CA19-9, Serum (Gastrointestinal)
Carcinoembryonic Antigen (CEA), Serum
Chorionic Gonadotropin (hCG, beta-HCG), Serum
Pregnancy-Associated Protein A, Serum

Background: AFP is a fetal serum protein and is one of the major carcinoembryonic proteins. Chemically it is related to albumin. In the fetus, AFP is synthesized in hepatocytes, yolk sac, gastrointestinal tract, and in the kidney. As a tumor related protein it occurs in primary hepatoma and in non-seminomatous germ cell tumors.

AFP as a tumor marker in hepatocellular carcinoma displays often >1000ng/mL and correlates negative with the prognosis.

Combining with human chorionic gonadotropin (hCG) AFP is used in monitoring germ cell tumors: In endodermal sinus tumors AFP is elevated, hCG normal ; in choriocarcinoma AFP is normal, hCG elevated; in embryonal carcinoma AFP and hCG are elevated, in seminoma AFP is normal, hCG may be elevated.

In prenatal screening, AFP, hCG and unconjugated estriol are used in combination to asses the risk for hereditary defects.

Low AFP direct attention to trisomy 21 and trisomy 18.

High AFP may indicate risk for anencephaly (low unconjugated estriol), atresia of the esophagus and duodenum, encephalocele, gastroschisis, hemolytic disease, liver necroses due to herpes infection, hydrocephalus, multiple gestation (hCG and unconjugated estriol are also high), myelomeningocele, omphalocele and trisomy 13.

Limitations: AFP is elevated in non-malignant diseases of the liver (necrosis, hepatitis, cirrhosis) but usually < 150 ng/mL

Sampling: 1 mL serum. Note week of gestation when used in prenatal screening.

Reference Interval:

Tumor marker (ng/mL)

Children	male	female
0-1 month	0.6-16.4	0.6-19.0
1-12 month	0.6-28.0	0.6-77.0
1-3 years	0.6-7.9	0.6-11.1
4-6 years	0.6-5.6	0.6-4.2
7-12 years	0.6-3.7	0.6-5.6
13-18	0.6-3.9	0.6-4.2
Adults	< 8	nonpregnant < 8 Pregnant see below

Prenatal screening (ng/mL)

week of gestation	median	twice median
16	29.9	59.8
17	33.0	66.0
18	37.6	75.2
19	42.3	84.6
20	47.6	95.2
21	54.0	108.0
22	60.5	121.0

1,4-alpha-D-Glucanohydrolase, Urine or Serum see Amylase, Total, Urine or Serum

ALT see Alanine Aminotransferase (ALT), Serum

Aluminium, Serum or Urine

Related Information: Calcium (Ca), Total, Serum
Synonyms: Al, Serum

Background: Transferrin is the carrier for Al as for other trace elements in the plasma, where 80% is bound and 20% are free or complexed with citrate or other molecules.

Bauxite is the commercial source of Al. A role in Alzheimer disease is currently discussed.

Useful in monitoring patients on parenteral nutrition, burn patients on intravenous albumin, patients with chronic renal failure, professional exposed individuals, patients undergoing dialysis.

Signs for intoxications: Encephalopathy, osteomalacia, osteodystrophy, proximal myopathy, progressive dementia, microcytic hypochromic anemia.

Sources of Al intake: Dialysis water, medications, phosphate binders, sucralfate, albumin concentrate, environmental exposure.

Sampling: Patient's preparation: Aluminium containing antacids (Amphojel®, Basaljel® Gelusil®, Maalox®, Mylanta®, and Sucralfate®) should be discontinued 1 day before sample drawing. 5 mL EDTA blood, for blood drawing, use plastic syringes and tubes only. Urine:
10 mL of a 24 h collected urine, kept cool; use an acid-pre washed metal free container.

Reference Interval:

Serum:	Normal individual 0-6 ng/mL, in dialysis patients < 40 ng/mL
Urine:	0-32 ng/day
Critical serum value:	> 100 ng/mL serum, CNS toxicity may occur
Toxic:	> 200 ng/mL

Amantadine, Serum

Related Information: Influenza Type A and B, Serology

Synonyms: Symmetrel®

Background: Amantadine (1-amioadamantane hydrochloride) is a cyclic amine that inhibits uncoating of viral RNA of influenza A virus within infected cells. Rimantadine is acting similar, but is 10 times more active.

Excretion in the urine unmetabolized, dose reduction is necessary in the elderly and in renal insufficiency.

Used as a prophylactic medication. Postexposure prophylactic procedure is controversial; it may reduce duration of fever and systemic symptoms by 1-2 days.

Adverse effects are gastrointestinal intolerance and central nervous system complaints.

Neurotoxicity may occur at high levels 1-5 µg/mL, particularly with concomitant antihistamines and anticholinergic drugs.

Bioavailability 50%-90%; urinary excretion 50%-90%; plasma binding 70%; volume of distribution 5-8 L/kg, lowers with age; half life time 12-20h, increases with age; peak time 1-4h; peak concentration 350-500 ng/mL after 100 mg orally.

Sampling: 2 mL serum

Reference Interval:	Therapeutic:	300-600 µg/mL
	Toxic:	> 1000 µg/mL

Aminolevulinic Acid see Delta-Aminolevulinic Acid, Urine

Amiodarone, Serum

Related Information: Digoxin, Serum
Procainamide, Serum

Synonyms: Cordarone®; Pacerone®

Test includes: Desethylamidarone

Background: An antiarrhythmic drug with substantial toxicity and a long half life, used in the therapy of atrial fibrillation and recurrent ventricular arrhythmias.

Amiodarone decreases hepatic enzyme systems for clearance of other drugs particularly cyclosporine, digitalis, flecainide, lidocaine, phenytoin, procainamide, quinidine, theophylline, and warfarin.

In 5-10% of patients hypo-or hyperthyreosis develops. Possible liver complications in 25% of the patients require monitoring by AST or ALT.

Bioavailability 25-70%, urinary excretion 0%, plasma binding 100%, volume of distribution 20-110L/kg, half life time 13-37 days, peak time 2-10 h, peak concentration 1.5-2.5 µg/mL after 400 mg/day orally steady state.

Sampling: 1 mL serum, protect from light. To reach steady state it takes 50-100 days. Time to peak concentration after oral dose is 4-7 h, of value is sample drawing after 18 h.

Reference Interval:

Therapeutic: 0.7-2.5 µg/mL, Desethylamidarone : 0.5-3 µg/mL

Toxic: > 5 µg /mL, may start at 3 µg/mL

Amitriptyline, Serum or Plasma

Related Information: Nortriptyline, Serum

Test includes: Nortriptyline

Synonyms: Elavil®; Endep®; Etrafon®; Limbirtol®; Triavil®

Background: Therapeutic as a tricyclic antidepressant in endogenous depression. It inhibits uptake of serotonin and norepinephrine. Active metabolite: Nortriptyline. The formation of nortriptyline is catalyzed by CYP2C19, CYP3A4 and other cytochrome P450's, formation of 10-hydroxy metabolites are catalyzed by CYP2D6.

Common side effects are anticholinergic. Seizure threshold may be lowered; arrhythmias or orthostasis are seldom observed. Avoid in pregnant or lactating women. Contraindicated in patients under monoamine oxydase inhibitors and in narrow angle glaucoma.

Amitriptyline: Bioavailability 37%-59%; urinary excretion 2%; plasma binding 95%; volume of distribution 12-18 L/kg, increase with age; half life 16-26h increase with age; peak time 2-5h; peak concentration 30-100 ng/mL after 100 mg/d in steady state.

Sampling: 1 mL serum.

Reference Interval:

Therapeutic value:	amitriptyline 80-200 ng/mL; nortriptyline: 50-150 ng/mL,
Optimal:	nortriptyline plus amitriptyline; 60-220 ng/mL
Toxic:	amitriptyline > 300 ng/mL.
	amitriptyline plus nortriptyline: > 500 ng/mL

Ammonia, Plasma

Related Information: Amino Acid, Screening, Plasma or Urine
Insulin, Serum
Lactic Acid, Whole Blood, Plasma or CSF

Synonyms: NH_3

Background: Elevated in liver diseases, Reye syndrome, urinary tract infection with distension or stasis, urea cycle disorders, in normal neonates within the first 48 h of life, gastrointestinal bleeding. Useful in neonatal diagnosis of unexplained nausea, vomiting, neurological deterioration in combination with plasma amino acids, organic and orotic acids in the urine.

Not a good predictor in hepatic coma patients. Not always high in urea cycle disorders. High protein intake may cause increased levels. Gastrointestinal hemorrhage may elevate levels.

Cigarette smoke may increase levels by 10-20 µg/dL per cigarette.

Sampling: 1 mL EDTA plasma. Avoid venous stasis, fill tube completely, keep tube tightly closed by stopper, place tube on ice immediately. Transport to laboratory within 60 min or centrifuge at 4°C and freeze plasma, stable 1 week at -70°C. Avoid hemolysis.

Reference Interval:		
	Neonates	64-107 µmol/L
	< 2 weeks	56-92 µmol/L
	Children	21-50 µmol/L
	Adults	
	Male	15-55 µmol/L
	Female	11-48 µmol/L

Amoeba Antibody, Serology

Related Information: Amoeba, Direct Examination, Stool
Clostridium Difficile
Echinococcosis, Serology
Giardia Lamblia, Microscopy
Helminths, Feces, Microscopy
Rota Virus, Serology
Toxoplasmosis, Serology

Background: Besides Giardia lamblia, Entamoeba histolytica is the most common protozoal infection worldwide. The clinical presentation with diarrhea and cramping abdominal pain is unspecific and vary with the immune competence of the host. E. histolytica is able to invade the intestinal mucosa, spreading to the liver and causing liver abscess. Humans are the primary reservoir, infections occur by ingestion of the cyst form on contaminated food or water.

Sensitivity is highest in extraintestinal amebiasis, lower in amebic dysentery, lowest in asymptomatic carriers. In the acute phase negative results are possible, in highly endemic areas antibodies are persistent and of minor value for diagnosis.

Sampling: 1 mL serum

Reference Interval: Antibody titer < 1:32

Amoeba Direct Examination, Stool

Related Information: Amoeba, Antibody, Serology
Clostridium Difficile
Echinococcosis, Serology
Giardia Lamblia, Microscopy
Helminths, Feces, Microscopy
Rota Virus, Serology
Toxoplasmosis, Serology

Background: see Amoeba, Antibody, Serology.

Sampling: Stool, ca 2 g, collect in sterile collection container, deliver to the laboratory within 1h. Longer transit times are possible with preservatives such as polyvinyl alcohol or formalin or zinc sulphate or sodium acetate acetic acid formalin fixative. Do not freeze! Cyclic peaks in E. histolytica: 7-10 days

Reference Interval:

Report on diagnostic findings: Negative result: No parasite, no WBC, no RBC no Charcot Leyden crystals seen by microscopy. A single negative result does not rule out parasitic infection. To enhance sensitivity, please send in 3 specimens on 3 different days.

Amphetamine, Urine

Synonyms: Crank, Bennies, Crystal, Dexies, Dexedrine®, Ferndex® Ice, Speed, Poppers

Test includes: Amphetamine, Methamphetamine, Methylenedioxyamphetamine, Metylenedioxymethamphetamine

Background: Amphetamines are used in severe obesity, hyperkinetic syndrome, narcolepsy. Amphetamine have a high potential for abuse. Tolerance develops if repeatedly used.
Half life: 10-20 h, volume of distribution 2-4 L/kg, protein binding 10%- 40%.

Limitations: Some over the counter amines give a positive result; many drugs are metabolized to methamphetamine or amphetamine such as amphetaminil, benzphetamine, clobenzorex, deprenyl, famprofazone, fencamine, fenethylline, fenproporex, furfenorex, mefenorex, mesocarb, propylamine.

Sampling: Random urine, 5 mL

Reference Interval: < 600 ng/mL
Critical value: 1000 ng/mL

Amylase Isoenzymes, Serum

Related Information: Amylase, Total, Serum
Amylase, Total, Urine
Bilirubin, Fractionated, Serum
Calcium (Ca), Total, Serum
C-Reactive Protein, Serum
Lipase, Serum

Test includes: Total amylase, pancreatic amylase, salivary amylase

Background: At least 6 isoenzymes are known, three originate in the pancreas, three in the salivary gland.

See also: Amylase, Total, Serum

Sampling: 1 mL serum

Reference Interval:

Total amylase:	28-100 U/L
Pancreatic amylase:	13-54 U/L
Salivary amylase:	< 46 U/L

Children up to 2 years do not synthesize pancreatic amylase.

Amylase Total, Serum

Related Information: Amylase, Isoenzymes, Serum
Amylase, Total, Urine
Bilirubin, Fractionated, Serum
Calcium (Ca), Total, Serum
C-Reactive Protein, Serum
Lipase, Serum

Synonyms: 1,4-apha-D Glucanohydrolase, Serum

Background: Useful in the diagnosis of abdominal pain. Elevated levels of lipase and amylase occur in pancreatic diseases such as acute or chronic pancreatitis, pancreatic pseudocyst, abscess, neoplasm, or trauma or common duct stones.

Non-pancreatic causes: inflammatory salivary lesions, mumps, peptic ulcer, intestinal infarction and obstruction, hepatic cirrhosis, peritonitis, appendicitis, burns, ketoacidosis, some carcinomas of the lung and ovary, type I hyperlipoproteinemia, ruptured ectopic pregnancy. Rare: Pinworm in the pancreatic duct.

80% of patients with pancreatitis present with increased serum amylase within one day. Amylase is renal secreted, renal failure increases serum levels. Urine levels persist longer than serum levels.

Increase of amylase is associated with drugs causing Sphincter Oddi spasm such as bethanechol, codeine, fentanyl, meperidine, morphine, pentazocine as well as pancreatitis inducing

substances such as aminosalicylic acids, amoxapine, azathioprine, chlorthalidone, cimetidine, clozapine, diazoxide, felbamate, luvastatin, glucocorticoids, hydantoin, hyro-flumethazine, isoniazid, mirtazapine, penicillamine, sulfamethoxazole. Other drugs are cisplatin, thiazide, and valproic acid.

For differentiation isoenzymes determination test for salivary and pancreas are available.

Sampling: 1 mL serum, increase within 2-12h after onset of pancreatitis, peak 12-30h, remaining increased for 3-4 days, shorter half life than lipase. Stable at room temperature for one week. Oxalate, citrate, lipemic sera may depress results.

Reference Interval: 28-100 U/L

Newborns: very low activity, no pancreatic type, mainly salivary type.

Children up to 2 years: no panctratic type of amylase activity

Children older than 3 years: reach adult reference range

Amylase Total, Urine

Related Information: Amylase, Total, Serum
Lipase, Serum

Synonyms: 1,4-alpha-D Glucanohydrolase, Urine

Background: Please see Amylase, Total, Serum

In addition to serum amylase and lipase, urine amylase is used in the diagnosis of acute pancreatitis: Increase in 4-8h, peak 18-38h return to normal in 7-10 days. Urine amylase persists several days after serum levels have returned.

To improve the specificity, determine amylase/creatinine clearance:

ACCR = [urine amylase (U/L) x serum creatinine (mg/L) : serum amylase (U/L) x urine creatinine (mg/mL)] x 100

The normal reference is approx 2.5%. Increased values are observed in most of the cases with increased serum amylase.

Macroamylase is a benign elevation of serum amylase and low urine amylase, ACCR is < 2%.

Limitations: Glucose >1000 mg/dL may interfere

Sampling: For most reliable results collect urine during a 2h to 4h period and keep on ice during the collection period. Specify duration of collection and total amount. Ship 5 mL to the laboratory.

Reference Interval: <500U/L or 0-17 U per hour

Anacin-3® see Acetaminophen, Serum

ANCA see Antineutrophil Cytoplasmatic Antibody (ANCA)

Androstenedione, Serum

Related Information: Cortisol, Serum or Plasma
Dehydroepiandrosterone Sulphate (DHEA-S), Serum
17-alpha-Hydroxyprogesterone (17-OHP), Serum or Plasma
Testosterone, Serum

Background: Androstenedione is produced in equal amounts by adrenal cortex and ovaries. Metabolized into estrogens by aromatase enzymes (fat tissue, liver) and androgens such as testosterone.

Values are increased in Stein-Leventhal syndrome, ovarian-stromal-hyperplasia, Cushing syndrome and adrenal tumors. 60% of female hirsutism will show elevation of androstenedione.

Diurnal Variation: Peak at 7 AM, a nadir at 4 PM. Sharp rise around the age of 20 years, abrupt decline after menopause.

Sampling: 1 mL serum. Fasting morning specimen preferred, also sample one week before or after menstrual period. Separate serum within 1 h after collection and freeze serum.

Reference Interval:

Age	Male (ng/dL)	Female (ng/dL)
1-5 month	5-45	5-35
1-9 year(s)	5-55	5-45
10-17 years	10-100	25-200
Adults	50-250	20-310
Post menopausal:		20-220

Angiotensin 1 see Renin

Angiotensin Converting Enzyme, Serum

Synonyms: ACE; Angiotensin-I- Converting Enzyme

Background: Known to release a dipeptide in an enzymatic reaction from angiotensin I to form an octapeptide angiotensin II, ACE is produced in epithelial cells of the lung and macrophages. Clinically used in the diagnosis of sarcoidosis with low sensitivity and specificity (prevalence in sarcoidosis 30-90%, depending on the study) it is mainly now used in monitoring the activity of the disease under therapy.

Used in Gaucher disease and in other granulomatous diseases, in diabetes mellitus, leprosy. Reports also on increased ACE in myeloma, amyloidosis, biliary cirrhosis.

Up to 35% of patients in acute histoplasmosis have elevated ACE levels.

Limitations: Increased ACE is observed during captopril, enalapril, lisinopril administration.

Sampling: 1 mL serum

Reference Interval: 20-60 U/L

values up to 50% higher in children and young adults under the age of 20.5% of the normal adult population display elevated levels.

To enhance sensitivity for diagnosis of sarcoidosis, genotype related reference ranges have been described:

Genotype II	4.6 -	30.6 U/L
Genotype ID	10.0 -	47.6 U/L
Genotype DD	17.9 -	64.3 U/L

Antibodies to Bacteria and Fungi

Overview, please see:
Aspergillus fumigatus, Serology
Bordetella pertussis, Serology
Borrelia, Serology
Brucella, Serology
Candida albicans, Serology and Culture
Coxiella burnetii (Q-Fever), Serology, Screening
Corynebacterium diphtheriae (Diphtheria)
Helicobacter Pylori
Legionella Pneumophila
Leishmaniasis, Serology
Leptospira, Serology
Listeria monocytogenes, Serology
Mycoplasma pneumoniae, Serology
Neisseria gonorrhoeae
Pneumococcal Antibody, Serology
Rickettsia see Coxiella burnetii, Serology
Salmonella, Culture, Serology
Shigella, Culture and Serology
Staphylococcus see Antistaphylolysin, Serum
Streptococcus see Antibody to Streptolysin O
Tetanus Antitoxin Antibody IgG
Treponema pallidum (TPAH Serology)
Yersinia enterocolitica and
Yersinia pseudotuberculosis, Culture and Serology

Sampling: for each test 2 mL serum

Antibodies to DNA

Overview, please see: Anti double stranded (ds-DNA) please see Antibodies, dsDNA
Anti single stranded (ss-DNA) please see Antibodies, ssDNA

Sampling: for each 1 mL serum

Antibodies to Parasites

Overview, please see: Amoeba, Antibody, Serology
Echinococcosis, Serology
Malaria
Toxocara Canis, Serology
Toxoplasmosis, Serology
Trypanosoma cruzi (Chagas Disease), Serology

Sampling: for each 1 mL serum

Antibodies to Viruses

Overview, please see: Adenovirus, Serology and Antigen
Central European tick-borne fever
Coxsackie Virus, Serology
Cytomegalovirus (HCMV, CMV), Serology
Echo Virus, Serology
Epstein Barr Virus (EBV), Serology
Hantavirus, Serology see Bunyaviruses, Serology
Hepatitis A Antibodies, IgG and IgM (IgG anti-HAV, IgM anti-HAV)
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis C Antibody (Anti-HCV)
Hepatitis D Antibody (Anti-Delta Serology)
Hepatitis E Antibody (Anti-HEV)
Herpes Simplex Virus Type 1, 2 (HSV), Serology
Human Herpesvirus Typ 6, Serology
HIV Type 1 and 2, Serology
Influenza Type A and B, Serology
Measles (Morbilli), Serology
Mumps Virus, Serology
Parainfluenza Virus, Serology
Parvovirus B19, Serology
Poliomyelitis Virus Type I, II, III , Serology
Rabies Antibody, Serology
Respiratory Syncytial Virus, Serology
Rota Virus, Serology
Rubella, Serology
Varicella-Zoster Virus, Serology

Sampling: for each 2 mL serum

Antibodies, ssDNA

Related Information: Complement C3 Complement (beta1C/beta 1A-Globulin), Serum
Synonyms: Antibodies to Single Stranded DNA;
Anti-ss-DNA Antibody,
ss-DNA- Antibody

Background: Present in most patients with active lupus erythematosus (SLE) as well as in more than 50 % of patients with inactive lupus. 20 - 50 % of patients with rheumatoid arthritis and mixed connective tissue disease present ssDNA antibodies. Less than 25 % of the cases with scleroderma-progressive systemic sclerosis, Sjoegren´s syndrome, dermatomyositis-polymyositis are ss-DNA antibody positive. SLE may present with more than 500 U/mL.
Limitations: Most individuals have IgM ssDNA antibodies, which have a lower affinity to DNA as compared to dsDNA antibodies, the sensitivity for SLE is therefore low.
Sampling: 1 mL serum
Reference Interval: Negative: titre < 1:10

Antibodies, dsDNA

Related Information: Complement C3 Complement (beta1C/beta 1A-Globulin), Serum
Synonyms: Anti-ds-DNA; Anti-Double Stranded DNA Antibodies;
Antibody to Native DNA

Background: Determination of IgG autoantibodies is a relatively specific test, besides anti - SM Antibodies, in Systemic Lupus Erythematosus (SLE) and is positive in 60-80 % of the SLE patients at some time during the course of the disease. Increase often precedes reactivation of the disease as well as falling C3 and C4 levels. ESR, WBC and urinary protein excretion may be early deterioration markers. Specificity is linked to the measured level, particularly SLE patients with renal disease have higher values.
Rarely cross reaction with some types of histone antibodies occur.
Sampling: 1 mL serum, refrigerate for extended transit time.
Reference Interval: Negative < 100 IU/mL

Antibody to Streptolysin O see Anti-Streptolysin O-Antibody

Anticyclic Citrullinated Peptide Antibody

Related Information: Lupus Anticoagulans/Lupus Inhibitors, Serum or Plasma
Rheumatoid Factor, Serum or Body Fluid

Synonyms: Anti CCP; Anticitrullinated Peptide Antibodies;
CCP Antibodies; Cyclic Citrullinic Peptide

Background: Citrulline is an amino acid occurring in filaggrin from the precursor profilaggrin during cell differentiation. Autoantibodies may be induced by the citrullinated form and are primary of the IgG class. The test is specific for rheumatoid arthritis (RA) in the early phase. Specificity 96 - 99 %, however, 60 - 88 % sensitivity. In combination with testing rheumatoid factor, specificity is even higher.

Sampling: 1 mL serum

Reference Interval: Antibody: < 1.0 COI

Antideoxyribonuclease-B Titer, Serum

Related Information: Antibody to Streptolysin O

Synonyms: Anti DNAse-B; Antistreptococcal DNAse-B; DNAse B antibody;
Streptodornase; Anti-streptodornase

Background: Used for detection of an immunological response to an extracellular product of Streptococcus pyogenes. The parameter is valuable in patients presenting with glomerulonephritis or rheumatic fever without clinical documentation of S. pyogenes infection.

Advantage over ASO: Value remains for a longer period elevated than ASO, less false positive results due to liver diseases than ASO. Titer is in the positive range in 80 - 85 % of the patients with Streptococcal infection. Rise is slow as compared to ASO, peak at 4-8 weeks, persist for several month. ASO together with antideoxyribonuclease-B Titer detects 95 % of Streptococcal infections.

Sampling: 1 mL serum. Acute and convalescent specimens should be performed concurrently.

Reference Interval:

Preschool children	< 60 IU/mL
School children	< 170 IU/mL
Adults	< 200 IU/mL

Antidiuretic Hormone, Plasma

Related Information: Methadone, Urine
Osmolality, Serum
Osmolality, Urine
Sodium, Plasma
Sodium, Serum

Synonyms: ADH; Vasopressin

Background: ADH is synthesized in the hypothalamus, released by the posterior pituitary gland responding to osmoreceptors and baroreceptors and is involved in water reabsorption in

the distal tubulus. Insufficient ADH results in polyuria, increase in serum and decrease in urine osmolality and hypernatremia.

Useful in the diagnosis of urine concentration disorders such as diabetes insipidus, inappropriate ADH syndrome, and ectopic ADH production. Increased plasma ADH occurs in acute intermittent porphyria, Guillain-Barre syndrome, tuberculosis, tuberculous meningitis, pneumonia, and nephrogenic diabetes insipidus. Decreased in neurogenic diabetes insipidus, nephrotic syndrome, and psychogenic polydipsia.

Tumors of the hypothalamus or pituitary gland causing diabetes insipidus are craniopharyngioma, ependymoma, germinoma, pinealoma, leukemia, metastases and sarcoidosis.

Sampling: 2 mL EDTA plasma. Patient should be calm during collection. ADH levels are influenced by: Nicotine, alcohol, caffeine, diuretics. Draw sample into pre chilled tube, place on ice, and transport to the laboratory within 1h or centrifuge immediately in a pre-chilled centrifuge at 4°C to separate platelets completely, since platelets contain ADH, and freeze plasma.

Reference Interval: 0.6-6.0 pg/mL

More specific values are derived by comparing to urine osmolality

ADH in pg/mL	Osmolality in mOsm/kg
<1.5	270-280
<2.5	270-285
1-5	285-290
2-7	290-295
4-12	295-300

Antiglobulin Test, direct (Direct Coombs)

Synonyms: Antihuman Globulin; Coombs Test, Direct ; DAT; Direct Antiglobulin Test; Direct Coombs

Test includes: Antiglobulin testing with polyspecific antiglobulin serum and use of monospecific reagents (anti IgG, anticomplement) when polyspecific reagent is positive.

Background: DAT detects nonagglutinating antibodies which are bound to the surface of red cells, detecting immunoglobulins and complement components. Useful in the work up of antibody induced hemolysis such as autoimmune hemolytic anemia, transfusion reactions or HDN.

Limitations: 4 % of patients with auto-immunohemolytic signs have a false negative direct Coombs test. Some drugs may cause false positive results with no hemolytic clinical signs (methyldopa, penicillin, cephalosporins, quinidine, insulin, sulfonamides, and phenacetin).

Sampling: 10 mL whole blood, do not (!) refrigerate. The correct patients identification and labeling of the tubes are critical. Please provide diagnosis, medications and transfusion history.

Reference Interval: negative

Antiglobulin Test, indirect (Indirect Coombs)

Synonyms: AHG, Indirect
Antibody Detection
Antibody screening
Antiglobulin Test, Indirect
Coombs indirect
IAT; Indirect Antihuman Globulin Test

Background: Serum is tested against group O screening cells to detect antiglobulin antibodies. Further antibody identification will be performed, depending on initial results such as antigen typing, cold and warm auto absorption, selective cell panels, enzyme panels.
The test detects 99.6 % alloantibodies, however, antibodies against very infrequent antigens are not detected since not represented in the in the identification panel. Also the sensitivity is low to week immunogenic antibodies.

Sampling: 10 mL whole blood

Reference Interval: negative

Antihistidyl Transfer tRNA Synthetase see Jo-1 Antibody

Antimitochondrial Antibodies

Related Information: Alkaline Phosphatase, Serum
Aspartate Aminotransferase, Serum
Bilirubin, Fractionated, Serum
Gamma-Glutamyl Transferase (Gamma-GT), Serum

Synonyms: AMA, Mitochondrial antibody

Background: Primary biliary cirrhosis (PBC), primary or secondary sclerosing cholangitis and duct obstruction may lead to cirrhosis. PBC is a chronic progressive autoimmune disease with antimitochondrial antibodies present in up to 95 % of the patients.

Sampling: 1 mL serum

Reference Interval: Negative: titer < 1:100
Patients with PBC present in 75 – 95% of the cases titers >1:160, however very low titres are seen in 10 % of PBC.
Patients with other autoimmune diseases often have 1:20 to 1:80 titers. Transient low titers occur in chlorpromazine or halothane sensitive patients.

Antineutrophil Cytoplasmatic Antibody (ANCA)

Related Information: Antimitochondrial Antibodies
Antinuclear Antibody

Applies to: C-ANCA, Proteinase-3 (PR3), and P-ANCA,
Myeloperoxidase Antibody (MPO)

Background: The class of ANCA is composed of antineutrophil cytoplasmatic antibodies (C-ANCA mainly directed against PR3) and perinuclear (P-ANCA, mainly directed against MPO-) antibodies. MPO is a 146kDa protein, functioning as a producer of bacteriotoxic O_2 radicals. PR3 is a 29kDa serineprotease with proteolytic activity on elastin, fibronectin, laminin, hemoglobin, collagen IV, and inhibitable by alpha$_1$ antitrypsin.

C-ANCA:
Class C-ANCA are present in Wegener Granulomatosis (WG). For PR3 diagnostic sensitivity is 75 % to 90 % in patients with systemic vasculitides and necrotizing glomerulonephritis and inflammation of the respiratory tract,
Diagnostic sensitivity is lower for polyangiitis (45 %), Chung Strauss syndrome (10 %), idiopathic glomerulonephritis (25 %).
Due to higher titers in C-ANCA during high activity of disease, C-ANCA is useful in monitoring therapy of polyneuritis cranialis, Tolosa Hunt Syndrome, peripheral neuropathies, polychondritis. Raising titers may precede reactivation of disease weeks to month.
PR3 antibodies (IgG class) may occur in pulmonary hemorrhages and in Schoenlein-Henoch Purpura (IgA class).
P-ANCA:
Occur in microscopic polyangiitis (45 %), Chung Strauss Syndrome (60 %)
Goodpasture Syndrome, hydralazine related nephritis/ Lupus Erythematodes.
P-ANCA also may occur in chronic inflammatory bowl disease (Morbus Crohn, Colitis Ulcerosa) primary sclerosing cholangitis, primary biliary cirrhosis, chronic polyarthritis, Systemic Lupus Erythematodes and autoimmune hepatitis, but PR3 specific antibodies are usually low, instead antibodies directed against other ANCA class antigens are elevated such as alpha enolase, elastase, lysozyme cathepsin G, lactoferrin and others.

Sampling: 1 mL serum, keep cool, stable for 3 days at 4°C, otherwise freeze at –20° to -70°C.

Reference Interval:		
	C-ANCA negative:	titer <1:20
	Proteinase-3 (PR3) negative:	<20 U/mL
	P-ANCA negative:	titer <1:20
	Myeloperoxidase negative:	< 20 U/mL

Differentiation of ANCA antibodies (such as alpha enolase, elastase, lysozyme, cathepsin-G, MPO, lactoferrin, others) by immunoblot: Report of diagnostic antibodies

Antinuclear Antibody

Related Information: Cardiolipin Antibody
Antibodies to DNA
Aspartate Aminotransferase (AST), Serum
C4 Complement (beta1-E), Serum
Rheumatoid Factor, Serum or Body Fluid

Synonyms: ANA, FANA

Background: ANA provides a sensitive test for screening for autoimmune rheumatic diseases particularly Systemic Lupus Erythematosus (SLE). However specificity is low, and SLE has a low prevalence of 50 cases per 100 000 individuals.
Criteria (in part) of the American College of Rheumatology Classification for SLE 1982:
Malar rash, discoid rash, photosensitivity, oral ulcers, nasal ulcers, arthritis in at least 2 peripheral joints, pleuritis, pericarditis, and renal disease with proteinuria >0.5g/day, hemolytic anemia, Laboratory: positive ANA, anti-ds-DNA antibody, anti-Sm antibody.

Titres >1:160 needs further work up. Recommendation to confirm SLE include anti-DNA, RNP, Smith (Sm) and Sjoegren antibodies as well as topoisomerase-I antibody, Scl-70, Jo-1, antiphospholipid antibody.
A good marker for monitoring SLE disease progression is anti-ds-DNA antibody and eventually C3 and C4.

Frequency of positive ANA in various clinical syndromes
(from Kavanaugh et al, Guidelines of Clinical Use ot the ANA Test and Test for Specific Autoantibodies to Nuclear Antigens, Arch Pathol Lab Med 2000, 124 pp 71-81)

Positive ANA in %	Disease or Syndrome
95-100	SLE
60-80	Systemic sclerosis
40-70	Sjoegren syndrome
30-80	Idiopathic Inflammatory Myositis
20-50 but of high prognostic value	Juvenile chronic oligoarticular arthritis/ uveitis
20-60 but of high prognostic value	Raynaud syndrome
100	Drug induced SLE
100	Autoimmune hepatic disease
100	Mixed connective tissue disease

There is a 5% to 50% prevalence of ANA in: Rheumatoid arthritis, Multiple sclerosis, idiopathic thrombocytopenic purpura, thyroid disease, discoid lupus, patients with silicone breast implants, fibromyalgia,
Limitations: Persons older than 80 years, particularly women have a 50% incidence of low ANA

titers. Up to 5% of healthy individuals have titers > 1:160, titers > 1:40 are seen in 20-30% of the normal population. Low titres (< 1:80) occur mostly in rheumatoid arthritis, scleroderma, necrotizing vasculitis., Sjoegren syndrome, discoid lupus, chronic active hepatitis, pulmonary fibrosis, pneumoconiosis, tuberculosis, malignancies also in inactive SLE or during therapy. Drugs, especially associated with elevated titres: para-aminosalicylic acids, carbamazepine, chlorpromazine, ethosuximide, griseofulvin, hydralazine, isoniazid, methyldopa, penicillin, phenylbutazone, phenytoin, hydantoin, primidone, procainamide, propylthiouracil, trimethadine.

Sampling: 1 mL serum

Reference Interval:	Negative	titer < 1:40
	Borderline	titer 1:80-1:160
	Positive	titer > 1:160

Using immunofluorescence methods the pattern of nuclear fluorescence may be reported:

Peripheral pattern:	Correlates with antibody to native DNA correlates with SLE, SLE activity and lupus nephritis.
Homogenous pattern:	Correlates to SLA or other connective tissue disease.
Speckled pattern:	Antibody binds to nuclear antigens (saline extractable), not DNA related), found in many diseases and SLE
Nuclear pattern:	Patients with progressive systemic sclerosis and Sjoegren's syndrome
Discrete speckled pattern:	Centromere specificity is selective for CREST variant of scleroderma.

Antiplasmin see $Alpha_2$ - Antiplasmin, Functional

Anti-Staphylolysin, Serum

Background: Staphylococcus aureus produces an alpha hemolysin (staphylolysin), which is targeted to the membrane of erythrocytes. An infection by Staphylococcus aureus is followed within 2-3 weeks by an increase of antibodies directed against staphylolysin. The serum concentration of the antibodies peak at 2-3 month post infection and return to normal within 5-7 month.

Low antibody concentrations are linked to superficial infections, high concentrations to sepsis or abscess. Negative results do not rule out infection.

Useful in culture-negative patients and patients with osteomyelitis.

Sampling: 2 mL serum

Reference Interval:

Negative:	<2 IU/mL
Positive:	cut off: 8 IU/mL : 80 % of patients had signs of severe infection
	cut off: 2 IU/mL : 80 % of patients had signs of superficial infection

Anti-Streptococcal Hyaluronidase, Serum

Background: Hyaluronidase is an enzyme synthesized by Group A and Group B, C, G, H, and L Streptococci. Since antibodies against hyaluronidase are produced during Streptococcal infection the antibody concentration can be used in diagnoses and monitoring the infection.

Sampling: 2 mL serum

Reference Interval: < 150 IU/mL

Anti-Streptolysin O-Antibody

Synonyms:
Streptolysin O Antibody
Antistreptolysin O
ASLA
ASO Titer

Background: Streptolysin is a haemolysin synthesized by Group A Streptococci and acts as an immunogenic antigen.

Used in the diagnosis of beta hemolytic Streptococcus Group A infection without clinical documentation. Elevated titers in 80% of patients with acute rheumatic fever and in 95% of patients with acute glomerulonephritis.

Rise in titer begins 1 week after infection, peak 2-4 weeks later, falls to baseline within 6-12 month. Anti-DNase B remains elevated in contrast to an already fallen ASO titer at the onset of rheumatic fever or glomerulonephritis.

Sampling: 1 mL serum

Reference Interval:

Children:	< 2 years	< 50 Todd units
	2-5 years	< 100 Todd units
	5-19 years	< 166 Todd units
Adults:		< 125 Todd units
	borderline	125-200 Todd units

Antithrombin III

Related Information:
Activated Protein C Resistance
Protein C
Protein S, Total

Synonyms:
AT III; Heparin Cofactor Activity; Antithrombin III; Serine Protease Inhibitor

Background: Decreased activity of the anticoagulant protein is associated with hyper coagulation and risk for venous thrombosis. AT III inhibits thrombin, the factors Xa, IXa XIa, XIIa and kallikrein. Heparan sulfates (endothelial cells), heparin, glycosaminoglycans enhance the activity of ATIII.

The hereditary form is prevalent in 0,2% of the population, reaching up to 5% in older patients with

thrombosis and is caused by one or more of more than 100 described mutations located in the thrombin gene. Homozygous forms are incompatible with life, heterozygous patients have a 5 fold risk to develop venous thrombosis and display values of ATIII of 45-80%.

At birth antithrombin levels are lower (40-90%), reaching adult levels a month 6. Decreased activity may occur during the use of oral contraceptives, or third trimester pregnancy

The more common form is the acquired AT III deficiency which includes decreased hepatic synthesis caused by liver diseases or L-asparaginase treatment, consumption of ATIII by DIC, proteinuria (nephritic syndrome), Colitis ulcerosa and pulmonary embolism. Coumadin may increase AT II levels

Patients with substantial decrease may need very high doses of heparin to obtain prolonged PTT (heparin resistance).

Since antithrombin III in a functional assays will not be able to distinguish between decreased function(less common hereditary form) or protein concentration, it is recommended to perform an immunogenic assay if the functional assay display decreased values.

Sampling: 4 mL citrate blood or 2 mL citrate plasma. When drawing the specimen, first draw 1-2 mL into a tube to discard and draw sample second into the citrate tube, avoiding contamination with tissue thromboplastin. Tube must be filled completely. Avoid contamination with heparin, when using a catheter to obtain the sample, discard the first 6-10 mL .Mix with citrate by inverting. Place on ice and transport to the laboratory within 4 h or separate plasma and freeze at -70°C.

Reference Interval: 80% - 120%

APC Resistance see Activated Protein C Resistance

Apolipoprotein A-1 and B-100, Serum

Test includes: Apolipoprotein A-1 and Apolipoprotein B-100

Background: Apolipoprotein A-1 (Apo-1) is the main HDL particle associated protein. It removes cholesterol from the tissue and is considered as beneficial in preventing stroke and coronary heart disease. It is used in the evaluation of low HDL in familary Apo-1 deficiency, Tangier disease or LCAT deficiency.

Apolipoprotein B-100 (Apo B-100) is a constituent of VLDL, IDL, LDL, Lp(a). It is synthesized by the liver and delivers cholesterol to the tissue. It is a risk factor for coronary heart disease.

Sampling. 2 mL blood or 1 mL serum, patient must be fasting for 14h. Separate serum as soon as possible, and refrigerate but do not freeze. Stable for a maximum of 12h.

Reference Interval:			
	Apolipoprotein A-1	Male:	110-180 mg/dL
		Female:	110-210 mg/dL
	Apolipoprotein B-100	Male:	60-140 mg/dL
		Female:	50-130 mg/dL

Aspartate Aminotransferase (AST), Serum

Related information:
Acetaminophen, Serum
Alanine Aminotransferase (AST), Serum
Alkaline Phosphatase, Serum
Antimitochondrial Antibody
Bilirubin, Fractionated, Serum
Ceruloplasmin (Cp), Serum or Plasma
Copper (Cu), Serum or Urine
Ethanol, Blood, Serum or Urine
Ferritin, Serum or Plasma
Gamma-Glutamyl Transferase (Gamma-GT), Serum
Glutamate Dehydrogenase (GLDH), Serum
Hepatitis A Antibodies, IgG and IgM (IgG anti-HAV, IgM anti-HAV)
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis C Antibody (Anti-HCV)
Hepatitis C Genotyping
Hepatitis C Virus RNA Quantification (HCV-RNA)
Hepatitis D Antibody (Anti-Delta Serology)
Hepatitis E Antibody (Anti-HEV)
Lactate Dehydrogenase (LDH), Serum

Synonyms: AST; Glutamic Oxaloacetic Transaminase; GOT; SGOT

Background: AST and Alanine Aminotransferase (ALT) are enzymes linked to liver diseases. AST is not specific for liver it is present in the heart, skeletal muscle, kidney, brain, pancreas, lung, leucocytes and erythrocytes. The highest concentration of AST is reached in the liver and skeletal muscle. Half life: approx.17h

Liver diseases: In alcoholic liver disease AST is moderate elevated up to 250 U/L , due to pyridoxine deficiency in patients with alcoholic abuses and a higher sensitivity of ALT to the deficiency, AST to ALT ratio is >2 in alcoholic hepatitis.

In viral hepatitis, AST: LD ratio is usually > 3. AST value is 3 to 100 fold the upper limit of the reference interval. In chronic hepatitis C AST: ALT ratio > 1 suggests cirrhosis.

AST increases in hemochromatosis or in hepatotoxicity by chemicals.

Cholecystitis and choledocholithiasis increases AST 5 to 10 fold above the upper reference value.

EBV infection cause AST increase (5 fold above upper reference value), and a higher LD increase as well as Reye syndrome.

In some cases of acetaminophen therapy AST levels of 2000 U/L to 30.000 U/L have been reported.

Acute Myocardial Infarct (AMI): AST increases 6-12h after onset of pain, maximum at 16-48h, usually up to 5 fold of upper reference value , if >10 fold of maximum reference value risk of mor-

tality is increased. Return to baseline within 3-6 days after onset. In AMI usually the ratio AST to ALT is > 2. AST has a diagnostic specificity for AMI of 86% and a sensitivity of 96%.

Skeletal muscle: Diseases of the muscle such as trauma, dystrophy, dermatomyositis, polymyositis, Duchenne muscular dystrophy

Drugs: Decrease AST levels: allopurinol, cyclosporine, progesterone

Elevate AST levels: acetaminophen, aminosalicyclic acid, amiodarone, amitriptyline, steroids, anticonvulsants, aspirin, carbamazepine, cephalosporins , chlorambucil, chlorthiazides, chlorpromazine, estrogens, erythromycin, fluconazole, gentamycin, hydralazine, ibuprofen, indomethacin, interferon alpha, isoniazid, levodopa, lovastatin, meprobamate, methotrexate, methyldopa, metronidazole, naproxen, niacin, nortriptyline, opiates, oral contraceptives, oxacillin, penicillin, phenobarbital, phenothiazine, procainamide, progesterone, pyrazinamide, quinidine, rifampin, streptomycin, sulfonamides, tamoxifen, ticarcillin , tobramycin, tolbutamide, verapamil.

Sampling: 1 mL serum or plasma. Avoid hemolysis, the concentration AST in erythrocytes is 40 fold of plasma concentration. AST is stable in serum for 1 week at 8°C.

Reference Interval:

Children (U/L)	Newborn	25-75
	1-3 years	10-50
	4-6 years	10-45
	7-12 years	10-40
	13-18 years	10-36
Adults (U/L)	male	10-38
	female	10-32

Aspergillus fumigatus, Serology

Related Information: Immunoglobulin E

Background: Test may be useful in the diagnosis of invasive aspergillosis in immunocompromised patients and in the assessment of hypersensitivity pneumonitis.

Limitations: Cross reactions possible to histoplasmosis, coccidiomycosis, and blastomycosis. A negative result does not exclude infection, sensitivity between 60%-90%.

Sampling: 1 mL serum, acute and convalescent serum is recommended to obtain optimal diagnostic results.

Reference Interval: Differentiation of immunoglobulin class:

IgM antibody	negative	< 50 IU/mL
	Borderline	50 – 70 IU/mL
	positive	> 70 IU/mL
IgG antibody	negative	< 50 IU/mL
	Borderline	50 – 70 IU/mL
	positive	> 70 IU/mL

Astrovirus Antigen, Feces

Background: Astroviruses belong to the family Astroviridae, are small (27-32 nm in diameter), non-enveloped single stranded (ss) RNA viruses. The virus is inactivated by heating over 60°C for 10 min, but resistant to alcohol.

Until 1975 only known in animal's diarrhea diseases they are now known to cause mild, gastro-enteritis with watery diarrhea in children under the age of 7 years and less common in adults. Incubation period is 3-4 days and the illness lasts 1-5 days. Besides diarrhea, fever occurs in 20%, vomiting in 10%.

Prevalence in community settings was found to be 7%-8% with an excretion rate in asymptomatic individuals of 2%. Astroviruses account for 3%-5% of diarrheas in hospitalized children. Outbreaks occur in dare care centers, hospitals, nursing homes. Half of the infected individuals remain asymptomatic. Attack rates during outbreaks were found to be 50%, and secondary transmissions 30%.

Most adults (75% at the age of 10 years) have antibodies, suggesting the infection occurs commonly.

Sampling: approx. 2 g of stool.

Reference Interval: Report on diagnostic finding. Antigen detection.

Autoantibodies

Overview:

Acetylcholine receptor see Acetylcholine Receptor Antibody, Binding
Antihistidyl Transfer tRNA Synthetase see Jo-1 Antibody
Antineutrophil Cytoplasmatic Antibody (ANCA)
Antinuclear (ANA) see Antinuclear Antibody
Cardiolipin (IgA, IgG, IgM) see Cardiolipin Antibody
Cyclic citrulline Peptid (CCP) see Anticyclic Citrullinated Peptide Antibody
DNA (double- and single strand) see Antibodies, dsDNA and see Antibodies, ssDNA
Endomysium (IgA, IgG) see Endomysial Antibodies
Extractable Nuclear Antigen (ENA) see Ribonucleoprotein U1-snRNP Antibody Smith (SM) Antibody
SS-A/Ro and SS-B/La Antibodies
Histone (H1, H2A, H2B, H3, H4) see Histone-Antibodies
Intrinsic Factor see Intrinsic Factor Antibody (IFA)
Liver/Kidney microsomal (LKM) antibodies please see
Liver Kidney Microsomal Antibodies (LKM Antibodies)
Mitochondrial (AMA) see Antimitochondrial Antibodies
Myeloperoxidase (MPO) see Antineutrophil Cytoplasmatic Antibody (ANCA)
P-53 see P-53 Antibody, Serum
Parietal Cell Antibody

Phosphatidyl-choline, -ethanolamine, -glycerin, -inositol, -serine IgA, IgG, IgM
see Phospholipid-Antibodies, Serum
Platelet, free antibodies (serum), bound antibodies (EDTA-blood)
see Platelet Antibodies (free, bound)
RNP-U1 see Ribonucleoprotein U1-snRNP Antibody
Proteinase-3 (PR3) see Antineutrophil Cytoplasmatic Antibody (ANCA)
Scl-70 see Scl-70 Antibody
Scleroderma Antibody see Scl-70 Antibody
Sm Protein (Smith) see Smith (SM) Antibody
Smooth muscle (ASMA) see Smooth Muscle Antibodies (SMA)
Smith (SM) Antibody
Soluble liver antigen see Soluble Liver Antigen (SLA)-Antibody (Anti-SLA)
Sjoegren Antibodies see SS-A/Ro and SS-B/La Antibodies
SS-A (Ro) see SS-A/Ro and SS-B/La Antibodies
SS-B (La, Ha) see SS-A/Ro and SS-B/La Antibodies
Thyroperoxidase (MAK)
Thyroid (thyroglobulin, microsomal, TSH-Receptor) see Thyroglobulin Antibody
Thyroperoxidase Autoantibody
Thyrotropin Receptor Antibody, Serum
Topoisomerase I Antibody see Scl-70 Antibody

Sampling: for each test 1 mL of serum

B- and T Lymphocytes see Lymphocyte Immunophenotyping

Bartonella henselae, Serology

Synonyms: Bacillary Angiomatosis Serology
Cat Scratch Disease Serology

Background: Bartonella species includes B. quintana and B. henselae, responsible for cutaneous bacillary angiomatosis, bacillary peliosis of the liver and spleen, fever and bacteriemia (Bartonella bacteremic syndrome), endocarditis (so called culture negative endocarditis). Associated only with B. quintana: trench fever and with B. henselae only: Cat scratch disease.
Patients presenting with cat scratch disease are in >80% younger than 20 years, an inoculation papule is seen in 50 % followed by local lymphadenopathy and cats bites or scratches in 75 %. B. henselae has been isolated from blood and tissue. In the normal population, approx. 15% of the people showed IgG titres > or = 1:128. In patients with cat scratch disease, 85 % display titres > or = 1:128. Cross reactivity within other Bartonella species occur, e.g. Bartonella quintana, associated with trench fever. Seroconversion may take up to 3 weeks post infection; a late specimen may be helpful.

Sampling: 1 mL serum early and a specimen 3-6 weeks post infection.

Reference Interval: Negative: titer < 1:64
A threefold increase in titre is considered significant.

Bence-Jones Protein see Free Light Chains Structure, Urine

Beta-2-Microglobulin, Serum or Urine see Microglobulin β-2-, Serum or Urine

Beta-Crosslaps, Serum

Related Information: Pyridinolines
Vitamin D, Serum

Background: Collagen alpha$_1$ or alpha$_2$ chains are linked at the carboxy or aminoterminal end with the helix of adjunct collagen by hydroxypyridiniumderivates. During proteolytic breakdown of collagen type I the hydroxypyridinium interlinked alpha$_1$ or alpha$_2$ chains are released into serum and urine and are known as N-terminal crosslaps (NTX), C-terminal crosslaps (CTX) and collagen type I C-terminal telopeptide. All peptides are released during the turnover of skin and bone tissue, however, the major amount in serum or urine of CTX and NTX are products of bone resorption.

Alpha-CTX is the non-isomerized form of aspartic acid; the beta form which is the isomerized form, forms spontaneously but delayed posttranslational. It indicates tissues degradation composed of mature collagen such as mature bone, but not recently formed bone tissue.

Sampling: All types of collagen resorption products have a circadian rhythm peaking during the night and with a low during daytime (plus/minus 30%)

Standard procedure:

Schedule sampling between 7:30 -8:30 in the morning after a strict 12h fasting period (only pure water allowed!). Sample into EDTA tube. EDTA whole blood is stable for 8h at room temperature; EDTA plasma is stable for 24h room temperature, 1 month at -20°C.

Reference Interval:			
	Male		< 0.60 ng/mL
	Female	< 45 years	< 0.60 ng/mL
		> 45 years	< 1.00 ng/mL

Levels increases after menopause in serum and urine by 50-70%

During anti-bone-resorptive therapy, levels are expected to decrease after 6 month by 55-70%

Bile Acids, Serum or Feces

Related Information: Bilirubin, Fractionated, Serum
Gamma Glutamyl Transferase (Gamma-GT), Serum

Synonyms: Cholylglycine; Bile Acid Conjugates; Cholic and Chenodeoxycholic Acid

Background: Bile acids are produced by hepatocytes from cholesterol. The two primary bile acids are cholic and chenodeoxycholic acids. In bile they solubilize cholesterol, thus being essential for cholesterol elimination and conjugate with glycine, taurine, amino acids. Theses primary bile acids undergo bacterial degeneration to form deoxycholic, lithocholic acids and oxidation products (ursodeoxycholic acids). 95% of bile acids are reabsorbed in the small intestine and undergo enterohepatic circulation. Normally < 1% of the bile acid pool is found in serum, but is elevated in cirrhosis, obstructive jaundice, hepatitis due to decreased clearance, but with normal ratio secondary to primary bile acids. In cirrhosis, a disproportionate decrease in cholic acid occurs with a reduced ratio of primary to secondary bile acids. In cholestasis, no secondary bile acids are formed.

Determination of bile acids in serum is one of the most sensitive methods to evaluate liver function.

Sampling: Serum: 1 mL serum. Overnight fasting sample preferred.
Feces: Collect feces for 24h in a sterile container without preservatives. Keep refrigerated during collection period. Note total weight on the request sheet. Before aliquoting approx. 2 g of stool, mix well.

Reference Interval: Serum: < 7.0 µmol/L
Feces: 410 - 1210 µmol / 24h

Bilharzia (Schistosomiasis) Serology

Background: For definite diagnosis of schistosomiasis identification of ova of S. haematobium, S. mansoni, S. japonicum in rectal or bladder biopsy in feces or urine is necessary.

Antibodies persist following therapy. Differentiation between recent or chronic infection is not possible; Positive results indicate chronic active or inactive schistosomiasis. No distinction between the sites of infection or the various forms of the fluke by serology.

Sampling: 1 mL serum, avoid hemolysis, avoid highly lipemic serum

Reference Interval: Serum antibody titer negative: < 1:16

Bilirubin Fractionated, Serum

Related Information; Acetaminophen, Serum
Alanine Aminotransferase (AST), Serum
Alkaline Phosphatase, Serum
Amylase, Isoenzymes, Serum
Amylase, Total, Serum
Amylase, Total, Urine
Aspartate Aminotransferase (AST), Serum
Ethanol, Blood, Urine
Gamma-Glutamyl Transferase (Gamma-GT), Serum
Hepatitis A Antibodies, IgG and IgM (IgG anti-HAV, IgM anti-HAV)
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis C Antibody (Anti-HCV)
Hepatitis C Genotyping
Hepatitis C Virus RNA Quantification (HCV-RNA)
Hepatitis D Antibody (Anti-Delta Serology)
Hepatitis E Antibody (Anti-HEV)
Leucine Aminopeptidase (LAP), Serum
Lipase, Serum
Prothrombin Time

Test includes: Total, conjugated and unconjugated Bilirubin

Synonyms: Total, direct, indirect Bilirubin

Background: Produced in the breakdown of heme and in the reduction of biliverdin, circulating in the plasma and is conjugated, called the direct form, by the liver to bilirubin diglucoronide, a water soluble pigment excreted in the bile.

Conjugated, direct bilirubin in serum is the most sensitive test for liver function and occurs in biliary diseases, intra-and extrahepatic lesions, hepatitis, cirrhosis, neoplasms, cholestatic drug reactions and in faulty excretory function of hepatocytes such as Dubin Johnson syndrome, Rotor's syndrome.

A total bilirubin increase is associated with:

Hemolytic diseases, hepatocellular dysfunction, diseases of hepatic ducts or common bile ducts. Also Gilbert's syndrome, an asymptomatic hereditary jaundice with increasing hyperbilirubinemia caused by Glucoronyl transferase deficiency. Dubin Johnson syndrome, anorexia, prolonged fasting, pulmonary embolism or infarction, congestive heart failure.

Limitations:

Drugs can interfere with the diazo method used for the test as well as causing jaundice in vivo. Such drugs are: diphenylhydantoin, azathioprine, phenothiazine, erythromycin, penicillin, sulfonamides, contraceptives, anabolic androgenic steroids, halothane, aminosalicylic acid, isoniazid, methyldopa, indomethacin, pyrazinamide.

False positive reactions with the diazo method are often seen during cephotetan, pansporin, cefuroxime therapy.

Sampling: 1 mL serum or capillary plasma (heparin or EDTA), avoid hemolysis, protect from light. Transport to laboratory within 4h or separate serum/plasma within 8 h and refrigerate thereafter.

Reference Interval:

Neonates: Bilirubin, total (mg/dL), maximum

Age	premature	full term
<1 day	8	6
24-48h	12	10
3-5 days	15	12
6-7days	15	10

Children and adults:	Total :	< 1.2 mg/dL
	Conjugated or direct bilirubin:	< 0.3 mg/dL
	Unconjugated or indirect bilirubin:	< 0.9 mg/dL

Critical value:

Newborn: Total bilirubin more than 15 mg/dL in term infants,
10-15 mg/dL in prematures.
Increase of more than 1 mg/dL per hour for more than 6 hours.

Biotin (Vitamin H), Serum

Background: Tissue biotin is a cofactor for carboxylation of pyruvate, acetyl-coenzyme A (CoA), propionyl CoA, and beta-methylcrotonyl CoA .

Deficiency presents as severe exfoliative dermatitis and alopecia, similar to zinc deficiency.

Secretion in the urine as intact biotin, and to lesser amounts as bis-norbiotin and biotin sulfoxide.

Sources for biotin are organs, egg yolk, milk, fish, and nuts. Biotin is stable to cooking.

Daily recommended intake approx. 30 µg, the bacterial intestinal flora contributes in part to the supply. Therapeutic large doses (5-10 mg) are applied to infants with seborrhea or genetic alteration of biotin dependent enzymes, no toxicity has been reported so far.

Sampling: 2 mL serum

Reference Interval: > 200 pg/mL
< 100 pg/mL interpreted as a biotin deficiency

Bordetella pertussis, Culture

Related information: Bordetella pertussis, Serology

Background: B. pertussis causes whopping cough. The disease begins with mild respiratory infection and develops within 2 weeks into the distinctive whooping cough. Pertussis like symptoms are also caused by Chlamydia trachomatis, adenoviruses, and respiratory syncytial virus. Diagnosis can be made by B. pertussis cultivation from nasopharyngeal specimens. Despite vaccination programs, pertussis is still one of the most common causes of death from infectious diseases worldwide. Pertussis is highly contagious, immunized persons can be transiently colonized and spread the organism.

Sampling: Perform a nasopharyngeal swap near septum and the floor of the nose under rotating. Inoculate at bedside immediately. Since routine agar does not support the growth of the organism, either the swap should be plated at beside on Bordet-Gengou agar plate, derived from the laboratory or a special transport medium (to order from the laboratory) has to be used. Successful cultivation even under optimal conditions is poor about 50%.

Reference Interval: Report on diagnostic finding
Growth or no growth of Bordetella pertussis or B. parapertussis

Bordetella pertussis, Serology

Related information: Bordetella pertussis, Culture

Background: The value of the antibody detection is limited by the time required for seroconversion. There is a lack of association between antibody levels and protective immunity. Patients with acute infection develop IgG and IgM and IgA antibody responses, vaccinated individuals show increase of IgM and IgG, IgA antibodies are lacking.

Sampling: 1 mL serum

Reference Interval: Differentiation of immunoglobulin class

IgA antibody negative:	< 9 RE/mL
borderline:	9-11 RE/mL
positive:	>11 RE/mL
IgG antibody negative:	< 9 RE/mL
borderline:	9-11 RE/mL
positive:	>11 RE/mL
IgM antibody negative:	< 9 RE/mL
borderline:	9-11 RE/mL
positive:	>11 RE/mL

Borrelia, Serology

Synonyms: Borreliosis; Lyme Disease

Test includes: B. burgdorferi, -afzelii, -garinii

Background: Borrelia spp. are irregular coiled spirochetes, Giemsa and silver stain positive, culturable from the tick vector but not from patient's specimens in serum containing media and transmitted by arthropods. Diseases caused are Lyme disease and relapsing fever.

Borrelia burgdorferi is the cause of Lyme disease transmission by Ixodes dammini, or I. pacificus. The reservoirs are mammals (white footed mouse) and large mammals. Feeding time of the ticks must exceed 24 h to transmit a sufficient dose for infection. In the US, the most common tick borne diseases are Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, relapsing fever, and tularemia.

B. burgdorferi is disseminated into heart, joints, CNS. The disease occurs stage wise: Erythema chronicum migrans, a non-pruritic red rash with a clear center at the site of the bite in 75% of the cases and later usually accompanied by flulike transient symptoms (arthralgias, headache, fever chills, fatigue).The second stage with heart and CNS involvement (neuroborreliosis) occurs after weeks to month (myocarditis, aseptic meningitis, neuropathies with Bell s palsy). The third phase is characterized by arthritis of the large joints and CNS symptoms.

B. recurrentis is transmitted by the human body louse and B. hermsii by soft ticks (Ornithodoros) with rodents as the reservoirs.

Antibodies of the IgM class are detectable after 2-3 weeks post infection, peaking at 3-6 weeks.

Treatment: Doxycycline, amoxicillin, penicillin G, ceftriaxone.

Prevention: Two Lyme disease vaccines have been developed: LYMErixTM by SmithKline Beecham Pharmaceuticals and ImuLymeTM by Pasteur Merieux Connaught, however the vaccine is not effective in all individuals.

Sampling: 1 mL serum

Reference Interval: Screening by EIA method. Validation by Western blot assay. Differentiation of immunoglobulin class for B. burgdorferi, -afzelii, -garinii antibody.

IgG antibody negative:	< 17 RE/mL
borderline:	17-20 RE/mL
positive:	> 20 RE/mL
IgM antibody negative:	< 15 RE/mL
borderline:	15-20 RE/mL
positive:	> 20 RE/mL

Brain Natriuretic Peptide, Serum

Related Information: Albumin, Serum
Creatinine, Serum or Plasma
Digoxin, Serum
Magnesium (Mg), Serum
Osmolality, Serum
Renin Activity, Plasma

Synonyms: B-Type Natriuretic Peptide; BNP; Natriuretic Peptide, Brain

Background: BNP, is a polypeptide, which is produced by the ventricular myocardium under stimulation of volume expansion and overload. The hormone displays natriuretic and vasodilatory effects, suppressing the renin angiotensin system.

BNP is a useful parameter in diagnosis and treatment of congestive heart disease (CHF) since correlating with severity and prognosis. Also helpful in the diagnosis of cardial versus non-cardial dyspnea.

Limitation: In the very early stage of acute CHF presenting with dyspnea or edema, BNP may be normal. Elevated levels may occur in pulmonary embolism, right heart failure, and pulmonary hypertension.

Sampling: 2 mL serum, place on ice, if transit time is less than 6h,otherwise freeze.

Reference Interval:

In healthy individuals < 125 pg/mL

Varies with age and sex.

Values correlate with degree of congestive heart failure.

	BNP pg/mL 5th-95th percentile approx	median approx (pg/mL)
Patients with cardiac disease, but without symptoms	15-499	95
Patients with limited ability to perform exercise	10-1100	220
Patients with limitations in ordinary physical activity	40-1300	450
Patients not able to perform exercise	150-1300	1000

Brucella, Serology

Background: Brucella species organisms are small gram negative rods. The major human pathogens are B. melitensis (reservoir goat and sheep) and B. abortus (cattle).

Transmission is via unpasteurized milk or cheese from infected animals of the domestic livestock or by skin contact.

The organism localize in the reticuloendothelial cells (liver, spleen, bone marrow, lymph nodes) and replicates intracellular. After an incubation period of 1-3 weeks, fever, chills, fatigue, malaise and weight loss occurs. The undulating fever occurs in a minority of patients. Liver spleen and lymph nodes are often enlarged.

Drug of choice: Tetracyclines plus rifampin

Sampling: 1 mL serum

Reference Interval: Antibody agglutination test: negative

Bunyaviruses, Serology

Background: Bunyaviruses are enveloped viruses, with helical capsid symmetry, 100 nm in seize circular single stranded with negative polarity RNA. The virus was first as isolated in Africa (Bunjamwera), causing encephalitis. Now 4 distinct Hantaviruses are known in N. America and more than 20 serotypes worldwide. As a member of the Bunyavirus family Hantaviruses cause Korean hemorrhagic fever in Europe and Asia with headache, petechial hemorrhages, shock, and renal failure. Mortality is about 10%. Hantaviruses are also classified as roboviruses for rodent borne viruses, since they are transmitted from rodents directly without an arthropod vector in opposition to arboviruses (arthropod born). In the early nineties, first in New Mexico an outbreak (hantavirus pulmonary syndrome) occurred clinically presenting influenza like syndromes (fever, myalgia), followed in 3-6 days by progressive cough and shortness of breath with pleural effusions and in serve cases by respiratory failure, tachypnea, tachycardia, hypotension. Laboratory chemistry revealed hemoconcentration, thrombocytopenia, increased partial thromboplastin time leucocytosis, increased serum lactate dehydrogenase and aspartate aminotransferase levels were observed. Antibodies may be present at the time of clinical symptoms. The virus is transmitted by inhalation of aerosols created from urine or feces from deer and mice (Peromyscus). Transmission from person to persons was observed in an outbreak in Argentina. Mortality in Hantavirus pulmonary syndrome is close to 40%. No vaccine, no effective antiviral drug available.

Sampling: 1 mL serum at the acute phase and follow up sera 2-3 weeks later.

Reference Interval: Differentiation of antibodies of immunoglobulin classes IgG and IgM for Hantaviruses (Hantaan, Puumala, Dobrava, Seoul) and Sandfly fever virus (Toscana virus)
(Method: Immunoblot)

C1 Esterase Inhibitor, Quantitative, Serum

Synonyms: C1 Inactivator; C1 Inhibitor

Background: The C1 esterase inhibitor is an alpha 2 globulin acute phase protein. It belongs to the serpin family of protease inhibitors, produced by hepatocytes, monocytes, fibroblasts and vascular endothelial cells. It inhibits the catalytic subunits of the first component of the classic complement pathway (C1r and C1s). Deficiency leads to activation of C1 with generation of C2 kinin which mediates angioedema, which may involve the airway and lung to a life threatening extent. Massive swelling of subcutaneus tissue and gastrointestinal tract symptoms may occur.

The C1 esterase inhibitor also inhibits factor XII and kallikrein in the intrinsic pathway of coagulation, and activates plasminogen to plasmin in the fibrinolytic system.

Useful parameter in the assessment of C1 inhibitor deficiency or dysfunction in acquired or hereditary forms in angioneurotic edema.

The inherited forms are autosomal dominant with one normal gene. The common form (85%) of hereditary angioneurotic edema (HAE) is caused by a decrease in the synthesis of the C1 esterase inhibitor, the less common form (15%) is due to altered function. In both forms, C1q is normal, C1s activity is uncontrolled and therefore decreases in C2 and C4 levels occur.

The acquired angioneurotic edema (AAE) affect elder adults with autoimmune or lymphoproliferative disorders. It is characterized by immune complexes consuming large amounts of C1q and C1 esterase inhibitors thus leading to quantitative and functional deficiency of the C1 esterase inhibitor In addition C1q. C2, C3, C4 levels may be reduced as well. The type II form is characterized by autoantibodies which inhibit the functional activity of the C1 esterase inhibitor.

	Antigen	Function	C1q level	C2, C4 level
Type I HAE	decreased	decreased	normal	decreased
Type II HAE	decreased or normal	decreased	normal	decreased
Type I AAE	decreased or normal	decreased	decreased	decreased

Type II AAE in addition to type I autoantibodies are present

Sampling: 1 mL serum

Reference Interval: 15 – 35 mg/dl

C1q Complement, Serum

Related Information: C4-Complement (β1-E), Serum

Background: C1q is a 400kD protein of the classical complement system pathway, able to bind to activated surfaces and to C1s, which split C4 and C2.

Decreased levels of C1q, C1r, C1s (as well as C2,C3,C4) does not significant affect the ability to defend against infections, however patients have a higher incidence of autoimmune diseases (most common are SLE or SLE- like diseases, rheumatic diseases, vasculitis, dermatomyositis).

In liver failure C1q is normal; C3 and C4 are decreased due to decreased production.

In malnutrition state C1q and C3 are decreased, C4 is normal
In nephrotic syndrome C1q, C2, C8 C9 may be decreased, C3 C3c, C4 are normal,
Patients with extended burns have decreased complement levels.

Sampling: 1 mL serum

Reference Interval: 10 – 25 mg/dL

C3-Complement (β1C / β1A-Globulin), Serum

Related Information: C4-Complement (β1-E), Serum
Cryoglobulin, Qualitative, Serum and Plasma

Background: C3 is synthesized mainly in the liver and comprises approx 70% of total complement protein. It is an essential compound for the classical and alternative pathway.
C3 determination is useful in the detection of congenital deficiency and in the evaluation of immunologic disorders with increased consumption of complement such as chronic hepatitis particularly in hepatitis C associated cryoglobulinemia vasculitis, immune complex diseases such as membranoproliferative glomerulonephritis.
Used in the evaluation of the activity of systemic lupus erythematosus. C3 is decreased in lupus nephritis and glomerulonephritis as well as in infective endocarditis and disseminated intravacular cougulation (DIC).
Hereditary C3 deficiency, a rare disorder, presents with recurrent infections particularly caused by encapsulated bacteria such as Neisseria meningitidis; Streptococcus pneumoniae, Hemophilus influenzae, clinically presenting as sinopulmonary infections, meningitis, paronychia, impetigo and immunocomplex diseases.
Deficiency in the complement function may lead to autoimmune diseases possibly due to the lack of clearance of apoptotic cells by macrophages.

Sampling: 1 mL serum

Reference Interval:

Children:	2 - 5 years:	90 – 140 mg/dL
	6 - 10 years:	100 – 150 mg/dL
	11 – 18 years:	100 – 170 mg/dL
Adults:		80 – 200 mg/dL

C4-Complement (β1-E), Serum

Related Information: HLA-B27

Background: C4 protein is encoded in the class III region of the major histocompatibility complex. The 2 known isotypes differ by 4 amino acids (C4A and C4B).
C4 is only involved in the classical pathway. Immune complex production will decrease hemolytic activity (CH50), C3 and C4. Decreased levels are observed in hereditary angioedema since lack of C1 esterase inhibitor leads to the lyses of C2 and C4 by the C1 esterase.

Clinically C4 deficiency presents with an increased incidence of bacterial infection particularly with S. pneumoniae.

In Alzheimer's disease complement activation may play a role.

C4 levels are used in the assessment of autoimmune diseases such as lupus erythematosus, rheumatoid arthritis, glomerulonephritis, chronic hepatitis, cryoglobulinemia, and hereditary angioedema.

Sampling: 1 mL serum

Reference Interval:	Children:	2 - 5 years	14 – 30 mg/dL
		6 - 10 years	16 – 32 mg/dL
		11 – 18 years	17 – 36 mg/dL
	Adults:		20 – 50 mg/dL

C-ANCA see Antineutrophil Cytoplasmatic Antibody (ANCA)

C-Peptide, Serum

Related Information: Glucose, Blood, Urine, Liquor
Insulin Auto-Antibody (human) (IAAB), Serum
Insulin, Serum

Synonyms: Connecting Peptide ; Insulin Connecting Peptide

Background: C-peptide is a 31 amino acid peptide segment connecting the 21 amino acid A chain and the 30 amino acid B chain of proinsulin. Proinsulin is processed to insulin and C-peptide in the secretory granules of the beta cells by the convertases PC2 and PC1/PC3 and by the carboxypeptidase H. Proinsulin has 10%-15% of the biological activity of insulin and has three times the half life time of insulin. C-peptide and insulin are secreted in equimolecular amounts into the portal vein, but in serum the ratio is 5:1 to 15:1 due to hepatic clearance of insulin. 50% of insulin is removed during the first passage through the liver, but there is no removal of C-peptide. In cirrhosis, serum insulin is increased due to reduced hepatic clearance. Half life of proinsulin and C-peptide is 30 min but 4-9 min for insulin.

Useful in differential diagnosis of hypoglycemia: Patients with insulinomas or hypoglycemia from surreptitious insulin administration or insulin secretagogues (sulfonylurea drug) display high levels of C-peptide, insulin and proinsulin.

Useful in the classification of diabetes mellitus: Patients with type 2 diabetes have normal to elevated C-peptide and insulin levels in the absence of beta-cell autoantibodies. In type 1 diabetes mellitus, serum C-peptide and insulin values are low to undetectable, up to 90% have beta-cell autoantibodies.

Further used in beta cell function assessment and evaluation of pancreas transplanted patients.

Limitations: Increased in renal failure, since reduced excretion by the kidney. Some insulinomas may lack the increase of C peptide.

Sampling: 1 mL serum or heparin plasma, fasting sample preferred. Separate serum soon and freeze.

Reference Interval: Fasting C-peptide levels 0.51 - 2.70 ng/mL. Higher in preterm neonates and in infants. After stimulation with glucose or glucagon, levels increase up to 5.6 ng/mL.

C-Reactive Protein, Serum

Related Information: Albumin, Serum
Alpha 1 Antitrypsin, Serum
Haptoglobin (Hp), Serum
Sedimentation Rate

Synonyms: CRP

Background: The increase of CRP starts a few hours after initiation of an inflammatory process. It is sensitive but not specific for acute injuries, bacterial infections, or inflammation.

Use: Assessing cardiac risk: Elevation of CRP may indicate high risk for cardiovascular and peripheral vascular disease. IL-6 and TNF alpha may be produced within plaques, which increase CRP production in the liver. Adding lipid levels, the assessment of cardiovascular risk is more precise.

Cardiac troponins and CRP determines day to month risk of adverse cardiac events, useful in patients with unstable angina pectoris, non-Q wave myocardial infarction, normal CK-MB levels. It is recommended to average the values of 2 samples, 2 weeks apart in a metabolic stable non-fasting or fasting patient. CRP levels <1 mg/L indicate low risk, 1-3 mg/L average risk, > 3 mg/l elevated risk.

CRP was found to be more sensitive in severity assessment in pelvic inflammatory disease or in sepsis, as compared to leukocyte count or temperature and may be useful as an additional marker for appendicitis.

Sampling: 1 mL serum, do not freeze, avoid hemolysis and lipemia.

Reference Interval:

	(mg/L)
Newborn (cord blood)	< 0.6
4 days - 1 month	< 1.6
Children	0.068-8.2

Adults (95% population distribution):

	male	female
25-34 years	0.08- 7.2	0.07-17.8
45-54 years	0.19-13.9	0.15-12.1
65-74 years	0.33-18.5	0.3-16.6
		Pregnancy at delivery <47

CA 15 - 3 (Breast), Serum

Related Information: Carcinoembryonic Antigen (CEA), Serum
HIV Type 1 and 2, Serology

Background: CA 15-3 is a high molecular carbohydrate antigen of 300kd of the mucin family. The marker is useful in monitoring metastasis of carcinomas of the mammary, but it fails, since lacking sensitivity, in screening for carcinomas.

The correlation for the sensitivity of CA 15-3 to detect the carcinoma and the stage of the carcinoma of the mammae are: During stage I sensitivity for detection is 4%-16%, stage II 13%-54%, stage III 65%, and stage IV 54%-91%. There is also a correlation with the location of metastasis.

Combination of CEA and CA 15-3 enhances the sensitivity for monitoring mammae carcinoma and detection of metastasis.

Carcinoma of the ovary increases CA15-3 in 39%-71% of the patients, and in 14%-26% of patients with carcinoma of the uterus, also in 10%-71% in patients with pulmonary carcinomas, and in 10-61% in gastric, pancreatic and liver cell carcinomas.

Limitations: Increased values are observed in dialyzed patients (20% >30U/mL), in HIV positive patients (up to 50% >18U/mL) and to a lesser extent during liver diseases or pulmonary diseases. In 4%-11% of patients with mastopathia or adenomas of the mammae values may exceed 25 U/mL.

Sampling: 1 mL serum

Reference Interval: < 30 U/mL

CA 19 - 9 (Gastrointestinal), Serum

Related Information: Bilirubin, Fractionated, Serum
Carcinoembryonic Antigen (CEA), Serum

Background: The tumor marker CA 19-9 is a monosialoganglioside with similarity to the Lewis-a-blood group antigen. CA 19-9 is mainly prevalent in carcinoma cells of the colon, stomach, and pancreas and in a lesser extend in carcinoma cells of the liver, the bile tract, the bronchial tract and the ovary. Useful in the diagnosis of pancreatic carcinomas, since CA19-9 is the marker with the highest sensitivity (70%-95%) and specificity (70%-90%). Furthermore, values correlate with stage of the tumor.

Lower sensitivity for liver cell carcinomas and bile tract carcinomas (20%-80%); for carcinoma of the stomach (26%-60%) but in combination with CEA a sensitivity of more than 50% is achieved. Sensitivity for carcinomas of the colon is 20%–60% and for ovarian carcinomas 15%-85%, depending on the histopathology.

The marker is useful in monitoring of carcinomas of the colon (second to CEA) and of carcinoma of the ovary (second to CA 125).

Limitations: CA 19-9 is elevated in up to 30% of the patients with cholecystitis, cholangitis, cirrhosis, cystic fibrosis. Complete biliary duct occlusion causes values up to 1000 U/mL. In up to 6% of chronic pancreatitis and up to 20% in acute pancreatitis levels up to 100 U /mL occur.

CA 19-9 is absent from the serum of individuals who have the Le (a-b-) phenotype, which is found in approx. 6% of the white US population and in 22% of the black US population. For Le/le, Se/Se individuals cut off values are < 10.3 U/mL. For Le/Le, se/se individuals cut off values are < 61.3 U/mL. There is also a wide intra and interindividual variability, therefore for monitoring purposes values are considered not to be significant if less than 40 to 50%.

Sampling: 1 mL serum or plasma

Reference Interval: < 37 U/mL (see also limitations)

CA 50, Serum (Gastrointestinal)

Related Information: Bilirubin, Fractionated, Serum
CA 19-9, Serum
CA 72-4, Serum (Stomach, Ovary)
Carcinoembryonic Antigen (CEA), Serum

Background: CA 50 is a non-organ-specific tumor marker and it is elevated in serum in a variety of malignancies, especially in gastrointestinal cancers (stomach, pancreas, liver, and colon). In contrast to CA 19-9, high CA 50 levels can also be seen in malignant tumors outside the digestive tract. CA 50 might be positive in Lewis negative patients not capable to synthesize CA 19-9, an observation which is supported by histoimmunological studies, although the clinical value is doubtful since in serum close correlation between CA 50 and CA 19-9 has been observed even in patients who have Lewis negative phenotype. The marker CA 50 is useful for the follow-up of patients with pancreatic cancers, but less useful in diagnosis. Results are comparable to CA 19-9. Overall sensitivity is reported to be 60%-95%, specificity 30%-40%.

- Pancreatic carcinoma:

  Up to 80% of the pancreatic cancer patients may display raised CA 19-9 and CA 50 serum levels. Both markers show a significant serum elevation during advanced stages of the disease. However, CA 50 is not considered to have a major advantage as a tumor marker as compared to CA 19-9. Combination of CA 19-9, CA 242, CA 50, and CA 72-4 may increase the diagnostic sensitivity up to 89%, and serial combined examination could increase the diagnostic specificity to 92%. If combining signs and symptoms with CA 50, the sensitivity may be enhanced to 91%, the specificity to 92%.

  The serum tumor markers levels decrease significantly after radical tumor resection.

- Colorectal carcinoma:

  The serum levels of CEA, CA 50 and CA 242 are elevated in 36%, 16% and 20% of colorectal cancer patients, respectively. The intra-individual fluctuations for CA 50 and CA 242 are up to 15%, but in up to 25% of the patients the serum levels of CA 50 are highly oscillating.

  Dukes stage C-D is associated with significantly higher levels of CEA and CA 50 (16%-21% elevated values in Dukes A and B tumors and 44%-47% in Dukes C and D tumors).

Limitations: Moderately elevated serum levels of CA 50 can be seen in benign hepatobiliary diseases, especially in jaundice cases. False positive results may occur in up to 12% of patients

with chronic pancreatitis, a rate which is comparable to CA 19-9. Overall false positive results in up to 33% of the patients.

Sampling: 1 mL serum

Reference Interval: < 19 U/mL

CA 72 - 4 (Stomach, Ovary), Serum

Related Information: CA 19-9, Serum
CA 125, Serum (Ovary)
Carcinoembryonic Antigen (CEA), Serum

Background: The antibody B72.3 reacts with the locus CA72.4 of the tumor associated high molecular weight glucoprotein. Tissue specific reactions are (84%-100%): breast carcinoma, lung-epithelia cell carcinoma, ovaria carcinoma and to a lesser extend with carcinomatous tissue of the endometrium, pancreas, prostata and stomach.

Clinically CA 72-4 is indicated as therapy and follow up marker in carcinomas of the stomach in combination, as a second marker, with CA 19-9 and CEA. CA 72-4 is useful as a second marker in carcinoma of the ovary and carcinoma of the colon.

Limitations: Elevated levels in up to 25% of the patients with cirrhosis, pancreatitis, non-malignant pulmonary diseases, rheumatic diseases, ovarian diseases, diseases of the breast, and GI tract disorders.

- Carcinoma of the stomach:

Diagnostic specificity >95%. Sensitivity overall is 40%-45% but up to 80%, also depending on the stage of the carcinoma. The tumor marker CA 19-9 has a lower sensitivity (30%), also CEA sensitivity is lower (20%-25%). A combined testing for CA 72-4 and CA 19-9 increases sensitivity by 15%. Values return to normal post-operative within 1-2 weeks. A relapse is indicated in 60%-70% of the cases by increasing levels of CA 72-4 (lower sensitivity for relapses for CA19-9 with 50% and CEA with 20%).

- Carcinoma of the colon:

Specificity 95-98%. Sensitivity 20%-43%; combination of CEA and CA 72-4 enhances sensitivity by up to 17%. Post-operative the marker decrease within 3 weeks. Increasing values are reported in up to 80% of the relapse cases and combination of CEA with CA 72-4 enhances sensitivity by 10%.

- Carcinoma of the ovary:

Specificity 85%-95%. Sensitivity 10%-80%, stage dependant. Combining CA 125 with CA 72-4 increase sensitivity by about 10%.

- Other carcinomas:

Increased values of CA 72-4 are reported in carcinomas of the gall ducts (35%-50% of the patients); of the pancreas (up to 35%) and carcinoma of the esophagus (up to 25%).

Sampling: 1 mL serum or plasma, stable for 1 week at 4ºC, otherwise freeze.

Reference Interval: < 5.3 U/mL

CA 125 (Ovary), Serum

Related Information: CA 15-3, Serum
CA 19-9, Serum
Carcinoembryonic Antigen, Serum
Heterophilic Antibodies

Synonyms: Cancer Antigen 125; Carbohydrate Antigen 125

Background: CA 125 is present in healthy individuals at levels < 35 U/mL with a half life time of 5 days. In patients with ovarian carcinomas half life is extended to 12 days and extending further in late stages or large tumor masses.

Clinically the tumor marker is relevant in monitoring ovarian carcinomas and as a second marker in carcinomas of the pancreas (first marker CA19-9).

Diagnostic sensitivity is reported 82%-96% for carcinoma of the ovary at a threshold of 35 U/mL, down to 88 % at 65 U/mL.

Diagnostic specificity is 99% for ovarian carcinomas as compared to healthy individuals, 83% as compared to patients with inflammatory diseases of the ovary or fallopian tubes and 92% as compared to patients with benign tumors of the ovary.

Limitations: Increased to more than 65 U/mL in acute inflammation of the ovary (up to 25%), acute peritonitis (60%), gastrointestinal diseases (8%), cholecystitis (23%), hepatitis (5%), and cirrhosis 35%).

Sampling: 1 mL serum. Since abdominal surgery increases CA 125 levels, specimen should not be drawn within 3 weeks after surgery.

Reference Interval: 0-35 U/mL (for 99% confidence interval)

CA 549 (Breast), Serum

Related information: CA 15 - 3, Serum (Breast)
Carcinoembryonic Antigen (CEA), Serum

Background: CA 549 is a mucinous circulating tumor marker recognized by two monoclonal antibodies (BC4E549 and BC4N154) directed against tumor and milk fat globule membranes.

Overall sensitivity of CA 549 for breast cancer is 77% and specificity 92% (as compared to 61% and 92% for CEA).

No false positive results have been reported in pregnant women.

Early breast cancer:

Sensitivity for detecting early breast cancer is reported 21%-22% for CA 549 (cut off = 12.6 U/mL), as compared to 20% for CA 15-3 (cut off = 25 U/mL) and 11% for CEA (cut off = 6 ng/mL).

CA 549 has a low negative predictive value (0.5) due to a low sensitivity in the detection of early breast cancer. The test has a high positive predictive value (0.9) reflecting a high specificity for the disease. False positive results have been reported in 1.5%-22% of women with benign breast disease, and in up to 26% of patients with nonmalignant liver disease. In metastatic

cancer of prostate, ovary, endometrium, colon, and lung CA 549 was elevated in 12% to 50% of the cases with levels less than 120 U/mL.

Metastatic breast cancer:

Sensitivity in detecting metastatic breast cancer is reported for CA 549 to be between 70% and 83% as compared to CEA 45%, MCA 59%, and CA 15-3 71%. Sensitivity increases only slightly (6%-8%) when two or more markers are simultaneously considered. Overall sensitivity of correlation with objective response is in the range of 50%-70% in patients with abnormal baseline marker values, and in the range of 40%-90% in patients with normal baseline values. The combination of two or more markers did not improve sensitivity, but decreased specificity of correlation with objective response.

Follow up:

In patients without clinical signs of disease after surgery abnormal CA 549 was reported in 11%-16% of the patients, in 82% of the patients with disease progression, in 70% with stationary disease, in 63%-76% with partial remission and in 23%-33% with complete remission.

Sampling: 1 mL serum or plasma

Reference Interval: < 12.1 U/mL

Calcitonin, Serum or Plasma

Related Information: Calcium, Serum
Carcinoembryonic Antigen (CEA), Serum
Catecholamines, Fractionation, Plasma
Catecholamines, Fractionation, Urine
Parathyroid Hormone, Intact, Serum
Phosphate, Inorganic, Urine

Synonyms: Thyrocalcitonin

Background: Calcitonin is synthesized by the parafollicular cells (C-cells)of the thyroid gland and to a minor extend by neuroendocrine cells of the bronchopulmonary system, the thymus and the adrenal medulla, Calcitonin is a monomer of 32 amino acid peptide of 3.5 kDa. The secretion of calcitonin is regulated by iodized calcium and the gastrointestinal peptide hormones in particular gastrin. Calcitonin is metabolized by the kidney within several minutes.

Calcitonin is the main calcium regulating factor, lowering calcium and phosphorus. Furthermore it directly inhibits osteoclastic bone resorption.

Used in assessment of medullary carcinoma of the thyroid, in postoperative monitoring and in the search for metastasis, CEA is the second useful marker in medullary carcinomas.

Increased concentrations occur in familiarly forms of C-cell hyperplasia, some forms of the disease display abnormal values after stimulation only.

Sampling: 1 mL serum, avoid hemolysis and keep refrigerated.

Reference Interval: < 13 pg/mL

Stimulation with pentagastrin or calcium: < 350 pg/mL in men and < 100 pg/mL in women.

Calcium (Ca) Total, Serum

Related Information:
Aluminium, Serum or Urine
Calcium (Ca), Urine
Hydroxyproline, Total, Urine
Magnesium (Mg), Serum
Magnesium (Mg), Urine
Osteocalcin, Serum or Plasma
Parathyroid Hormone, Intact, Serum
Phosphate, Inorganic, Serum
Phosphorus, Inorganic, Urine
Potassium, Serum or Plasma
Potassium, Urine
Pyridinolines
Vitamin D, Serum

Background: With approx 1 kg of calcium it is the fifth most prevalent elements in the body and the most common cation. 99% is bound in the bone as hydroxyapatite. 50% of serum calcium exists in the free ionized form, 10% is complexed with anions (lactate, bicarbonate, phosphate and citrate), 40% is bound to plasma proteins (80% to albumin). Plasma protein binding is ph dependent; alkalosis promotes decreased binding, acidosis an increase.
Ionized calcium in the extracellular fluid is kept around 1.25umol/L by PTH and 1,25-dihydroxyvitamin D_3, targeting bone, kidney and the intestine. PTH in combination with 1,25-dihydroxyvitamin D_3 acts on the bone by releasing calcium and on the kidney by increasing phosphorus secretion and calcium resorption.

Hypercalcemia:
-Primary hyperparathyroidism is characterized by elevated ionized calcium (80% have elevated total serum calcium levels), hypophosphatemia and normal kidney function. In some cases coexistence with endocrine tumors.
-Parathyroid hormone-related protein cause in carcinomas without bone metastasis (primary squamous cell carcinoma of the lung, head, neck, breast, kidney liver bladder, ovary) increase of serum calcium.
-Minor hypercalcemia is seen in dehydration, sarcoidosis, and other granulomatous diseases.
-Abuses of calcium containing ulcer medications and vitamin D-hypervitaminoses.
-Hypercalcemia may occur in hyperthyroidism, Addison disease, acromegaly, pheo-chromocytoma, idiopathic hypercalcemia of infancy, Williams's syndrome, liver diseases, bacteremias, cat-scratch disease.
-Drugs: lithium, thiazides, antiestrogens, estrogens.

Decreased Calcium:
Since about 40% of calcium is bound to albumin, and the important fraction of calcium is the unbound ionized form, total calcium has to be adjusted in a decreased albumin state of the patient. Calculate calcium in a decreased albumin state:

Calcium (mmol/L) = measured calcium (mmol/L) + 0.02 X (mean normal albumin – measured albumin (g/L))

Alternative approximation: Add 0.1 mmol/L to the calcium concentration for every 4 g/L of albumin that albumin is below 40 g/L and a similar subtraction for raised albumin.
Decreased total calcium levels are associated with renal failure, hypoparathyroidism with high phosphorus, vitamin D deficiency, osteomalacia, malabsorption, pancreatitis, bacteremia, hypomagnesemia. .
drugs: Barbiturates, calcitonin, corticosteroids, gastrin, glucagon, glucose, insulin , magnesium, methicillin.
Sampling: 1 mL serum. Hemolysis increase calcium levels therefore avoid any forced blood drawing; take blood samples if necessary uncuffed. Citrate containing blood transfusions increase total calcium but decrease ionized serum calcium.

Reference Interval:

	(mmol/L)
Cord	2.05 - 2.80
Premature	1.55 - 2.75
0-10 days	1.90 - 2.60
10 days -2 year	2.25 - 2.75
2-12 years	2.20 - 2.70
Adults	2.10 - 2.58

Critical value: < 1.75 mmol/L may evoke tetany and seizures.
> 3 mmol/L clinically presents with polyuria, anorexia, nausea, constipation, rare cause of coma.

Life threatening: < 1.5 mmol/L
> 3,5 mmol/L

Calcium (Ca), Urine

Related Information:
Aluminium, Serum or Urine
Calcium (Ca), Total, Serum
Hydroxyproline, Total, Urine
Magnesium (Mg), Serum
Magnesium (Mg), Urine
Osteocalcin, Serum or Plasma
Parathyroid Hormone, Intact, Serum
Phosphate, Inorganic, Serum

Phosphorus, Inorganic, Urine
Potassium, Serum or Plasma
Potassium, Urine
Pyridinolines
Vitamin D, Serum

Background: See also Calcium, Total, Serum. Urinary excretion is useful in the evaluation of the skeletal turnover of calcium. In the fasting state, intestinal and renal calcium resorption and excretion are stable and values > 0.04 mmol/L per 100 mL of glomerular filtration (>0.16mg) indicates osteoclastic bone resorption.

Formula for calculation:

Urine Ca (mg/100mL glomerular filtration) = (Urine Ca (mg/dL) x serum creatinine (mg/dL)) / urine creatinine (mg/dL)

Sampling: 10 mL aliquot of a 24 urine collection, ph < 3 adjusted by 25% hypochloric acid. Note total quantity.

Reference Interval: On a average calcium intake diet of 600-800mg/24h:

Male: < 7.5 mmol/24h
Female: < 6.2 mmol/24h

Calcium to Creatinine ratio:
Adults with constant muscle mass:
Calcium (mmol/L) / creatinine (mmol/L) < 0.4
Children: 2.25 at 1 month and dropping to 1.2 at the age 3 years to adult values at the age of 10 years.

Candida albicans, Serology and Culture

Background: Candida albicans is oval yeast with a single bud. In tissue the organism occur also as pseudohyphae. It is part of the normal flora of the mucous membranes of the upper respiratory, gastrointestinal and female genitale tracts. As an opportunistic pathogen, Candida may overgrow in the mouth as white patches (thrush), in high ph vulvovaginitis, diabetes or during antibiotic therapy and in immunosuppressed patients the organism may disseminate into organs. In warm and moist environments Candida albicans may lead to chronic mucocutaneous candidiasis.

Antibody directed against Candida antigen screening on a regular base (weekly) is a valuable tool to monitor patients for therapy and stage of infection.

In contrast, the value of antigen testing is limited, since the sensitivity of the antigen test is low and a negative result can not preclude an antifungal therapy, particularly in immunocompromised patients. Test specificity is high, but most of the patients also have positive blood cultures.

Risk factors for Candida infection: Prolonged ventilation, urinary catheters, intravascular lines, broad spectrum antibiotic therapy, immunosuppression, iv nutrition, ITU stay.

Sampling: Serology: 1 mL serum
Direct detection by culture: genital swab, tracheal fluid, 2g stool

Reference Interval:

Serology:	Differentiation of immunoglobulin class		
	IgA antibody	negative:	< 60 U/mL
		borderline:	60 – 80 U/mL
		positive:	>80 U/mL
	IgG antibody	negative:	< 40 U/mL
		borderline:	40 – 100 U/mL
		positive:	>100 U/mL
	IgM antibody	negative:	< 60 U/mL
		borderline:	60 – 80 U/mL
		positive:	> 80 U/mL

Culture: Report on diagnostic finding: Direct detection by microscopy and culture.

Cannabinoids (Marijuana Metabolites)

Related information: Ethanol, Blood or Urine

Background: The major active compound of marijuana is tetrahydrocannabinol (THC), leading to euphoria, relaxation, altered reception impaired memory. The major metabolite 11-carboxy –THC is excreted in the urine and detectable in chronic smokers for up to 6 weeks, due to the lipophilic nature it is stored in body fat.

Half Life 1-2 days ; volume of distribution 4-19 L/kg ; protein binding 95-98%

Sampling: 10 mL random urine

Reference Interval:

negative: < 50 ng/mL (Confirmation cut off 15 ng/mL), depending on the legal rules.

Detection: for 3 – 4 days after minor consumption. Detection in heavy smokers for weeks to months after last consumption

Carbamazepine, Serum

Related Information: Carbamazepine-10,11-Epoxide, Serum
Phenytoin (Diphenylhydantoib,DPH), Serum
Valproic Acid, Serum or Plasma
Verapamil, Serum or Plasma

Synonyms: Carpamazepinum; Carbategretal®; Carbatrol®; Carbazep®; CBZ; Epitrol®; Tegretol®-XR

Background: Carbamazepine is a tricyclic antidepressant structurally and mode of action similar to phenytoin.

Carbamazepine blocks sodium channels and inhibits uptake of and release of norepinephrine, but does not influence GABA uptake.

Carbamazepine is the drug of choice in partial seizures and used for generalized tonic clonic seizures, trigeminal neuralgias and mania.

Steady state is reached after 4-8 days. Peak levels after 6-8 h after oral administration; bioavailability 80%; volume of distribution 1L/kg; protein binding 60-80%; half life 36h initially, 20h through.

Carbamazepine is completely metabolized by the liver; one metabolite is the active carbamazepine 10-11-epoxide.

Plasma levels may be decreased by P450 system inducing drugs such as phenytoin, primidone, phenobarbital. Levels may be increased by P450 inhibiting drugs as isoniazid, fluoxetine, propoxyphene, quetiapine, verapamil, stripentol.

Dose related side effects are diplopia, ataxia, gastrointestinal upsets, and drowsiness. The incidence of leukopenia is 10%. There is an up to 8 fold increased risk to develop aplastic anemia and agranulocytosis as compared to the normal population.

Sampling: 1 mL serum, steady state after 4-8 days.

Reference Interval:

Therapeutic	Total level: 4-10 µg/mL ; in combination with other anticonvulsants 4-8 µg/mL
	Free carbamazepine: 0.5-4 µg/mL
Toxic	Total > 15 µg/mL; Free > 4 µg/mL

Carbamazepine-10,11-Epoxide, Serum

Related Information: Carbamazepine, Serum

Background: Carbamazepine-10,11-epoxide is an equipotent active metabolite synthesized in the liver from Carbamazepine. Accumulation of the metabolite, which occurs in patients additionally on valpromide or progabide therapy may lead to toxicity despite normal levels of carbamazepine. Phenytoin and valproic acid may also increase the epoxide to carbamazepine ratio.

Sampling: 1 mL serum

Reference Interval: 0.5-2.5 µg/mL

Carbohydrate Deficient Transferrin (CDT)

Related Information:
Alanine Aminotransferase (ALT), Serum
Alkaline Phosphatase, Serum
Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Ethanol, Blood, Serum or Urine
Folic Acid, Serum
Gamma-Glutamyl Transferase (Gamma-GT), Serum

Background: CDT is increased either in alcohol abuses or in patients with autosomal recessive disorders of infancy or childhood, named carbohydrate-deficient glycoprotein syndrome or congenital disorders of glycosylation(CDG), characterized by mental retardation, liver dysfunction, cerebellar hypoplasia, muscular weakness.
Useful as a marker of alcohol consumption, monitoring of alcoholism and for diagnosis of CDG. However, the marker is not highly specific (90%) or sensitive (60%-70%) for alcoholism, since it is affected by smoking, body mass index, hypertension, liver damage.
Half life of CDT is 2 weeks.
Sampling: 1 mL serum. Refrigerate or freeze immediately or ship to the laboratory immediately.
Reference Interval: < 2.9%

Carboxyhemoglobin, Blood

Related Information: Cotinine, Serum, Plasma or Urine
Methemoglobin (MetHb), Whole Blood
Synonyms: Carbon Monoxide Hemoglobin; COHb ; CO-Hemoglobin;
Background: Carbon monoxide is a colorless, tasteless and odorless gas. By binding with a 250 times higher affinity to hemoglobin as oxygen, blood oxygen carrying capacity in the presence of carbon monoxide is reduced. CO also binds to myoglobin and cytochromes oxidases. Half life of carboxyhemoglobin is approx. 6h and even with 100% oxygen administration still remains at 1.5h, which can be reduced under hyperbaric oxygen to 35 min at 3 atmospheres.
Sampling: 1 mL EDTA, citrate or heparin blood. Cape tube tightly, keep tube capped. Keep refrigerated.

Reference Interval			
	Nonsmoker		< 3%
	Smoker	1-2 pack/day	5%
		> 2 packs /day	10%
	Newborn		10%-12%
	Fatal		30%-80%
	Immediate death		> 80%

Carcinoembryonic Antigen (CEA), Serum

Related Information: Alpha1 Fetoprotein, Serum
CA 15-3, Serum
CA 19-9, Serum
CA 125, Serum
Homovanillic Acid (HVA), Urine
Occult Blood in Stool (Hemoccult)
Background: CEA is a 180 kDa glycoprotein (50% carbohydrates). CEA is not organ specific, but highest concentrations up to 500 fold as compared to the normal colon tissue are assayed

in adenocarcinomas of the colon and liver metastasis, to a lower degree in carcinomas of breast (CA15-3 is superior), lung , pancreas and the stomach.
CEA is used in staging and monitoring patients with colorectal carcinoma and as a follow up marker after tumor resection. It is not effective as a screening assay.
Limitations: CEA is moderately elevated in smokers, during infections and inflammations, sometimes during liver diseases, inflammatory bowl diseases, and acute pancreatitis. It is not effective as a screening assay since, in the early stage (Dukes A) 95% are negative, late stage (Dukes D) up to 35% are false negative.
Also recurrent colorectal cancer may be false negative in up to 30%, however CEA is a useful marker for tumor relapse if values progressively increase.

Sampling: 1 mL serum
Reference Interval: < 5.0 ng/mL

Cardiolipin Antibody

Related Information: Prothrombin Time
Very Low Density Lipoproteins, Serum
Synonyms: ACA; Anti-Cardiolipin Antibodies
Background: Cardiolipin is the diphosphadidyl glycerol part of phospholipid membranes. The binding of the antibodies is mediated by beta2 glycoprotein-1 (apolipoprotein H) which is thought to inhibit thrombin generation. The binding changes the phospholipid exposing new epitopes and stimulates antibody production against the new structures.
ACA belong to the group of antiphospholipid antibodies, causing the antiphospholipid antibody syndrome which presents as thrombosis of the arteries and veins and a positive test for lupus anticoagulant or ACA. The autoantibodies are present in patients with systemic lupus erythematosus, in lupus like disease, during infectious diseases, and in drug reactions. Laboratory abnormalities associated with ACA may be thrombocytopenia, reactive VDRL, SS-A/Ro antibodies, prolonged activated partial thromboplastin time. Patients with lupus like disease are often ANA negative. Lupus anticoagulant with anticardiolipin antibodies are present in 70% of the antiphospholipid antibody syndrome patients. Lupus anticoagulant is present in 20-40% and ACA in 50% of patients with SLE.
In chronic hepatitis C patients ACA is higher than in patients with other inflammatory hepatic disease.
Elevated IgG ACA titers are present in cerebrospinal fluid of patients with symptomatic cerebral lupus, probably due to intrathecal IgG production.
Limitations: Cross reactions to a minor extend with reagin antibody of syphilis and lupus anticoagulant.
Sampling: 1 mL serum

Reference interval: Differentiation of immunoglobulin class:

IgA antibody negative:	< 12 RE/mL
IgG antibody negative:	< 12 RE/mL
IgM antibody negative:	< 12 RE/mL

Carnitine, Serum or Plasma

Synonyms: Beta-hydroxy-gamma-trimethylammonium butyrate; Carnitor; Levocarnitine

Background: L-Carnitine, as the active form, is synthesized in tissues from lysine residues starting with the formation of 6-N-trimethyllyine involving S-adenosylmethionine and for further steps, ascorbic acid, niacin, pyridoxine and iron is required.

Dietary carnitine is delivered by meat and dairy products. Cereals do not contain carnitine.

Carnitine is involved in the oxidation of fatty acids, aerobic metabolism of carbohydrates, oxidative phosphorylation, and increases the excretion of organic acids.

Primary deficiency, in part caused by an insufficient transport of carnitine into the muscle cell and faulty renal reabsorption, is observed in inherent disorders leading to storage of fat in muscle cells with dysfunction in cardiac and skeletal muscles. The systemic form is characterized by low plasma, muscle and liver carnitine concentrations with muscle weakness, cardiomyopathy, impaired ketogenesis, and fasting hypoglycemia. The myopathic form presents with muscle weakness, carnitine plasma concentrations are normal.

Secondary deficiencies are characterized by increased urinary excretion due to renal tubular disorders or long term hemodialysis.

Also disorders with increased circulating organic acids may lead to carnitine deficiency due to the excretion promoting function of carnitine.

Toxicity: L-carnitine up to 15 g/day is well tolerated, but DL-carnitine produces myasthenia gravis like symptoms by the inhibitory activity of the D isomer on the L isomer function and uptake.

Sampling: Plasma: 2 mL serum or plasma .
Urine: 10 mL aliquot of a 24h urine, collected without preservatives in a clean container.
Seminal fluid: 1 mL

Reference Interval:

Plasma	0.8 – 1.5 mg/dL
Urine	15 – 40 mg/24h
Seminal fluid	> 4.0 mg/dL

Cat Scratch Disease see Bartonella Henselae, Antibody, Serum

Catecholamines Fractionation, Plasma

Related Information: Catecholamines, Fractionation, Urine
Homovallinic Acid (HVA), Urine
Vanillylmandelic Acid, Urine

Synonyms: Adrenalin®, Noradrenalin®

Test includes: Epinephrine (E) (Adrenalin®) and Norepinephrine (NE) (Noradrenalin®) and Dopamine (D)

Background: The catecholamines are synthesized in the adrenal medulla, brain, sympathetic nervous system. Pheochromocytoma secrete large amounts of E, NE or both. Half live is 2 min.

Sampling: 2 mL EDTA or heparin plasma. Patient must be in calm, relaxed state and in a supine position for 30 min prior to collection. Catecholamine levels vary with posture, cold anxiety, pain. Epinephrine like drugs such as Aldomet®, Inderal®, should be withdrawn 8 days prior to sampling. Place EDTA or heparin blood specimen immediately after drawing on ice. Transport the specimen on ice to laboratory for separation of plasma within 1h or separate plasma by centrifugation at 4°C and freeze at –70°C.

Clonidine suppression test: Test to be conducted after an overnight fasting period. Patient remains in recumbent position during the test. After baseline specimen is drawn, 4.3 ug/kg body weight is given per os. Clonidine suppresses catecholamines in patients with essential hypertension but not in pheochromocytoma.

Reference interval:

Norepinephrine	supine 70 – 750 pg/mL	upright: 200-1700 pg/mL
Epinephrine	supine < 110 pg/mL	upright <140 pg/mL
Dopamine	< 30 pg/mL (independent of posture)	

Catecholamines Fractionation, Urine

Related Information: Calcitonin, Serum or Plasma
Catecholamines Fractionation, Plasma
Homovanillic Acid, Urine
Metanephrines, Urine or Plasma
Vanillylmandelic Acid, Urine

Background: Please see Catecholamines Fractionation, Plasma.

Useful in the diagnosis of catecholamine secreting tumors. Most of them (>95%) are adrenal pheochromocytomas, less common are paragangliomas and neuroblastomas.

Limitations: Increased values occur post surgery, injuries cold, anxiety, and some acute or chronic illnesses.

Sampling: 20 mL aliquot of a 24h urine, collect in 10 mL of 20% hydrochloric acid (do not use boric acid). Store during collection refrigerated. Please note total quantity.

Reference Interval:

Epinephrine (µg/24 h)	
< 1 year	0-2.5
1-2 year(s)	0-3.5
2-3 years	0-6.0
4-9 years	0.2-10
10-15 years	0.5-20
>16 years	0-20

Norepinephrine (µg/24 h)	
<1 year	0-10
1 year	1-17
2-3 years	4-29
4-6 years	8-45
7-9 years	13-65
>10 years	15-80

Dopamine (µg/24 h)	
<1 year	0-85
1 year	10-140
2-3 years	40-260
>4 years	65-400

CD4$^+$ and CD8$^+$ Cells see Lymphocyte Immunophenotyping

Cell Count, Liquor see Cerebrospinal Fluid (CSF, Liquor)

Cerebrospinal Fluid (CSF, Liquor)

Background (general): Useful in the evaluation of meningitis, encephalitis, meningoencephalitis, bacterial, viral or fungal infections, parasitic diseases, malignancies, lymphomas of the CNS, trauma, vasculitis, degenerative processes.

Sampling (general): CSF. Concurrently, a sample of peripheral blood should be obtained in case CSF glucose levels (infectious diseases) or oligoclonal bands (demyelinating diseases) are due to investigation. Blood cultures are valuable in infectious causes, particularly prior of initiation of antibiotic therapy.

Samples should be delivered to the lab promptly.

For the diagnosis of meningitis, culture and gram stain and cell count have priority over antigen or other testing, followed by glucose and protein.

1. Cell count

Reference Interval:

Premature neonates	<29 cells / mm^3
<1 month	<32 cells / mm^3
1 month to12 month	< 10 cells/ mm^3
1-4 years	< 8 cells/ mm^3
5-14 years	< 5 cells/ mm^3
adults	0-5 cells/ mm^3 , lymphocytes and monocytes, no red cells.

2. Protein

Background: The protein concentration in the CSF is less than 1% of plasma concentration. Proteins in the CSF are of lower molecular weight as compared to plasma proteins, normally comparable small amounts of beta lipoproteins, alpha $_2$ macroglobulin, IgM or haptoglobulins are part of CSF.

Elevated protein should trigger further tests such as IgG / albumin index, IgG synthetic rate, electrophoresis for oligoclonal bands.

Increased:

- Bacterial meningitis (100-500 mg/dL, occasionally higher) including mycobacteria
- Brain abscesses
- Syphilis in 10-20% with primary syphilis, up to 70% with secondary stage disease
- Carcinomas
- Diabetes mellitus
- Arachnoiditis
- Demyelinating diseases (MS patients display normal or slightly elevated levels)
- Dehydration
- Disc herniation
- Drug related such as gentamicin, vancomycin, ampicillin, phenothiazine
- Subarachnoid hemorrhage
- Trauma
- Obstruction of the spinal canal (e.g. tumor) due to lacking reabsorption of protein by arachnoidal cells
- Froin syndrome (protein >200 mg/dL, clotting of CSF due to fibrinogen)
- AIDS patients with CNS involvement (up to 50% of the patients display elevated CNS protein, 10-30 % oligoclonal bands, the percentage is stage dependent.)

Normal to slightly (50-80 mg/dL) elevate:

- In some psychiatric disorders
- Multiple sclerosis

Viral meningitis (usually less than 100mg/dl)

Decreased (10-20mg/dL):

Water intoxication,

CSF leaks (beta 2 transferrin typically elevated)

Leukemia

Hyperthyroidism

Limitations:

Fresh blood increases CSF protein test values. The protein levels can be adjusted by the CSF erythrocyte count

Ery / ul	corrected protein concentration by subtraction of
500	7.7 mg/L (2%)
1000	15.4 mg/L (4%)
2000	30.8 mg/L (8%)
4000	61.6 mg/L (15%)
8000	123.0 mg/L (30%)

Reference Interval: Protein

Infants (lumbar) (approximate)

1-8 days	26-135 mg/dL
3-30 days	26-115 mg/dL
1-2 month	18-86 mg/dL
2-3 month	10-74 mg/dL
older 6 month	15-45 mg/dL

Adults

lumbar	18-43 mg/dL
ventricular	5-15 mg/dL
cisternal	15-25 mg/dL

The higher protein levels in infants can be explained by increased blood brain barrier permeability.

3. Glucose

Background: CSF glucose is useful in the distinction of bacterial versus viral meningitis. CSF glucose is low <40mg/dL (<2.2 mmol/L) in bacterial or tuberculous meningitis and normal in viral meningitis.

Low CSF glucose occurs in sarcoidosis and neurosyphilis, in meningeal cysticercosis, trichinosis, and during intrathecal drug therapy. Subarachnoid hemorrhage, carcinomas and leukemias may also lower CSF glucose.

Limitations: High contamination with blood may increase CSF glucose due to higher blood glucose levels. Delayed delivery to the laboratory in cases of bacterial presence or contami-

nation may decrease glucose due to utilization of glucose.
CSF. Blood glucose is valuable, ideally taken 2h prior to lumbar puncture (equilibration time)

Reference Interval:

Adults:	50-80 mg/dL or 60-70% of plasma glucose
Infants and young children:	Slightly higher than adults: 60-80 mg/dL (SI 3.4-4.5 mmol/L). Plasma/CSF ratio: In premature and newborn infants, CSF glucose may be 80% or more of blood glucose levels (adults: 60%-70%). Critical value: less than 40%.

4. Humoral Immunoglobulin Production

Background: Antibodies are not synthesized during healthy state of the CNS. Antibodies entering via the blood brain barrier from the blood are as low as 0.2% for IgG and 0.03% for IgG of the blood concentrations. The humoral reaction in the CNS may characterize a CNS disease and is a valuable tool in diagnosis. Humoral reactions of the CNS may last in diseases such as neurosyphilis and herpes encephalitis after successful treatment for several years to decades.

Early stage CSF pattern:

No IgG, IgA or IgM	Early stage of bacterial, virus encephalitis, Guillain Barré
Predominant IgG	Multiple sclerosis (but up to 20% IgM or rarely IgA), neurosyphilis (sometimes IgM), HIV encephalitis
Predominant IgA	Neurotuberculosis (sometimes IgG or IgM), abscesses
Predominant IgM	Neuroborreliosis (sometimes IgA and IgG), mumps encephalitis, non-Hodgkin lymphoma of the CNS, neuro trypanosomiasis
Mixed IgG, IgA, IgM	Infections during immunodeficiency

Reference Interval:

IgG 10-40 mg/L (serum 7-18 g/L)
IgA 0.5- 6.0 mg/L (serum 0.9-4.5 g/L)
IgM 0.05-0.8 mg/L (serum 0.6-2.8 g/L)

5. Albumin

Background: Albumin is synthesized outside of the CNS. It is the ideal protein to represent changes in the blood brain barrier. For other parameters such as IgG, IgA IgM and known serum and CSF concentrations the intrathecal production can be determined if the serum Albumin to CSF ratio has been determined.
The ratio for proteins in CSF/serum depends on molecular seizes:

Protein	MW (kDa)	ratio [mean]
Albumin	69	1:205
IgG	150	1:440
IgA	160	1:800
IgM	971	1:3400

The ratio of the concentrations of CSF albumin / albumin serum (Q alb) is considered as a parameter for the function of the blood brain barrier and serves as the reference for other proteins such as immunoglobulins NSE, S100B, cystatin c resulting in an blood-brain barrier function independent measurement of intrathecal production of the protein of interest.

Ratio CSF IgG / CSF albumin <0.27

Index (CSF IgG / CSF albumin) / (serum IgG / serum albumin) < 0.7

The CNS IgG production rate in mg/day is calculated by Tourtellotte as used for the diagnosis of MS:

5 x [{CSF IgG - serum IgG/369} - {(CSF albumin - serum albumin /230) x 0.43 x (serum IgG/serum albumin) }]

Reference Interval: CSF albumin: 110-350 mg/L (serum albumin: 35-55 g/L)

6. Electrolytes

Reference Interval:

	CSF	Serum
Osmolality	281 mosm/kg	289 mosm/kg
Urea	16.3 - 34.7 µmol/L	16.7 - 32.5 µmol/L
Calcium ionized	1.05 -1.35 mmol/L	1.15 - 1.35 mmol/L
Chloride	116 - 127 mmol/L	92-105 mmol/L
Glucose	1.1 - 4.4 mmol/L (20-79 mg/dL)	3.9 - 6.1 mmol/L (70 - 110mg/dl)
Lactate	1.2 - 2.1 mmol/L	0.5 - 2.2 mmol/L
Magnesium	0.9 - 3.2 mg/dl (0.38-1.4 mmol/L) total Mg	total Mg: 1.8 - 2.7 mg/dl (0.75 - 1.1 mmol/L) Ionized Mg : 1.1 - 1.5 mg/dl (0.46 - 0.6 mmol/L)
Phosphate anorganic	1.1 mmol/L	0.8 - 1.45 mmol/L
Potassium	2.7 - 3.9 mmol/L	3.6- 4.8 mmol/L
Sodium	138 - 150 mmol/L	135 - 145 mmol/L

7. Lactate, CSF

Background: Used, but not reliable parameter to differentiate between bacterial from other forms of meningitis. Elevated also in cerebral infarct, Creutzfeldt Jacob disease, cerebral hemorrhage, subarachnoid hemorrhage, hypertension, hepatic encephalopathy, diabetes mellitus, head injury.

Reference Interval: Increased in the first 2 weeks of life
Adults 10-22 mg/dL (1.1-2.4 mmol/L)

8. Interpretation, CSF

Infectious condition for lumbale CSF of adults

	pressure mmH2O	cell count	protein mg/dl	glucose
normal	50-150	<5 lymphocytes	15-60	60-70% of serum glucose (74-106 mg/dl = 4.1-5.9 mmol/L)
bacterial meningitis	elevated	200-10 000, 95% PMN	usually>100	lower(<50mg/dl)
viral meningitis	elevated	normal -1000, predom.lymphocytes	usually 50-100	normal
tuberculosis or fungal	elevated	normal -500, predom.lymphocytes	100-several thousands	low (<50 mg/dl)
brain abscess	elevated	usually <500 predom.lymphocytes	50-100	normal to low

Non infectious condition for lumbale CSF of adults

subarachnoidal hemorrhage	normal to elevated	slightly elevated	elevated	normal to low
Guillain Barré syndrome	normal	normal	elevated	normal

Infectious condition for lumbale CSF of adults

Parasitic Disease	Protein g/L	Glucose mg/dL	Cell count/ul	
Neurocysticercosis	up to 16	mean 42 mg/dl decreased down to 6 mg/dl	mean 60 up to 2000	In up to 60 % of the patients display CSF abnormalities, most common: elevated protein, predominant mononuclear cells, seldom decreased glucose. In 50% eosinophils increased
Bilharziosis of the CNS	elevated	Occasionally decreased	Up to 100	200 mio humans affected by schistomiasis, but CNS infection rare. Oligoclonal IgG, antibodies in the CSF occur in 70% of the patients.
Nematode infection of the CNS	Elevated		Elevated	Usually presents as meningitis, myelitis, radiculitis. Predominant eosinophiles in the CSF
Strongyloidiasis infection of the CNS			Elevated	High eosinophile count, IgG and IgA elevated in 80% of the patients
African Trypanosomiasis				IgM predominant (95% of the cases present with intrathecal IgM production, with IgG 70% only). Note that the European population has higher serum albumin levels (35-55 g/l) as compared to the African population, but the albumin ratio CSF/serum is comparable in trypanosomiasis patients.

Ceruloplasmin (Cp), Serum or Plasma

Related Information: Copper (Cu), Serum or Urine

Background: Cp is a glycoprotein, MW 132 kDa, with 9% carbohydrates. Cp binds 6-9 Cu atoms. Cp is synthesized in hepatocytes and Cu is intracellular ATP dependent incorporated. In patients with Morbus Wilson, the ATPase is impaired. The physiologic function of Cp is to make Fe available for erythropoiesis by ferroxidase activity, inhibiting the oxidizing properties of lipids, thus preventing atherosclerosis and neurotoxicity.

70% of the body copper is bound to Cp, 7% to transcuprein, 20% to albumin, and 2% to amino acids.

Cp is decreased in 75% of the patients with Morbus Wilson (WD). WD is characterized by toxic accumulation of copper in liver, basal ganglia e.g. globus pallidus hypodensity in some cases fronto-temporal, cerebellar, and brain stem atrophy. WD is autosomal recessive hereditary disease with a homozygote prevalence of 1:50.000 to 1:100.000. Symptoms occur in late puberty, and since the disease is treatable with the chelating penicillamine or trientine dihydrochloride, it is advisable to screen young patients with cirrhosis or CNS signs such as tremor, dysarthria, dysphagia, dyskinesias, dementia, micrographia, personal changes, and psychiatric symptoms. In liver failure caused by WD characteristically the ratio aspartate aminotransferase (AST) to ALT (alanine aminotransferase) is >2, alkaline phosphatase more likely to be decreased and AST is moderate increased. Cp in WD is usually < 20 mg/dL, however 20% of the patients with hereditary Cp defects, renal Cp losses, after severe burning, or decreased synthesis in serve liver diseases present decreased Cp.

Menkes disease, a defect liked to the chromosomal locus Xq13.3 lacking an intracellular Cu binding protein and presenting in early childhood with seizures, mental retardation, impaired joint function and facial dysmorphism. The prognosis is poor. Cp and serum copper is decreased.

Limitations:

Cp is an acute phase protein, interpretative caution is necessary. Oral contraceptives or estrogens cause dose dependent an increase of Cp up to 30%.

Sampling: 1 mL serum, transport to laboratory soon, otherwise centrifuge and freeze.

Reference Interval:

Children	(mg/dL)
1 day to 4 month	15-56
5-6 month	26-83
7-18 month	31-91
18-36 month	32-90
4-9 years	26-46
10-12 years	25-45

Female	(mg/dL)
13-19years	22-50
>19 years	25-60
>19 and on oral contraceptives	27-66
>50 and on estrogen therapy	30-50
Pregnancy	<130

Male	(mg/dL)
13-19 years	15-37
>19 years	22-40

Chagas see Trypanosoma cruzi, Serology

Chlamydia

Test includes: Chlamydia trachomatis serology, C. trachomatis direct DNA detection, C. pneumoniae serology

Background: The genus Chlamyddia includes C. trachomatis. The genus Chlamydophila includes C. pneumoniae, C. psittaci. Chlamydiaceae are obligate intracellular organisms. The cell wall resembles gram negative bacteria but lack muramic acid.Two forms are known, a non-replicating, infectious dense particle (elementary body) and a larger intracellular form (the metabolically active reticulate body). C. trachomatis is transmitted by direct contact and by vectors such as flies and contaminated towels. In industrialized countries, C. trachomatis is the most common bacterial STD, reaching 20% in young sexually active people. C. pneumoniae is a respiratory pathogen worldwide distributed. In tropical countries infections are common in the first year of life. Seroconversion reaches 25%-50% at the age of 15, rising further in the elder population which indicates either chronic or repeated infection.

Diseases caused by C. trachomatis are in female's cervicitis (incidence 30%), endometritis, pelvic inflammatory disease (10%-70%), and rarely perihepatitis, bartholinitis; in male's urethritis (10%-30%) and epididymitis. Conjunctivitis and reactive arthritis are seen in both sexes, in neonate's conjunctivitis and infant pneumonitis.

Diseases caused by C. pneumoniae are pneumonia: endemic (10%) or epidemic (up to 50%). Also acute bronchitis (5%) and rarely otitis media, sinusitis, carditis, vasculitis, reactive arthritis. Chronic infections may lead to chronic obstructive lung disease, asthma, sarcoidosis, in up to 50% to arteriosclerosis.

Classification

In the rRNA-based tree of life, four bacterial phyla comprising the Planctomycetes, Verrucomicrobia, Chlamydiae and Lentisphaerae, form together with the candidate phyla Poribacteria and

OP3 a monophyletic group referred to as the PVC superphylum. The Chlamydiaceae is a phylogenetically distinct Gram-negative bacterial family, encompassing two genera (Chlamydia and Chlamydophila), which are subdivided into three (Chlamydia muridarum, Chlamydia suis, and Chlamydia trachomatis) and six (Chlamydophila pneumoniae, Chlamydophila abortus, Chlamydophila caviae, Chlamydophila felis, Chlamydophila pecorum, and Chlamydophila psittaci) defined species, respectively.

Sampling: 1 mL serum

A PCR assay for direct detection is available for Chlamydia trachomatis. For swabs use a special swab, STD-PEN for males, STD-EZE for females. Punctate, tracheal fluid and 10ml first void urine is suitable for direct detection. Collect in a sterile container.

Reference Interval:

Chlamydia trachomatis; Serology
Differentiation of immunoglobulin class

IgA antibody	negative:	< 8 RE/mL
	borderline:	8 – 10 RE/mL
	positive:	> 10 RE/mL
IgG antibody	negative:	< 8 RE/mL
	borderline:	8 – 10 RE/mL
	positive:	> 10RE/mL

Chlamydia trachomatis, Direct detection by PCR
Report: DNA not detectable, detectable

Chlamydophlia pneumoniae, Serology
Differentiation of immunoglobulin class

IgA-Antibody	negative:	< 11 RE/mL
	borderline:	11 – 15 RE/mL
	positive:	>15 RE/mL
IgG-Antibody	negative:	< 11 RE/mL
	borderline:	11 – 15 RE/mL
	positive:	> 15 RE/mL

Chloride (Cl), Liquor see Cerebrospinal Fluid (CSF, Liquor)

Chloride (Cl), Serum

Background: Used in the diagnosis of alkalosis or acidosis and in the calculation of the anion gap. Increased in mineralocorticoid deficiencies, hyperchloremic metabolic acidosis, hyperinfusion of saline, diarrhea, renal tubular acidosis.

Decreased in overhydration, inappropriate ADH syndrome, vomiting, respiratory acidosis, Addison's disease, burn wounds, metabolic alkalosis, diabetic ketoacidosis, pyloric stenosis in early infancy, diuretic drug therapy.

Sampling: 1mL serum or plasma

Reference Interval:

	(mmol/L)
Adults	95-105
Children	
1day – 1 week	96-111
1 week – 1 month	96-110
1month – 6 months	96-110
6 months – 1 year	96-108
older than 1 year	96-109

Critical: < 80 mmol/L or > 115 mmol/L

Chloride (Cl), Urine

Related Information: Potassium, Urine
Sodium, Urine

Background: Used in the differentiation between Cl sensitive form and Cl resistant form of hypochloremic metabolic alkalosis:

The Cl sensitive (responding to chloride intake by restoring body stores) form is associated with vomiting, diuretic drugs medication and is caused by loss of H and Cl ions or it is caused by Cl loss in the feces by villous adenomas. Urinary Cl may be as low as <10mmol/L.

The Cl resistant forms are caused by primary and secondary hyperaldosteronism and Bartter Syndrome. Urine Cl varies according to Cl intake, urinary Cl is usually > 20mmol/L.

Sampling: Random urine 5 mL or to obtain more reliable results send in an aliquot of 5mL of a 24h collected urine, note total quantity.

Reference Interval:

Infants	2-10 mmol/24h
Children	10-40 mmol/24h
Adults	85-200 mmol/24h

Cholesterol, Total, Serum or Plasma

Related Information: Apolipoprotein A-I and B-100, Serum
C-Reactive Protein, Serum
Endomysial Antibodies
High Density Lipoprotein Cholesterol, Serum or Plasma
Homocysteine, Total, Plasma
Low Density Lipoprotein Cholesterol, Serum or Plasma
Triglycerides, Serum or Plasma

Background: Elevated serum cholesterol levels are considered a major risk factor for coronary heart disease (CHD). Screening is advisable in persons with diabetes mellitus, elevated blood pressure, family history of hyperlipidemia or early CHD, xanthomata or xanthelasmata.
In the diagnosis of anemic patients, levels below 150 mg/dL may indicate celiac disease.

Sampling: 1 mL serum

Patient preparation:
Stable diet for 3 weeks, stable body weight and fasting for 10h.
Cholesterol levels may be 10%-20% lower in recumbent position after 20 min.
Plasma cholesterol may be 10% lower than serum values.

Reference Interval:

Newborn	60 – 120 mg/dL
Children	90 – 190 mg/dL
Adults Desiderable	< 200 mg/dL
Borderline	200-239 mg/dL
High	>240 mg/dL

Chorionic Gonadotropin (hCG, β-hCG), Serum

Related Information: Alpha$_1$-Fetoprotein (AFP), Serum
Progesterone, Serum

Background: HCG is used to assess pregnancy, to support ultrasound diagnosis of ectopic pregnancy and to detect trisomy 21. It is also used as a marker for gestational trophoblastic neoplasias (molar gestations, placental trophoblastic carcinomas, choriocarcinomas), nonseminomatous germ cell tumors and for seminomas.
During pregnancy beta-hCG doubles every 1-3 days, in ectopic pregnancies more slowly. It is recommended to determine hCG and progesterone every other day to detect slower than normal rising levels in ectopic pregnancy.
Mothers carrying fetuses with in trisomy 21 have lower serum AFP levels, lower unconjugated estriol levels but an increased concentration in hCG at week 16.
Decreased levels of hCG are found in trisomy 18.
Limitations: Rarely false positive results are due to heterophilic antibodies.

Sampling: 1 mL serum. Serum is stable at room temperature for 1 day and 4 days at 4°C, otherwise freeze.

Screening:

First (day 74-97) and second (week 16-18) trimester screening (including AFP and unconjugated estriol) of maternal serum for Down syndrome (trisomy 21) and Edwards syndrome (trisomy 18).

Reference Interval:

Male	< 2,0 mIU/mL
Female	< 3,0 mIU/mL
Pregnancy	
Week of gestation	
1	5 – 50 mIU/mL
1 – 2	50 – 500 mIU/mL
2 – 3	100 – 5 000 mIU/mL
3 – 4	500 – 10 000 mIU/mL
4 – 5	1 000 – 50 000 mIU/mL
5 – 6	10 000 – 100 000 mIU/mL
6 – 10	15 000 – 200 000 mIU/mL
10 – 12	10 000 – 100 000 mIU/mL

HCG increases rapidly during the first 6 weeks of pregnancy, peaking between day 60-70. Concentrations less than 2000 mIU/mL and increase of hCG less than 65% within 48h may suggest abortion or ruptured ectopic pregnancy.

Chromogranin A, Serum

Related Information: Catecholamines, Fractionation, Plasma
Calcitonin, Serum or Plasma
5-Hydroxyindoleacetic Acid (5-HIAA), Quantitative, Urine

Background: Chromogranin A is a soluble 50 KD protein of neuroendocrine cells mainly stored in chromaffin granules. It is released from the adrenal medulla together with catecholamines. It is also present in other neuroendocrine tissues.

It may be elevated in pheochromocytoma and small cell lung carcinomas.

Sampling: 1 mL serum or EDTA plasma, separate immediately, freeze and ship frozen.

Reference Interval: < 100 ng/mL

CK-Isoenzyme (CK-MM, CK-BB, CK-MB) see Creatinine Kinase Isoenzymes, Serum

Clobazam, Serum

Background: Clobazam, a 1,5 benzodiazepine, is metabolized to N-desmethylclobazam. Clobazam is used as adjunctive therapy in the treatment of epilepsy, however with waning effectiveness after weeks of continuous therapy. It may be used in short term treatment of anxiety disorders.

Bioavailability 85%-90%, peak time 0.5-2.5h, half-life time 11-77h (average 18h, longer in elderly than young males (48h versus 17h), peak time 1-4h after dosing, peak plasma concentrations were 290-410 ng/mL decreased in cirrhosis and hepatitis after a dose of 20 mg.

Sampling: 2 mL serum

Reference Interval:

Therapeutic	100 – 400 ng/mL
Desmethylclobazam	1000 – 4000 ng/mL

Clonazepam, Serum

Related Information: Diazepam, Serum

Synonyms: Iktorivil®; Klonopin®; Rivatri®

Background: Clonazepam belongs to the class of benzodiazepines. It is a long acting drug used in prevention of absence seizures, in myoclonic seizures, tonic-clonic seizures and in reducing tardive dyskinesia. The drug is under investigation in infantile spasm, neuralgia, Parkinson's disease, and bipolar disorders. Pronounced sedative effects limit the use, by paradoxical hyperactivity in children and by development of tolerance.

Bioavailability 98%; urinary excretion 1%; plasma binding 86% lower in neonates; volume of distribution 3.1-3.3 L/kg ; half life time 18-28h, increased in the elderly; peak time 1.2-3.8h after a 2 mg oral dose; peak concentration 12-22 ng/mL after a single 2 mg dose orally.

Steady state reached after 5-10 days. Active metabolites have longer half-life times.

Sampling: 2 mL serum

Reference Interval:

Therapeutic:	30-60 ng/mL
Steady state for seizure control:	5-70 ng/mL
Toxic:	>80 ng/mL
Highly toxic:	>100 ng/mL

Clostridium difficile

Background: C. difficile antibiotic-associated diarrhea and pseudomembranous colitis is a major cause of hospital acquired diarrhea. Toxic strains usually produce toxin A, an enterotoxin and toxin B. Since not all C. difficile strains produce toxin and the amount of toxin must exceed a level to cause colitis, false positive culture results are common. Toxin testing is a more reliable parameter.

Limitations: In up to 20% of adults and in up to 50% of newborns non-toxin producing C. difficile may be isolated. In 40%-60% of hospitalized patients, toxin may be detected but without any symptoms.

Sampling: Fresh stool, patient must have diarrhea. Keep specimen cool and process soon. Repeated testing does not improve sensitivity.

Reference Interval:

Report on diagnostic finding:

Culture result: Growth of C. difficile

Toxin detection by EIA: Toxin A and B

Clostridium tetani

Related Information: Tetanus Antitoxin Antibody IgG

Background: Spores are widespread in nature and wound sites even very small (such as skin popping by drug abusers) are portals of entry. Hypoxic sites such as necrotic tissue favor infection. Neonatal tetanus (the C. tetani enters through a contaminated umbilicus) is a major problem in developing countries. After infection, the C. tetani produces an polypeptide toxin which is carried intra-axonal and blocks the activity of inhibitory mediators at ganglioside receptors.

Clinically, patients present with lockjaw, risus sardonicus, opisthotonus, and spastic paralysis (botulism: flaccid paralysis).

Laboratory diagnosis: C. tetani is rarely isolated from the wound site, there is no the serologic diagnosis in the early stage.

Treatment: Immunoglobulin for neutralization of the toxin, metronidazole and penicillin.

Sampling: Biopsy material, wound swap

Reference Interval:

Report on diagnostic finding

Culture result

Clostridium Tetani Immunity see Tetanus Antitoxin Antibody IgG

Cocaine, Urine

Synonyms: Coke; Crack; Dama Blanca; Gold Dust; Liquid Lady; Nose Candy; Rock; Snow; Toot; White Lady

Background: Cocaine is a highly potent natural central nervous system stimulant. The hydrochloride salt or the sulfate salt appears as a fine powder for inhalation, mixed with sodium bicarbonate it becomes the solid form for smoking called crack. Administration via smoking, intravenous injection or orally, also sublingual, rectal, vaginal.

Alcohol inhibits cocaine degradation. Cocaine is the cause of microvesicular steatosis and necrosis of the liver. Myocardial effects are cardiomyopathies, myonecrosis, dysrhythmias, angina

pectoris, ischemia, and infarction. Renal failure, rhabdomyolysis, disseminated intravascular coagulation may occur. Fetal growth and development are altered.
Metabolites are benzoylecgonine and ecgonine methyl ester. Benzoylecgonine is detectable in the urine as early as 2-3h for 1-3 days after intake. For long term exposure, hair analysis indicate cocaine use for month, assuming a hair growth rate of 13 mm per month
Half life : Cocaine 1h; benzoylecgonine 5-10h; ecgonine methyl ester 3-4h;
ethylcocaine 2h. Bioavailability for cocaine 30-70%, volume of distribution 3-5 L/kg
Sampling: 5 mL random urine. Keep refrigerated. To rule out dilution for forensic purposes, request urine creatinine.
Reference Interval: Immunological drug screen: negative : < 300 ng/mL

Cold Agglutinin Titer

Related Information: Cold Fibrinogen
Cryoglobulin, Qualitative, Serum or Plasma

Background: Mycoplasma activates several classes of immunoglobulins. Cold isohemaggglutins are usually of the IgM class, clumping erythrocytes at 4°C. M. pneumoniae has an I antigen similar to an I like antigen on human RBC s . During Mycoplasma pneumoniae infection, 50% of the patients develop titers against I antigen. Cold agglutinins rise at week one after onset, peaking after 2-3 weeks and decline after 4 weeks.
Limitations: False positive results are linked to rubella, adenovirus, infectious mononucleosis, connective tissue diseases.
Sampling: 10 mL whole blood, allow to clot warm (37°C), separate cells from serum in a prewarmed centrifuge, send in blood clots and serum
Reference Interval:
Negative: not detectable
Positive: Titers > or = 64 or 4 fold increase in titer

Cold Globulins see Cryoglobulin, Qualitative, Serum or Plasma

Copper (Cu), Serum or Urine

Related information: Ceruloplasmin (Cp), Serum or Plasma
Iron (Fe), Serum
Transferrin and Total Iron Binding Capacity, Serum
Zinc (Zn), Serum or Urine or Seminal Fluid

Background: Copper is an essential trace element, serving as a cofactor in metalloenzyme systems and is part of the hemoglobin synthesis pathway. Cu is necessary for bone formation, pigmentation, CNS development, growth, and connective tissue. In the serum it is bound to

ceruloplasmin as the major transport protein. Cu is absorbed in the stomach and duodenum regulated by metallothionein (MT). MT is induced by Cu and to a higher degree by zinc to a low degree by cadmium and iron), both binding to MT. Zinc inhibit Cu absorption by strongly inducing MT, leading to a high amount of MT in mucosal cells with trapped Cu. The cells are sloughed into the intestinal lumen and lost into the stool.
Absorption is inhibited by molybdenum by forming insoluble complexes with Cu, used in therapy of Wilson disease.
Cu is transported into the liver by albumin and histidine, and synthesized to ceruloplasmin. Peripheral tissue uptake of Cu depends on the ceruloplasmin form; 50%-80% of the Cu in the peripheral blood is bound to ceruloplasmin.
Ceruloplasmin usually parallels serum Cu, except in acute Cu intoxication, were ceruloplasmin may remain normal with elevated fee serum Cu and elevated levels of total serum Cu and in Wilson's disease with chronic low ceruloplasmin leading to more free serum Cu with normal or decreased total Cu.
Secretion occurs largely eliminated by excretion into the bile; a small fraction is secreted into the urine. Abnormal urine excretions occur in burns, Menkes syndrome or during therapy with chelating drugs.

Useful test

- in combination with serum ceruloplasmin for screening for Morbus Wilson with decreased or normal serum Cu but, due to decreased excretion of Cu into the bile, increased excretion into the urine. In addition, for Wilson's disease and ICC, the liver tissue Cu concentrations are diagnostic.
- to monitor adequate parental nutrition.
- in the diagnosis of primary biliary cirrhosis and primary sclerosing cholangitis.
- to monitor Cu deficiency in premature infants during serious illnesses leading to decreased Cu absorption.
- in Cu intoxication (increased serum Cu, increased urine Cu)
- in the diagnosis of Indian Childhood Cirrhosis (ICC) during penicillamine therapy. ICC is caused by inherited factors, such as defective basal production of MT, and toxic exposure of the child to milk boiled in brass vessels.
- in Menkes syndrome (decreased serum Cu, increased urine Cu). Menkes disease is a severe X-linked Cu deficiency syndrome presenting early at the age of 2-4 month and is due to a defective Cu transporting ATPase, leading to Cu accumulation in the intestinal mucosa and kidney and subsequently a lack of Cu in the peripheral tissue and in the liver.
- in the diagnosis of Occipital Horn Syndrome (OHS) (Ehlers-Danlos syndrome type IX), an inherited disorder. OHS which is characterized by low serum Cu and ceruloplasmin and low fibroblast lysyl oxidase activity as well as low intestinal Cu absorption.
- to rule out Cu deficiency in iron resistant anemia, characterized by reduced ceruloplasmin synthesis leading to a microcytic or normocytic anemia.

- to rule out Cu deficiency in scurvy like bone disease
- to rule out Cu deficiency in depigmentation

Limitations:
Cu binding Ceruloplasmin increases during acute inflammations such as rheumatoid arthritis, therefore increasing serum Cu. Estrogen increases ceruloplasmin, elevating Cu during pregnancy and during contraceptive drug intake.
Drugs increasing Cu: carbamazepine, phenobarbital, phenytoin, valproic acid.
Decreased serum Cu levels occur: Low serum protein, malnutrition, ACTH therapy, glucocorticoid therapy.

Sampling:
Serum:
2 mL serum. Container must be metal free (certified trace metal free blood collection tubes), draw sample through a plastic catheter preplaced in the vein. Use during drawing powder free gloves.

Urine:
Collect 24h urine in a pre-washed metal free plastic container. Acidify to ph 2 with hydrochloric acid. Avoid contamination with dust. Ship 10ml to the laboratory, note total quantity.

Reference Interval:

Serum:	70-140 µg/dL

Diurnal variation with a peak in the morning

Urine:	5-60 µg/24h

Coproporphyrin see Porphyrins, Urine, Stool, Quantitative

Cordarone® see Amiodarone, Serum

Cortisol, Serum or Plasma

Related Information: Adrenocorticotropic Hormone (ACTH), Plasma
Androstenedione, Serum
Cortisol, Free, Urine
17-alpha-Hydroxyprogesterone
Testosterone, Serum

Synonyms: Compound F; Hydrocortisone

Background: Cortisol is secreted in a circadian rhythm with a maximum in the morning (5-25ug/dL) and a minimum in the early evening (3-16ug/dL).

Cortisol is bound to cortisol binding globulin (CBG), with serum concentration of 35-40 ng/L and albumin. Estrogens can increase CBG up to 120 ng/L. Half life of serum cortisol is approx 90 min. After inactivation in the liver the metabolites are excreted in the urine, only 1% is excreted in the free, unchanged form.

High cortisol levels are caused by adrenocortical hypersecretion, adrenocortical hyperplasia, adenoma, carcinoma excess pituitary or ectopic (small cell carcinoma of the lung) ACTH production.

To verify a cortisol excess, at least one of the following tests should be done: Midnight serum cortisol, urine free cortisone determination, a dexamethasone suppression test (DST).

DST overnight: 1 mg oral dose of dexamethasone at 11 PM, sampling at 8 AM: cortisol <3ug/dl is evidence against Cushing syndrome.

DST low dose: Protocol includes collection of 24h urine samples at day 1 through 4. At day 2 in the morning, the patient is given a dose of 0.5 mg dexamethasone and subsequently every 6 h 0.5 mg for a total of 8 doses. Baseline cortisol levels are drawn at day 1 at 8 AM and 8 PM and at day 5 at 8AM. Normal suppression: Corticol (Urine and Serum) on day 4: 50% below baseline.

DST high dose: Same as low dose, but dose is 2mg dexamethasone. A 50% suppression in urine and serum levels < 10 µg/dL occurs in patients with pituitary ACTH secreting adenomas, but lacks in patients with adrenal tumors secreting cortisol or ectopic corticotropin releasing tumors.

Low cortisol levels may be due to pituitary failure, failure of the adrenal glands (adrenogenital syndrome, primary adrenocortical insufficiency, Addison disease. Expected values at 8 AM for serum cortisol are < 5 µg/dL, exclusion of diagnosis if values> 20 µg/dL in patients without stress factors.

Sampling: 1 mL serum or heparin plasma. Diagnosis can not be based on one single test!

Reference Interval:

Children:		8 AM	
		5 days:	0.6 - 20 µg/dL
		2 - 12 months:	2.4 - 23 µg/dL
		5 - 15 years:	2.5 - 23 µg/dL
		16 - 18 years:	2.4 - 29 µg/dL
Adults:	> 18 years	8 AM:	5.0 - 25 µg/dL
		4 PM:	3.0 - 16 µg/dL
		8 PM:	50% of 8 AM leveL
		Midnight:	< 1.8 µg/dL

Cortisol free, Urine

Related Information: Cortisol, Serum or Plasma
17-alpha-Hydroxyprogesterone, Whole Blood, Plasma or Serum

Background: Please see also Cortisol Serum or Plasma.

The advantage of urine cortisol is the independence from cortisol binding globulin and since collection covers 24h, independence of circadian rhythm.

In patients with Cushing, free urine cortisol usually is >120 µg/24h, but additional testing is needed.

Sampling: 10 ml aliquot of a 24h urine, collected in a container prefilled with 1 g acid, note total quantity. Creatinine variation between several 24h urine collection periods should not exceed 10%, otherwise collection may be incomplete and results due to ciardian variation may be false.

Reference Interval: 30-120 µg/24 h

Corynebacterium diphtheriae (Diphtheria)

Background: Corynebacteria species organisms are gram positive rods, arranged in palisades or V and L formation and appear beaded by polymerized polyphosphate. Humans are the only host for C. diphtheriae. C. diphtheriae resides in the upper respiratory tract and transmission occurs by air borne droplets. Skin can be infected if lesions are present, predominant in the tropics. Endotoxin production, mediated by a temperate beta bacteriophage, is necessary for infection.

Diphtheria is now a rare disease in industrialized countries due to vaccination, performed by three doses at the age of 2, 4, 6 month of age and a booster at 1 and 6 years. Immunity does not last life long.

Sampling:

Serology: 1 mL serum

Culture: Throat swab, nasopharyngeal swab, if pseudomembranes are present, swab should be taken from beneath the membrane.

Reference Interval:

Serology:

Diphtheria toxoid specific IgG antibodies, quantitative

Recommendations for vaccination

Immunity absent:		
	< 0.1 IU/mL	immunization immediately
	0.1 – 0.2 IU/mL	borderline, booster immediately
Immunity present:		
	0.2 – 1.0 IU/mL	booster recommended in 3 years
	> 1.0 – 1.5 IU/mL	booster recommended in 5 years
	> 1.5 – 2.0 IU/mL	booster recommended in 7 years
	> 2.0 IU/mL	booster recommended in 10 years

Culture:

Report on diagnostic finding

Corynebacterium sp. or Corynebacterium diphtheria isolated. Toxin producing strains can not be distinguished from non-toxin producers.

Coxiella burnetii (Q-Fever) Serology, Screening

Background: First recognized in Queensland in the 1930s, Coxiella burnetii is now known worldwide as an obligate intracellular organism. It has been included into the Rickettsiaceae, but it is more closely related to Legionella species and Francisella species. It is as Gram-negative, pleomorphic coccobacillus 0.2-1.0 um, displaying morphologic and phase changes. The bacterium is resistant to extreme environmental conditions for years and a low dose (one organism) of infection is needed, resulting in ready transmission of infection by aerosol inhalation. The most important animal reservoirs are cattle, sheep, goat besides a wide range of arthropods and mammals. The infected animals have high numbers of bacteria in blood and tissue, shedding viable organism in milk. Target cells for Coxiella spp. are monocytes and macrophages, particularly alveolar macrophages. Protected by a potent acid phosphatase it replicates intracellular.

Coxiella can be recovered from blood, urine, body fluids during acute infection.

Serology:

IgG phase II antigen peak at week 8 after onset of symptoms, whereas phase I develop very slow and remain on low titers. In chronic Q fever, IgG titers to phase I and phase II are high, and IgA phase I is usually associated with chronic infection. Thus elevated levels of IgG (>1:200) and IgM (1:25) to phase II but not phase I antigens indicate acute infection, while high titers of IgG (1:800) and IgA (1:50) to phase I antigen is more predictive to chronic infection.

Sampling: Highly infectious organism. Handle with extreme care. Serology: 1 mL serum.

Reference Interval:

Antibody titer including IgA, IgG and IgM phase I and II: <1:10

Coxsackie Virus, Serology

Related Information: Echo Viruses Serology

Background: Coxsackieviruses belong to the enteroviruses. Two groups are known. Group A (24 serotypes) causes herpangina, characterized by fever, sore throat, vesicles in the oropharynx and hand-foot-and-mouth disease which presents with a vesicular rash on hands and feet and ulcerations in the mouth. Group B coxsackieviruses (6 serotypes) causes pleurodynia (Bornholm disease, epidemic myalgia) with fever, chest pain, and signs of congestive failure and in severe cases dilated cardiomyopathy. In the mouse model Coxsackie B4 causes diabetes due to pancreatic damage.

Coxsackie A and B both are the cause of respiratory symptoms, rash, and aseptic meningitis.

The viruses are transmitted via the fecal oral route; respiratory aerosols play a minor role. Replication takes place in the oropharynx and in the intestinal tract. There is a summer and fall peak.

Sampling: 1 mL serum. Acute and convalescent sera should be drawn 2 weeks apart.

Reference Interval:

Differentiation of immunoglobulin class

IgA antibody	negative:	< 30 IU/mL
	borderline:	30 – 50 IU/mL
	positive:	>50 IU/mL
IgG antibody	negative:	< 80 IU/mL
	borderline:	80 – 100 IU/mL
	positive:	> 100 IU/mL

Creatine Kinase (CK, NAC-activated)

Related Information: Creatinine Kinase Isoenzymes, Serum
Lactate Dehydrogenase (LDH), Serum
Myoglobin, Blood,Serum or Plasma
Troponin T, Serum

Synonyms: CK; CPK; Creatinine Phosphokinase

Background: Please see: Creatinine Kinase Isoenzymes, Serum

Useful in diagnosis of acute myocardial infarct.

CK is a marker in patients with skeletal muscular disease or damage particularly in Duchenne's muscular dystrophy, levels reaching up to 5000 - 40000 U/L; CK is increased in females carrying the disease.

Increased levels occur in muscular stress, polymyositis, dermatomyositis, myocarditis, myositis after grand mal seizure, rhabdomyolysis and in advanced stages of cancer as well as obstructive lung disease. Multiple cardioversion shocks may give false positive CK and CK-MB results.

Limitations: Reference values in persons of African ancestry are up to 30% higher than those of European ancestry.

There is a day to day variation of CK in healthy adults of 20% to 30%.

Exercise has a major influence on CK values: Persons exercising aerobically have lower levels than those who do not exercise but complete inactivity (hospitalized patients) lowers CK. Short intensive exercise can increase values 10 -100 fold.

Sampling: 1 mL serum, avoid hemolysis.

Reference Interval:

Cord blood		175-402 U/L
Neonates		468-1200 U/L
< 5 days		195-700 U/L
5 days – 6 month		41-330 U/L
6 month -18 years		24-229 U/L
Adults:	male	55-170 U/L
	female	30-135 U/L

Creatine Phosphokinase MB-Isoenzyme see Creatinine Kinase Isoenzymes, Serum

Creatinine Clearance

Related Information: Creatinine, Serum or Plasma
Creatinine, Urine
Cystatin C, Urine
Protein, Quantitative, Urine
Uric Acid, Serum

Background: Useful in the evaluation of renal function. Due to exponential rise in serum creatinine with the decline in GFR, slight changes in serum creatinine represent a far greater decrease in GFR.

Sampling: 1 mL aliquot of a 24h urine collection, note total quantity and 1 mL serum. Exact timed collection period is essential. Also provide patients sex, age, height and weight. Patient must be well hydrated during the collection. Urine flow above 2 mL/minute is required. Keep collected urine refrigerated.

Reference Interval:

Newborn:	40 – 60 mL/min
up to 6 months:	60 – 75 mL/min
6 – 12 months:	75 – 100 mL/min
> 1 year:	100 – 140 mL/min
Male:	98 – 156 mL/min
Female:	95 – 160 mL/min

Critical value for moderate renal impairment: 40 mL/minute; severe renal impairment: less than 30 mL/minute

Alternatively, corrected for body surface area

(Body surface area in cm^2 = weight in kg $^{0.425}$ x height in cm $^{0.725}$ x 71.84)

Corrected creatinine clearance in ml/minute = ((urine volume per minute x urine creatinine) / serum creatinine) / (1.73/surface area body in m^2)

Children	70-140 mL/minute/1.73 m^2
Adults male	85-140 mL/minute/1.73 m^2
Adults female	75-115 mL/minute/1.73 m^2

For each decade after 40 years, decrease is 6-7 mL/minute/1.73m^2

For more precise calculation of GFR in adults:

GFR = 170 serum creatinine in mg/dL $^{-0.999}$ x age $^{-0.178}$ x (0.762 if female or 1.180 if black) x serum urea nitrogen in mg/dL $^{-0.170}$ x serum albumin in g/dL $^{+0.318}$

Creatinine Kinase Isoenzymes, Serum

Related Information: Creatine Kinase (CK, NAC-activated)
Myoglobulin, Blood, Serum or Plasma
Troponin T, Serum

Synonyms: CK-Isoenzymes (CK-MM, CK-BB, CK-MB), CK Isoforms ;
CK-MB and Total CK; CPK Isoenzymes ;
Creatinine-Phosphokinase-MB and Total Creatinine Phosphokinase;
Creatinine-Phosphokinase-MB Isoenzyme.

Background: Energy for muscle contractions are supplied by ATP and restored by CK through converting creatinine phosphate to creatinine and ATP. CK requires Mg. It is a dimer with a M (muscle) subunit and a B subunit (brain) of 40 kDa each. Three resulting forms may be released into the serum: CK_1 (BB); CK_2 (MB) and CK_3 (MM). There is a different mitochondrial form of CK (64kDa). Rarely CK_1 or CK_2 form oligomers with a molecular weigh of up to 250 kDa, (Macro CK). CK is found in small amounts in nearly all tissues, but high concentrations are only reached in the brain, which do not cross the blood brain barrier and in the muscle.

Tissue distribution in relative percentage:

	CK_1 (BB)	CK_2 (MB)	CK_3 (MM)
Skeletal muscle	0	0-7	93-100
Cardiac muscle, normal	0	2-3	97-98
Cardiac muscle, injured	0	10-15	85-90
Lung	20-50	0-5	30-60
Brain	97-98	2-3	0
Smooth muscle of the intestinum	90-95	0	5-10
Prostate	95-100	0-2	0-5
Placenta	100	0	0

Day to day variation of CK: 20%-30%; The half life of CK-MM is 20-24h; of CK-MB is 10-12h and of CK-BB is 1-2h.

Useful in the diagnosis of acute myocardial infarct (AMI). CK-MB usually starts to raise 6 h after onset of chest pain, peeks at 15-20h and returns to baseline by 72 h. Troponins stay elevated up to 2 weeks, CK-MB therefore serves as a good marker for reinfarction.
Limitations: The abrupt rise and fall of CK-MB is characteristic for AMI, for other damaging agents such as chronic myopathies or renal failure values change with a slower rate.
CK-MB elevation may occur in hypothyroidism.
CK-BB may be elevated in intestinal ischemia, malignancies, prostate cancer, small cell carcinoma of the lung and intestinal malignancies
In neonates CK-MB may be increased to 5%-10% of total CK, due to an increased skeletal

muscle proportion during fetal life.

Macro CK may increase total CK levels mainly in older women, in patients with HIV infection, in autoimmune diseases, in association with autoantibodies to CK-BB.

Sampling: 2 mL serum, avoid hemolysis.

Reference Interval:

CK-MM	< 174 U/L (= CK, total)	(95 – 100% of total CK)
CK-MB	< 12 U/L	(0 – 6% of total CK)
CK-BB >18 years	< 2 U/L	(< 1% of total CK, neonates < 12%)
Makro-CK	not detectable	
CK mitochondrial	< 2 U/L	

Creatinine, Serum or Plasma

Related Information: Creatinine, Urine
Creatinine Clearance
Cystatin C, Urine
Digoxin, Serum
Lactic Acid, Whole Blood, Plasma or CSF
Osmolality, Serum
Osmolality, Urine
Parathyroid Hormone, Intact, Serum
Uric Acid, Serum

Background: Creatine is the storage compound for high energy phosphate. Synthesized in the liver from arginine, glycine, methionine and to 98% distributed into the muscle to be converted in phosphocreatine and spontaneously into the cyclic amide creatinine. Creatinine is not metabolized further and is excreted.

Creatine is filtered by the glomeruli but completely reabsorbed, whereas creatinine is filtered and not reabsorbed under normal conditions.

Creatine and creatinine are proportional to the muscle mass with a daily turnover rate of creatine approx. 1.6% to 1.7%.

Serum creatinine is an approximation to the glomerular filtration rate to be used as a renal function test, particularly to monitor nephrotoxicity of drugs.

Causes of Increased creatinine: Renal diseases and insufficiency, urinary tract obstructions. Shock, dehydration, heart failure increases creatinine by reduction of renal filtration. Serum creatinine >2mg/dL in necrotizing pancreatitis indicate poor prognosis. Hypertension, diabetes mellitus may increase creatinine levels.

Low creatinine is associated with small stature, decreased muscle mass, liver disease, corticosterol therapy, muscle diseases, dermatomyositis.

Limitations: Creatinine is a late indicator for renal dysfunction, abnormal serum creatinine occurs

after destruction of more than half of the nephrons.

Sampling: 1 mL serum or plasma (heparin or EDTA or citrate)

Reference Interval:

Children	1-5 years	0.3-0.5 mg/dL
	5-10 years	0.5-0.8 mg/dL
Adults	Men	0.6-1.2 mg/dL
	Women	0.5-1.0 mg/dL (during pregnancy slightly lower)

In children with normal muscle mass GFR can be calculated:

GFR in ml/minute/1.73 m^2 = (a x body length in cm) / serum creatinine in mg/dL

Mean values for a

Low birth weight infants under 1 year	0.33 mg/dL
At term born under 1 year of age	0.45 mg/dL
Children 2-12 years	0.55 mg/dL
Male13-21 years	0.7 mg/dL
Female 13-21 years	0.55 mg/dL

Critical value

Chronic renal insufficiency:	1.5 – 3.0 mg/dL
Chronic renal failure:	> 3.0 mg/dL

Creatinine, Urine

Related Information:
Creatinine Clearance
Creatinine, Serum or Plasma
Osmolality, Serum
Osmolality, Urine
Sodium, Serum or Plasma
Sodium, Urine
Uric Acid, Urine
Vanillylmandelic Acid, Urine

Background: Creatinine, Serum or Plasma

In combination with serum creatinine a useful marker for renal function.

To differentiate between prerenal and renal causes in acute renal failure the following urinary parameters are useful:

Parameter	pre-renal	renal-tubular
Sodium concentration (mEq/L)	< 20	>40
Fraction Na%	<1	>1
Urine to plasma creatinine	>40	<20
Urine osmolality (mOsm/kgH2O)	>500	<350

Fraction Na% = [(Urine Na/serum Na) + (urine creatinine/serum creatinine)] x 100

Sampling: 5 mL aliquot of a 24h collected urine, keep cool, no preservatives added, note total quantity.

Reference Interval:

Children	2-3 years	6 - 22 mg/24h
	>3 years	12 - 30 mg/24h
Adults	Male	1.0 - 2.0 g/24h
	Female	0.8 - 1.8 g/24h

Alternatively, given per kg body weight:

Infants	8-20 mg/kg/day
Children	8-22 mg/kg/day
Adolescents	8-30 mg/kg/day
Adults male under the age of 40	14-26 mg/kg/day
Adults female under the age of 40	11-20 mg/kg/day

For each decade after 40 years, urine creatinine decreases up to 10 mg/kg/day

Cryoglobulin Qualitative, Serum or Plasma

Background: Cryoglobulins are immunoglobulins aggregating below 37°C in vivo and in vitro. They are associated with lymphoproliferative, infectious and autoimmune diseases, particularly such as Sjoegren syndrome, hepatitis C, macroglobulinemia Waldenstroem.

Clinically patients present with purpura, vasculitis, polyarthralgia, peripheral neuropathy, renal impairment, Raynaud syndrome.

Classification

Type 1: Cryoglobulins are composed of IgA or light chains complexed with monoclonal IgM or IgG immunoglobulins and are associated with lymphoproliferative or plasma proliferative diseases. Patients are asymptomatic or present with Raynaud syndrome, purpura or acrocyanosis. Typically precipitation occurs within 24h, concentrations are high (>500 mg/dL)

Type 2: Monoclonal IgM complexes with polyclonal IgG as an antigen (mixed cryoglobulinemia). As the most common form, it is often associated with hepatitis C, also with lymphoproliferative diseases and connective tissue diseases.
Clinically it presents also as arthralgias, glomerulonephritis, vasculitis, neuropathy and purpura.
Typically precipitation occurs within 1-7 days at 4°C

Type 3: Polyclonal IgM complexes with polyclonal IgG (mixed cryoglobulinemia). Associated with hepatitis C, chronic infections (such as CMV, bacterial endocarditis, leprosy, fungal and parasitic infections), autoimmune diseases (SLE, rheumatoid arthritis) and inflammatory bowl diseases.
Clinically often asymptomatic.

Precipitation may take 7 days at 4°C, concentrations are low (<1 mg/dL)

Sampling: Patient preferably in a fasting state. 10 mL whole blood drawn into a pre-warmed container, allow to clot at 37°C, centrifuge at 37°C, ship serum and clots to laboratory. Do not refrigerate or freeze. Results cannot be interpreted if the specimen is improperly handled. Please give brief clinical history.

Reference Interval: Not detectable

Cyanocobalamin see Vitamin B 12, Plasma or Serum

Cyclic Citrullinic Peptide (CCP) see Anticyclic Citrullinated Peptide Antibody

Cyclosporine A Monoclonal

Synonyms: Ciclosporin, Neoral®, Sandimmun®

Background: Cyclosporine is an immunosuppressive agent used in organ transplant in the treatment of graft versus host disease in hematopoietic stem cell transplantation. Also used in autoimmune disorders as a low dosage regime (less than 7 mg/kg/day).

The drug is a fat soluble cyclic polypeptide of 11 amino acids produced by the fungus species Beauveria nivea and acting in the antigen induced differentiation of T cells. Cyclosporine binds to cyclophilin, an intracellular protein of the class immunophilins, forming a complex that inhibits a phosphatase (calcineurin) which is part of the activation pathway for a T cell specific transcription factor NF-AT involved in the production of IL-2, IL-3, and IFN-gamma.

Oral bioavailability 10%-46%; urinary excretion <1%, plasma binding 90%-95%, volume of distribution 0.1 -15 L/kg decreased in aged and increased in children, half life time 4h-53h decreased in children, peak time after oral administration 1.5h-6h depending on the formulation, peak concentration 900–1800 ng/mL for soft gelatin capsules or 500-1600 ng/mL for Sandimmune®.

Cyclosporine is metabolized by the P-450 system and excreted by the bile.

Toxicities including nephrotoxicity, hypertension, hyperglycemia, liver function impairment, hirsutism, cholelithiasis. Possibly increases the risk for lymphomas.

Sampling: 3 mL EDTA plasma

Therapeutic Values 150 – 400 ng/mL

CYFRA 21 – 1, Serum

Related Information: Carcinoembryonic Antigen (CEA), Serum

Synonyms: Cytokeratin -19-fragment

Background: Cytokeratins is a class of approx 20 polypeptides which account with actin and microtubuli for the cytoskeletal structure of the cell.

CYFRA 21-1 is a fragment of cytokeratin 19 which is soluble in the serum and expressed in normal epithelia cells and malignant epithelial derived cells, predominant in lung tissue.
Useful in diagnosis of squamous cell carcinoma of the lung and as a prognostic marker, indicating poor prognosis
Used also in the diagnosis of carcinoma of the bladder.
Limitations: Since CYFRA 21-1 is present in various tissues in the body, it may be elevated in benign diseases. This feature influences the usefulness of the CYFRA 21-1 for lung carcinoma monitoring. Elevated levels are associated with pneumonias, sarcoidosis, bronchitis, asthma, tbc, emphysema.

Sampling: 1 mL serum.

Reference Interval:

Normal individuals: 80% display CYFRA 21-1 < 1.5 µg/L

Upper limit for a 95% specify for malignant diseases by organ:

Healthy individuals	1.7 µg/L
Disease of the lung	3.3 µg/L
Disease of the gastrointestinal tract	6.9 µg/L
Diseases of the ovary and uterus	3.1 µg/L
Disease of the bladder	2.4 µg/L
Renal insufficiency	5.2 µg/L

Cystatin C, Urine

Related Information: Creatinine Clearance
Creatinine, Serum or Plasma
Creatinine, Urine

Background: Cystatin C is a 13 kDa proteinase inhibitor prevalent in all nucleated cells. It is filtered in the glomerulus and reabsorbed by the proximal tube. No extrarenal route of excretion. Children over 1 year of age display the same serum level as adults. There is no diurnal variation, but day to day levels variation averages 13%, which is higher than creatinine variation. In renal transplant patients, cystatin c correlates better with GFR than serum creatinine.

Sampling: 10 mL aliquot of a 24h urine, no preservatives required. Note total volume. Stable at 20°C for 1 week.

Reference Interval: 0.5 – 1.0 mg/L

Cystic Fibrosis (CF) Gene Mutation

Synonyms: CFTR Gene Mutation

Background: CF is an autosomal recessive disease linked to mutations in the cystic fibroid transmembrane conductance regulator gene on chromosome 7q31.2, encoding a 1480 amino acid protein (CFTR), regulating chloride channels in epithelia cells in the lung, the pancreas, and

sweat glands. The deltaF508 mutation accounts for 70% of all CF mutant alleles in Caucasians, 10 mutations contribute to 85% of the more than 1000 known alleles. Using a panel of 31 mutations approx. 90% of mutations are detected and in 1%-2% no so far known mutation is detectable in clinical diagnosed CF patients. Carrier rate in Caucasians is 4%, prevalence 1 in 3000 live birth.

Useful in the diagnosis of CF, to evaluate chronic respiratory diseases, to assess carrier state, to evaluate infertility in men with congenital bilateral absence of the vas deferens (in 70% of the patients CFTR gene mutations, causing 5% of male infertility, but some of the patients without CF), to evaluate chronic idiopathic pancreatitis (up to 35% have a CFTR mutation without CF), to investigate infants with foul smelling stools or hepatosplenomegaly, to evaluate newborns with meconium ileus.

Limitations: Although the 31 one mutations included in the test panel, not detecting a mutation does not rule out CF.

The detection of 2 mutations confirms CF. 20%-30% of CF patients have one mutation, 70%-80% have two. 1%-2% have no mutation detectable. In carrier status, 90% have one detectable mutation.

Sampling: 2 mL EDTA blood. Amniotic fluid to be taken between the 12th and 14th week of gestation, chorionic villus specimens between week 8 and 12. Do not freeze, transport to laboratory soon.

Reference Interval: Report on diagnostic finding
Mutations on CFTR-gene out of 31 mutations tested for

Cystine, Urine

Related Information: Amino Acid Screening, Plasma or Urine

Background: Cystinuria is an autosomal recessive disease. Patients present frequently cystine urinary stones and urinary tract infections.

Not a diagnostic test for cystinosis.

Limitations: Chelating agents such as penicillamine cause false negative results

Sampling: An aliquot of 10 mL of a 24 h urine, collected in a clean container prefilled with 1 mL of glacial acetic acid. Note total quantity.

Reference Interval:

Normal	40 - 60 mg cystine / g creatinine
Heterozygotes	< 300 mg cystine / g creatinine
Homozygotes	> 250 mg cystine / g creatinine

Cytomegalovirus (HCMV, CMV), Antigen

Related Information: Cytomegalovirus (HCMV, CMV), DNA Detection
Cytomegalovirus (HCMV, CMV), Serology

Synonyms: CMP pp65 Detection

Background: The presence of the CMV specific protein (pp65) in infected peripheral blood leucocytes can be used to quantify the amount of CMV particularly in immunocompromised patients. As compared to viral CMV culture as the gold standard for active replicating virus, the assay has a sensitivity of 70-90% and a specificity of 95%-99%. Patients with antigenemia may be asymptomatic.

Sampling: 1 mL EDTA blood. Specimen must be processed within 6 hours.

Reference Interval: Report on diagnostic finding
Negative: pp65-AG not detectable

Cytomegalovirus (HCMV, CMV), DNA Detection

Related Information: Cytomegalovirus (HCMV, CMV), Serology
Cytomegalovirus (HCMV, CMV), Antigen

Background: 80% of the adult population has been infected with CMV in the past, usually asymptomatic, as indicated by antibodies.

In immunosuppressed in individuals early CMV detection has become a marker for intervention. CMV DNA detection is also useful in the diagnosis of congenital CMV infection, which may lead, if infection occurs during early pregnancy, to multiorgan failure CNS disorders. A high CMV load in amniotic fluid correlates with symptomatic infection. Infected newborns shed CMV with the urine.

Although DNA detection is highly sensitive false negative results occur. False positive results may be due to contamination.

Sampling: 1 mL CSF, EDTA blood, bronchoalveolar lavage, 10 mL urine, cervical swab

Reference Interval: Negative: CMV DNA not detectable

Cytomegalovirus (HCMV, CMV), Serology

Related Information: Cytomegalovirus (HCMV, CMV), Antigen
Cytomegalovirus (HCMV, CMV), DNA Detection

Background: Primary CMV infection can establish as an infectious mononucleosis like disease, interstitial pneumonia, hepatitis, meningoencephalitis intrauterine infection with congenital infection. After the primary phase CMV in the latent phase may be reactivated particularly in immunocompromised patients presenting as retinitis, colitis, and pneumonitis.

However the majority of CMV infections remain asymptomatic. The IgG type antibody will persist for lifetime. IgM antibodies are synthesized in low levels during reactivation and in higher levels during primary infection.

Intrauterine infection can occur even if a maternal immunity exists due to reinfection with a different CMV strain. However, maternal antibodies protect to a higher degree the fetus from infection.

Sampling: 1 mL serum

Differentiation of immunoglobulin class

IgG antibody negative:	<0.4 IU/mL
borderline:	0.4 – 0.6 IU/mL
positive:	> 0.6 IU/mL
IgM antibody negative:	< 15 AU/mL
borderline:	15 – 30 AU/mL
positive:	> 30 AU/mL

D-Dimers

Synonyms: Fibrin Breakdown Product-D-Dimer

Background: Plasmin degrades fibrin clots to D-dimers and other fibrin degradation products (FDP). D-dimers are formed by plasmin degradation of fibrin, it is not formed from intact fibrinogen, indicating preceding fibrin forming. D-dimers and FDP are positive in disseminated intravascular coagulation (DIC), thrombosis, liver diseases (decreased hepatic clearance). Increased values occur during pregnancy, post operatively, during bleeding, hemodialysis, eclampsia, sickle cell crisis, and in cancer patients.

Clinically useful in the diagnosis of DIC, of deep venous thrombosis and pulmonary embolism. Used in monitoring thrombolytic therapy, which increases D-dimers.

Sampling: 3 mL of citrate plasma. Stable at room temperature for 8h, on ice 1 day.

Reference Interval: <0.5 µg/mL

Dehydroepiandrosterone Sulphate (DHEA-S), Serum

Related Information: Adenocorticotropic Hormone (ACTH), Plasma
Androstenedione, Serum
Cortisol, Free, Urine
Cortisol, Serum or Plasma
Estradiol, Serum
17-alpha-Hydroxyprogesterone (17-OHP)
Testosterone, Serum

Background: DHEA-S and dehydroepiandrosterone are synthesized by the adrenal cortex controlled by adrenocorticotropin (ACTH).In men, in addition to the adrenal cortex, approx. 5% of DHEA-S and 10%-25% of DHEA are produced by the testes. DHAE and DHAE-S are week androgens but are converted by peripheral tissue into androstenedione and testosterone and into estrogens. Half life time of DAEH-S is 10-20h of DHEA is 1-3h, resulting in an up to 500 times higher serum concentration of DAEH-S. DHEA in opposite to DHEA-S, has a diurnal variation similar to cortisol.

In men DHEA–S levels are linked to greater fitness, higher testosterone levels. DHEA was added in 1996 to the list of prohibited substances by the International Olympic Commission.

Used in the assessment of

-adrenal hyperfunction: DHEA is elevated in congenital adrenal hyperplasias (11 beta hydroxylase and 21 beta hydroxylase forms) as well as in adrenal neoplasms.

-adrenal insufficiency: resulting in low basal DHEA-S levels.

Sampling: 1 mL serum

Reference Interval: (µg/dL)

Age	Male	Female
Children		
1-5 days	12-254	10-248
1 month to 5 years	1-41	5-55
6-9 years	2-145	2-140
10-11 years	15-115	15-260
12-17 years	20-555	20-535
Adults		
18-30 years	125-619	45-380
31-50 years	59-452	12-379
51-60 years	20-413	post menopausal 30-260
61-83 years	12-285	

Dengue Fever, Serology

Background: The Dengue virus is an arthropod borne virus (Arbovirus). Transmitted by the Aedes aegypti mosquito (also a vector for yellow fever) dengue virus infects 20 million people/year worldwide in tropical areas, especially in the Caribbean. Humans and monkeys are reservoirs.
Two clinical courses are known: Classic dengue (breakbone fever) with a sudden influenzalike onset and serve muscle and joint pain. Leukopenia and maculopapular rush is common. Spontaneously resolving after 1-2 weeks, rarely fatal.
Dengue hemorrhagic fever initially resembles classic dengue fever but shock and hemorrhage in the gastrointestinal tract and skin develop. Fatality rate 10%. The severe form occurs particularly in southern Asia. There is no antiviral drug or vaccine available.
Sampling: 2 mL serum, each at the beginning and convalescent sample
Reference Interval: Antibody titer IgM, IgG negative: < 1:10

11-Deoxycorticosteron (DOC), Plasma

Related Information: Cortisol, Serum or Plasma
11-Deoxycortisol, Plasma
21-Deoxycortisol, Plasma

Background: DOC and 11-hydroxycortisol are precursors of aldosterone. Both have also mineralocorticoid activity, and may be the cause of hypertension.
The most prevalent (95%) congenital enzyme defect of the adrenal cortex is due to 21 hydroxylase deficiency, less prevalent are 11-hydroxylase, 17-hydroxylase, 3-beta hydroxysteroid dehydrogenase; 20-22-desmolase and the 18-hydrolase and 18-hydroxysteroid dehydrogenase defects.

DOC is increased in serum (besides other metabolites of corticosterone) in 18-hydroxylase defects and present clinically as adrenocortical insufficiency (salt loss) without virilization, without hypertension and normal sexual development.

Sampling: 2 mL heparinized plasma

Reference Interval:

Premature:	<105 ng/dL
Newborn: (first week)	<105 ng/dL
Children:	
1 month to 1 year	7 – 49 ng/dL
2 to 10 years	2 – 34 ng/dL
Adult:	2 – 15 ng/dL
after ACTH stimulation:	< 90 ng/dL

Diazepam, Serum

Related Information: Ethanol, Blood, Serum or Urine

Synonyms: Aliseum®; Alupram®; Atensine®; Diastat®; Diazemuls®; Di-Tran®; Lamra®; Solis®; Stesolid®; Tensium®; T-Quil®; Valium®; Valrelease®; Vatran®; Vazepam®; Zetran®.

Background: As a tranquilizer, diazepam is indicated in anxiety, panic attacks, muscle spasm, control of seizures in acute situations, and treatment of ethanol withdraw syndrome. It is metabolized to the active compound nordiazepam (N-desmethyldiazepam) with a half life of 2-4 days. Bioavailability 100%; urinary excretion 1%; plasma binding 98% lower in renal disease, cirrhosis, nephritic syndrome, pregnancy, neonates, burn patients elderly; volume of distribution 1 L/kg increased in cirrhosis, hypoalbuminemia, elderly; half life 30-56h increased in elderly, cirrhosis; bioactive CNS half life 1h; peak time 1-2h; peak concentration I.V.: 400-500 ng/mL after 5-10 mg IV dose, oral: 300-350 ng/mL after 10 mg oral dose.

Sampling: 2 mL serum, do not freeze. Peak 1h after oral dose, 15 min after IV.

Reference Interval:

Diazepam	Therapeutic values	200 - 500 ng/mL	
		300 - 400 ng/mL	provides anxiolytic effect
		> 600 ng/mL	provides control of seizures
	Toxic values	> 1000 ng/mL	
N-desmethyldiazepam	Therapeutic values	600-1500 ng/mL	

Digitoxin, Serum

Related Information: Digoxin, Serum

Background: Digitoxin differs from digoxin by the absence of a hydroxyl group at C12 resulting in a less hydrophilic compound. The compound is not available in the US.

Bioavailability 90%; urinary excretion 32%; plasma binding 90%-97%; volume of distribution 0.7L/kg; half life time 150-250h.

Limitations: Patients on digoxin cannot be monitored for digitoxin!

Sampling: 2 mL serum taken 6-12h after dosing

Reference Interval:

Therapeutic values:	15.0 – 30.0 ng/mL
Toxic values:	Levels of > 35 ng/mL are in 80% of the patients associated with clinical toxicity

Digoxin, Serum

Related Information: Amiodarone, Serum
Digitoxin, Serum
Flecainide, Serum or Plasma
Magnesium (Mg), Serum
Magnesium (Mg), Urine
Potassium, Serum or Plasma
Verapamil, Serum or Plasma

Synonyms: Allocar®; Cardioreg®; Digacin; Lanocor®; Lanoxicaps®; Lanoxin®; Lenoxin®; Purgoxin®

Background: Digoxin is used in atrial fibrillation and in the treatment of heart failure.

Bioavailability 60%-80%; urinary excretion 50%-70%; plasma binding 20%-25% decreased in renal disease; volume of distribution 7 L/kg; plasma half life 26%-52% decreased in hyperthyreoid patients and increased in renal disease, congestive heart failure, elderly, hypothyroid patients, peak time 1-3h.

Steady state reached after 5 days. Levels are increased by quinidine, verapamil, amiodarone, cyclosporine, spironolactone, propafenone through decreased clearance.

Limitations: Low frequent cross reaction with digitoxin, results therefore are not valid in patients on digitoxin. Other digitalis derivates cross react too.

Sampling: 2 mL serum, at least 6 h after dose, best immediately before next dose.

Reference Interval:

Therapeutic	0.7-2 ng/mL, (revised to 0.5-0.8 ng/mL)
Toxic	starting to be possibly harmful >1.2 ng/mL, particularly in hypokalemia or hypomagnesemia patients.
Highly toxic	>2.4 ng/mL. Concentrations of 1.7, 2.5 and 3.3 ng/mL are found to be associated with 10%, 50% and 90% probability of digoxin induced arrhythmias, respectively.

Dihydrotestosterone, Serum

Related Information: Testosterone, Serum

Synonyms: DHT

Background: 5-alpha reductase, located in the skin, prostate, internal genitalia, metabolize testosterone to DHT. Since testosterone, which has less androgenic potency than DHT, can be converted to estradiol or to DHT, deficiency in 5-alpha reductase in a rare autosomal recessive disorder in 46XY phenotypic males, patients may develop hypospadia, urogenital sinus opening to the perineum, a blind vaginal pouch and normal testes. Testosterone levels are normal at puberty but DHT is low.

DHT is the parameter which correlates well with male sexual function.

Sampling: 2 mL serum

Reference interval:

Males	< 20 years	150 – 1240 pg/mL
	20- 39 years	155-553 pg/mL
	> 40 years	150-980 pg/mL
Females	20-39 years	50-250 pg/mL
	> 40 years	50-137 pg/mL

Diphtheria see Corynebacterium diphtheriae

Dopamine, Plasma see Catecholamines, Plasma

Dopamine, Plasma see Catecholamines, Urine

Drug of Abuse Screen, Urine

Related Information: Amphetamine, Urine
Cannabinoids (Marijuana Metabolites) Immunological Drug Screen, Urine
Cocaine, Urine
Diazepam, Serum
Ethanol, Blood, Serum or Urine
Flunitrazepam, Urine
Methadone, Urine
Opiates, Quantitative, Urine

Test includes: Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates (codeine, heroin, morphine), pH of the urine

Sampling: 10 mL random urine, keep refrigerated. If forensic, take precautions to make sure the sample is not substituted, diluted or chemicals added for drug destroy or test disturbance. Ph of the urine is included in the test, further precautions are specific gravity, creatinine to rule out adulteration.

D-Xylose Absorption Test, Serum see Xylose Absorption Test, Serum

Echinococcosis, Serology

Background: Larval stages of the cestodes (tapeworms) E. granulosus, E. multilocularis and E. vogeli causes diseases in humans.

E. granulosus is one of the smallest tapeworms composed of a scolex and 3 proglottides. Definitive hosts are dogs or other canids, the intermediate host are sheep, caribou, deer, moose, pigs or men. The life cycle involves the canid's intestine where eggs are liberated and may be ingested by the intermediate host. The oncosphere embryos emerge in the small intestine and migrate primarily to the liver but also to the brain, the lung or into bones where they develop in a unilocular fluid filled hydatid cyst. The inner layer produces protoscoleces which may infect dogs by contaminated food.

E. multilocularis: Main definitive hosts are foxes; the intermediate hosts are various rodents. Human infection is due to accidental ingestion of food contaminated with fox feces, affecting primarily hunters and trappers. Endemic areas are in northern Europe, Siberia, Western Canada, and Alaska. In the human liver, the larvae form multiloculated cysts with few protoscoleces. Since an outer fibrous capsule is not build up, cysts can proliferate and honeycomb like tissue may form (alveolar form).

Polycystic hydatid disease of E. vogeli very rarely occurs in humans.

Limitations: Serologic sensitivity for the alveolar form is higher, also higher for the liver than for pulmonary infection. Non specific cross reactivity with other helminths is up to 50%. False positive results are rarely seen in patients with cirrhosis and lupus. False negative sometimes in cases of large cysts or dead cysts.

Sampling: 1 mL serum

Reference Interval: Report of diagnostic finding of the immunoblot antibody assays for E. granulosus and E. multilocularis

Echo Virus, Serology

Background: Echo is an acronym for enteric cytopathic human orphan. Echoviruses have a similar structure as other enteroviruses which are members of the single stranded RNA picornavirus family. The transmission modus of the more than 40 serotypes is the fecal oral route. The viruses in the group are the cause of aseptic meningitis, upper respiratory tract infection, febrile

illnesses, with or without rash, diarrhea, hemorrhagic conjunctivitis. There is no vaccine available and immunity after infection dos not last life long.

Sampling: 1 mL serum obtained at onset of the disease and after 2-3 weeks.

Reference Interval: Differentiation of immunoglobulin class

IgA antibody negative	< 30 IU/mL
Borderline	30-50 IU/mL
Positive	> 50 IU/mL
IgG antibody negative	< 80 IU/mL
Borderline	80-100 IU/mL
Positive	> 100 IU/mL

Electrolytes, Liquor see Cerebrospinal Fluid (CSF, Liquor)

ENA see Ribonucleoprotein U1-snRNP Antibody Smith (SM) Antibody SS-A/Ro and SS-B/La Antibodies

Endomysial Antibodies

Related Information: Gliadin IgG/IgA Antibodies

Background: Endomysium is an intracellular antigen, mainly a collagen associated enzyme, the tissue transglutinase, occurring in the oesophagus and jejunum. Gliadin is a substrate of the tissue transglutinase. Gliadin is a major constituent of wheat protein and other cereal proteins in rye and barely. Gliadin consists of approx 50 components with a MG of 15-40 KD, triggering antibody production of all classes. Particularly IgA class antibodies are triggered to endomysium, IgG and IgA to gliadin.

Celiac disease, the cause of sprue or gluten sensitive enteropathy is a disease of the jejunum and proximal ileum characterized by villous atrophy. Clinically sprue presents with malabsorption, diarrhea, flatus, steatorrhea, impaired growth, and anemia or weight loss. Normal cholesterol concentration may rule out celiac disease, low serum iron (<60ug/dL), low ferritin (50ug/dL), low Hb may indicate celiac disease. There is an association with HLA-DQ2 and HLA-DQ8. The onset is in infants at the age of 4 -24 month and rarely later between 20-30 years. Dermatitis herpetiformis, a bullous skin disease, is associated with celiac diseases.

The sensitivity of the test for sprue is 94%-98%, specificity 95%-100%. There is a good correlation between the antibody titer and the severity of the enteropathy and the degree of histopathology changes. During gluten free diet, titers decrease after 6-12 month.

Sampling: 2 ml serum or plasma

Reference Interval: IgA and IgG autoantibody titer negative: < 1:10

Entamoeba histolytica see Amoeba, Direct Examination, Stool

Entero Viruses see Coxsackie Virus, Serology and Echo Viruses, Serology

Enterohemorrhagic Escherichia coli (EHEC), E.coli O157:H7

Background: The verotoxin producing E. coli is associated with hemorrhagic colitis presenting with abdominal pain and bloody diarrhea and with the hemolytic-uremic syndrome (HUS) characterized by hemolytic anemia, thrombocytopenia and acute renal failure. Besides the most frequent E.coli strain O157:H7, several other serotypes have also been isolated.

Pathogenesis: Plasmid encodes adherence factors and cytotoxin production are pathogenic factors. The typical O157:H7 strain produces a stripe-like cytotoxin acting on renal endothelial cells and causes lesions (A/E type) on the gut enterocytes characterized by localized destruction of brush border microvilli, intimate bacterial adhesion and cross cytoskeletal reorganization. Atypical EHEC strains do not produce A/E lesions or do not possess the typical 60 MDa plasmid.

There are mild clinical courses known with non-bloody diarrhea and severe hemorrhagic forms particularly in children and the elderly.

Treatment is controversial since antibiotic treatment results in higher rates of HUS due to lysis of bacteria which may increase the release of toxins.

Sampling: approx. 2 g of stool

Reference Interval: Report of diagnostic finding
culture result

Enteropathogenic Escherichia coli (EPEC)

Related Information: Enterohemorrhagic Escherichia coli (EHEC), E.coli O157:H7

Background: EPEC is important as a cause of diarrhea in infants and in young children. Clinically EPEC presents with mild non-bloody diarrhea or a more severe form. The organism causes lesions (A/E type) on the gut enterocytes is similar to the EHEC form, characterized by affecting microvilli and intimate adherence of bacteria to the epithelium cell membrane. Attachment is mediated by Bfp which is encoded by EAF plasmids, inducing various signaling pathways. Intimate adherence to the epithelial cells is mediated by an outer membrane protein and three other secreted proteins play a role in A/E histopathology.

Antibiotic treatment has shown in some studies to be of some benefit.

Sampling: 2 g stool

Reference Interval: Report of diagnostic finding
culture result

Eosinophil Cationic Protein (ECP)

Related Information: Eosinophil Count
Immunoglobulin E (IgE)
Pregnancy Associated Protein A, Serum

Background: Eosinophiles are the hallmarks of immune reaction in parasite infection and allergic responses. The intracytoplasmatic granules contain four basic proteins: Major basic protein (MPB) surrounded by eosinophil cationic protein (ECP), the eosinophilic neurotoxin (EDN), and the eosinophil peroxidase (EPO). ECP is a zinc metalloenzyme with a MW of 16-22 kDa, gene location is on chromosome 14, six forms are known, and serum half life time 1h.

Main functions of ECP are cytotoxicity on parasites, tumor cells, bacteria, and viruses. Inhibitory to T-cell proliferation, stimulation of histamine release from basophiles, release of mucus from airway cells, interaction with the complement system and adhesion molecules. Procoagulant properties, inhibitory to heparin and ECP may contribute to thrombosis.

Used in evaluation of pulmonary diseases such as asthma, (correlation with degree), idiopathic inflammatory bowl disease, eosinophilic cellulites (Wells syndrome, ECP and IL-5 elevated and correlates with clinical activity).

Limitations: The amount of released ECP from the cells may be influenced by temperature, transit time, and other factors.

Sampling: 1 mL of serum, separate immediately, stable for 1 day at 4°C.

Reference Interval: < 24 ng/mL
Children: 95 percentile 19 µg/L
Adults: 95% interval 2.3-15.9 µg/L
Diurnal variation with morning peak.

Epinephrine, Plasma see Catecholamines, Plasma

Epinephrine, Urine see Catecholamines, Urine

Epstein Barr Virus (EBV), Serology

Background: EBV (common name) is a human herpesvirus (double stranded DNA, external lipid envelope, internal nucleocapsid, 150-300 nm in diameter), according to taxonomy classified as human herpesvirus-4, subfamily Gammaherpesviridae, genus Lymphocryptovirus. EBV seroprevalence is 70-95% and the virus is transmitted by oral secretions. The primary sites of infection are epithelial cells of the oropharynx. It gains access to B-cells and acts as a B cell mitogen, stimulating growth and immortalization of B-cells by preventing apoptosis. EBV also alters the interaction of the virus with the immune system. Sites of latency are B-cells, possibly epithelial cells of the nasopharynx and the submandibular glands.

Clinically infectious mononucleosis (glandular fever) presents as fever, malaise (may persist for weeks), sore throat, cervical lymphadenopathy, hepatomegaly splenomegaly, hemolytic anemia. Occasionally encephalitis, myocarditis, pericarditis, neuropathy. Ampicillin treatment may lead to a rash, but does not indicate a life long ampicillin allergy. Chronic courses and relapses have been described. Incubation period 3-5 weeks.

In the rare X-linked lymphoproliferative (Dunca´s syndrome) form of EBV infection young males have an immune defect responding to EBV infection. The course of the infection is a fulminant mononucleosis, hepatitis, aplastic anemia.

Burkitt lymphoma (90% association with EBV) patients are young and have large swollen lymph nodes involving the jaws and orbital cavities. Nasopharyngeal carcinoma (100% association) occurs in older males in South East Asia. Hairy leukoplakia and polyclonal lymphoid hyperplasia are also associated with EBV.

The role of EBV in Hodgkin´s disease remains still to be clarified.

Immunocompromised Patients are on risk to develop lymphoproliferative disorders after EBV infection. In AIDS patients, EBV is associated with lymphocytic intestinal pneumonia and in the diffuse form of rapidly progressing encephalitis.

A conventional screening test for infectious mononucleosis are heterophil antibodies (Monospot® or Paul-Bunnell) but up to 20% may be negative in the early phase, disappearing after approx. 3 month, however false positive in this conventional test occur in hepatitis, parvovirus infection, lymphoma, leukemia, rubella, malaria, SLE.

Interpretation:

	no infection	current infection	previous infection
IgG anti VCA	negative	positive	positive
IgM anti VCA	negative	positive	negative
IgG anti EBNA	negative	negative	positive

Early antigen antibodies are detectable for a very short time. Persistent absence of antibody response to viral capsid is strong evidence against infection.

Sampling: 1 mL serum

Reference Interval: Differentiation of immunoglobulin class

Anti-EBNA (EBV nuclear antigen) IgG antibody	negative:	< 15 U/mL
	borderline:	15 – 20 U/mL
	positive:	> 20 U/mL
Anti-VCA (virus capsid antigen) IgG antibody	negative:	< 15 U/mL
	borderline:	15 – 20 U/mL
	positive:	> 20 U/mL
Anti-VCA IgM antibody	negative:	< 15 U/mL
	borderline:	15 – 20 U/mL
	positive:	> 20 U/mL
Anti-early Antigen IgG antibody	negative:	< 10 U/mL
	borderline:	10 – 20 U/mL
	positive:	> 20 U/mL

Improved diagnostic procedure by immunoblot.

Erythema Chronicum Migrans see Borrelia, Serology

Erythema Infectiosum see Parvovirus B19, Serology

Erythropoietin (EPO), Serum

Related Information: Ferritin, Serum or Plasma
Iron and Total Iron Binding Capacity/Transferrin, Serum
Reticulocyte Count

Background: Erythropoietin, a 18kDa protein mapped on chromosome 7 and produced in the kidney (fetal in the liver) is hypoxia inducible, stimulates proliferation, growth, and differentiation of erythroid precursor cells, increasing erythrocyte count and has a minor effect on megacaryocytes. For maximal stimulation of BFU-E IL-3 and GM-CSF are required.

Disorders:

Polycythemia Vera (PV) presents with autonomous, EPO independent erythropoiesis, usually with depressed EPO. In other, secondary forms of polycythemias, EPO is normal or elevated. In PV patients, leucocytosis, thrombocytosis, splenomegaly, pruritus erythromelalgia may be present.

EPO may be increased in cyanotic heart diseases, venous arterial shunts, pulmonary causes of hypoxia, in patients with mutant hemoglobins, in Cushing syndrome, renal cysts and arterial stenosis. Drugs which may elevate EPO are anabolic steroids, androgens, TSH, ACTH, angiotensin, epinephrine, fenoterol, and growth hormone.

Decreased in nephrotic syndrome due to renal protein loss, in amphotericin B, cisplatin, furosemide, theophylline treatment.

Sampling: 1 ml serum. To achieve best results, a morning sample is preferred due to circadian rhythm. Maximum EPO occurs at midnight, minimum in the morning. Stable for 2 weeks at room temperature.

Reference Interval:

Children 1-18 years	1-21 mU/mL
Adults	2.6-34 mU/mL

Higher in pregnancy before week 24.
The normal EPO level is a function of the hematocrit, with an increases of EPO if hematocrit < 40%.

Estradiol, Serum

Related Information: Follicle Stimulating Hormone (FSH), Serum
Luteinizing Hormone (LH)
Progesterone, Serum

Synonyms: 17-beta-Estradiol; Estradiol-17 beta

Background: Estradiol is the most active estrogen, synthesized mainly by the ovary under the control of FSH. During pregnancy, the placenta is a source too. In males, 75% is derived from testosterone, catalyzed by an aromatase in the periphery tissue, 25% is testis derived.
Diagnosis of decreased values: If test is combined with LH and FSH determination, useful diagnosis of primary (FSH and LH increased) and secondary ovarian failure.
Test may help to decide on the second dose of gonadotropin medication in assisted reproduction.
Rare tumors produce estradiol.
Ethinyl estradiol with or without norgestrel is used for emergency contraception.

Sampling: 1 mL serum, stable for 1 day at room temperature. Note on the request form please phase of menstrual cycle.

Reference Interval:

Children 6 month to 6 years	< 15 pg/mL
Male	< 52 pg/mL
Female	
follicular phase	10 – 165 pg/mL
ovulatory peak	50 – 530 pg/mL
luteal phase	30 – 200 pg/mL
post menopausal	< 38 pg/mL

Ethanol, Blood or Serum or Urine

Related Information: Acetaminophen, Serum
Alanine Aminotransferase (ALT), Serum
Alkine Phosphatase, Serum
Aspartate Aminotransferase (AST), Serum
Cannabinoids (Marijuana Metabolites) Immunological Drug Screen, Urine
Cocaine, Urine
Gamma- Glutamyl Transferase (Gamma-GT), Serum
Osmolality, Serum

Synonyms: Alcohol; Ethyl Alcohol; EtOH

Background: Ethanol peak levels are reached after 20-30 min post ingestion. The kinetics of decline is linear: for example, a 70 kg man metabolizes 7-10 g of ethanol per hour.

Endogenous alcohol production in the gastrointestinal tract (GI) may account for up to 0.005%. EtOH levels are monitored during i.v. ethanol treatment in methanol or ethylene glycol intoxication. Ethanol should be considered as a cause of coma, mimicking diabetic, cerebral trauma or drug overdose conditions.

The fetal alcohol syndrome includes low birth weight and small seize with failure to meet seize or weight target, and/or mental retardation, and/or birth defects particularly facial and cardiac abnormalities.

Interactions: Acetaminophen in therapeutic use and regular ethanol intake can cause serve liver injury. Synergistic effects occur with barbiturates and benzodiazepines.

Sampling: 1 mL of blood or 0.5 mL of Heparin or EDTA plasma or 0.5 mL of serum or 1 mL urine. Prepare venipuncture site with alcohol-free disinfectant (e.g. Betadine or Zephiran). Immediate transport to laboratory in tightly closed tube. 12%-18% higher values in serum or plasma than in whole blood.

Reference Interval: not detectable

Critical Values: Clinical intoxication 180 – 700 mg/dL
fatal >700 mg/dL, but critical values are lower with ingested other drugs such as hypnotics or tranquilizers.

Ethosuximide, Serum

Related Information: Phenytoin, Serum or Plasma

Synonyms: Suxinutin® ; Zarontin®

Background: Ethosuximide is a safe and efficient first choice drug in absence seizures treatment. The drug reduces low threshold Ca^{2+} currents particularly since reaching therapeutic levels in thalamic neurons. The T-type calcium currents provide in the thalamic neurons a pacemaker responsible for generating the rhythmic cortical discharge typical for the absences.

The drug is metabolized completely to the inactive hydroxylzed form.

Interaction with valproic acid: Decrease in ethosuximide clearance and higher steady state

concentration.

Toxicity: Psychosis, CNS depression, ataxia, stupor, coma, hypotension. Chronic: Lethargy, confusion, skin rush, ataxia, proteinuria, hematuria, hepatic alteration.

Urinary excretion 10%-40%; plasma binding <1%; volume of distribution 0.7 L/kg; half life 35-55h decreased in children; peak time 2-5h; peak concentration 24-44 µg/mL after 250 mg orally steady state.

Sampling: 2 mL serum. Steady state is reached after 5 -15 days.

Reference Interval:	Therapeutic:	60 -100 µg/mL (up to 125 µg/mL)
	Toxic:	> 150 µg/mL

Extractable Nuclear Antigen (ENA) see
Ribonucleoprotein U1-snRNP Antibody Smith (SM) Antibody; SS-A/Ro and SS-B/La Antibodies

Factor II Mutation (Prothrombin Mutation)

Background: A common hereditary predisposition to venous thrombosis is linked to a mutation at position 20210 in the prothrombin encoding proteingene on chromosome 1q23. The heterozygous form is present in 2% of the population and in 6% of patients with venous thrombosis. In familial thrombosis it is present in 18%. Heterozygous individuals have an up to 3 fold increased risk for venous thrombosis. The risk for arterial thrombosis is still under discussion.

Sampling: 2 mL EDTA or citrate blood. Do not freeze, store at room temperature or at 4˚C. Ship to laboratory within 5 days.

Reference Interval: Normal: G20210A Mutation not present

Factor V Leiden Screening Test see Activated Protein C Resistance Protein

Factor V Mutation (Leiden Mutation)

Related Information:
Activated Partial Thromboplastin Time
Activated Protein C Resistance Protein
Antithrombin III
Protein C
Protein S, Total

Background: The factor V Leiden mutation is a point mutation on chromosome 1q23 replacing guanine at position 1691 by an adenine, which substitutes arginine with glutamine at amino acid residue 506 leading to activated protein C resistance. There is at least one more, very rare factor V mutation. The DNA based method allows determination of heterozygosity and homozygosity for the mutation.

Clinically, as in other congenital biochemical defects in hypercoagulation states, a family history is usually present. The thromboses are in most cases venous, and may occur in large veins of the abdomen. First episodes usually occur in early adulthood rather than in childhood.
Functional test with high sensitivity and specificity to detect factor V mutation is PTT (activated partial thromboplastin time) done on plasma samples

Sampling: 2 mL EDTA or citrate blood for genetic testing

Reference Interval: Report on diagnostic findings
Factor V gene/chromosome 1q23
mutations not detectable/detectable

Fecal Pancreatic Elastase 1

Synonyms: Cholesterol–Binding Pancreatic Proteinase ;
Pancreatic Elastase

Background: Human pancreatic elastase is a steroid binding protein and an endoprotease. It binds to bile acids and sterols for transportation of cholesterol and metabolites through the intestinal tract.
There is a linear correlation between elastase 1 secretion and pancreatic secretion of lipase, amylase and trypsin
Elastase 1 is not degraded during intestinal passage, in opposite to chymotrypsin which undergoes a 99.5% degradation, the fecal elastase is a parameter for pancreatic function.
Useful test in the assessment of severity of pancreatitis, in the differentiation malabsorption from maldigestion in cases of steatorrhea. Useful in the diagnosis of Cystic Fibrosis, with a sensitivity and specificity of 90%-100%.

Sampling: Approx 2 g of stool, stable for 3 days at 20°C

Reference Interval:

Children:	Rising during the first month of life and stay	> 500 µg / g during childhood
Adults:	Normal exocrine pancreatic function	200-2500 µg / g stool
	Mild exocrine pancreatic insufficiency	100-200 µg / g stool
	Severe exocrine pancreatic insufficiency	<100 µg / g stool

Ferritin, Serum or Plasma

Related information: Blood Count, Complete
Cooper (Cu), Serum or Urine
Erythropoietin (EPO), Serum
Hemochromatosis, DNA Test
Iron (Fe), Serum
Iron (Fe), Urine

Occult Blood in Stool (Hemoccult)
Porphyrins, Quantitative, Urine, Stool
Transferrin and Total Iron Binding Capacity, Serum

Background: Ferritin is an ubiquitous protein with iron sequestration and storage function. Apoferritin (MW 440 kDa) is composed of heavy and light chains and can bind up to 4000 iron molecules of the Fe^{3+} form, moved into the interior of the molecule and growth of the core of ferric hydroxyphosphate. Ferritin is present in all cells, especially in erythroid precursor cells, in macrophages, and in hepatocytes. Ferritin production is induced by iron and cytokines regulate transcription and translation as well. Small amounts are released into the plasma, which is proportional to the intracellular ferritin stores.

Useful parameter in the diagnosis of hypochromic, microcytic anemias to differentiate into

1) iron deficiency anemia with low ferritin, low serum iron, low saturation, high total iron binding capacity (TIBC) and transferrin
2) anemia due to chronic diseases with low serum iron, high to normal ferritin, normal to low transferrin and TIBC
3) and thalassemia with normal to high ferritin

Increased in iron overload and decreased in iron deficiency anemia.

Hemochromatosis: ferritin and iron saturation are usually increased, but a better screening test for hemochromatosis is transferrin saturation which may indicate hemochromatosis if levels are in men >60% or in women >50%.

Please also see Iron (Fe), Serum.

Limitations: Loss of ferritin from hepatocytes in liver cirrhosis, autoimmune hepatitis, chronic hepatitis increases ferritin levels. As an acute phase reactant ferritin may be elevated in infectious diseases, acute renal failure. It may be elevated hemolytic anemias, malignancies such as leukemias, or lymphomas.

Extreme high levels up to 400 000 µg/L have been reported in HIV infected patients with histoplasmosis or hemophagocytosis.

Sampling: 1 mL serum or plasma

Reference Interval:

		(µg/L)
Newborns		25-200
First month		200-600
2-5 month		50-200
0.5 – 15 years		22-75
Adults		
Male		35-250
Female	< 40 years	35-122
	> 40 years	35-250

Fetoprotein, Alpha$_1$ see Alpha$_1$-Fetoprotein (AFP), Serum

Fibrinogen Functional

Related Information: Activated Partial Thromboplastin Time
D-Dimers
Prothrombin Time
Thrombin time

Synonyms: Factor I

Background: Thrombin converts fibrinogen to a fibrin clot. Fibrinogen is synthesized by the liver; it may be decreased during liver diseases, particularly in late stages. In disseminated intravascular coagulation (DIC) fibrinogen is decreased by excessive thrombin generation; in advanced DIC with poor prognosis, fibrinogen may be elevated. Fibrinogen is decreased during thrombolytic therapy or fibrinolysis, since plasmin split fibrinogen and fibrin.

Fibrinogen is an acute phase reactant. It is elevated during pregnancy, physical activity, and may be a marker for increased risk for myocardial infarction.

Rare forms of hereditary deficiencies of fibrinogen have been described. Clinically they may present with bleeding symptoms such as epistaxis, gastrointestinal bleeding, miscarriage, intracranial hemorrhage. Usually, symptoms are milder than those caused by factor VIII or IX deficiencies.

Genetics allow classifying three forms: The homozygous quantitative form or afibrinogenemia with bleeding, the heterozygous quantitative form or hypofibrinogenemia with a moderate decreased fibrinogen level and little tendency of bleeding and the qualitative form or dysfibrinogenemia, with little or no bleeding history which is characterized by various mutations, producing dysfunctional fibrinogen. Clinically it may present with an increased risk for venous thrombosis and in a minor group of arterial thrombosis. Prevalence in patients with thrombosis is estimated 0.8%.

Useful in the evaluation of disseminated intravasal coagulation, prolonged PT and PTT and in the evaluation of bleeding.

Limitations: Fibrinolytic degradation products >100 µg/mL and heparin >0.6 U/mL falsely lower fibrinogen values. Dysfibrinogenemia also lowers fibrinogen test results.

Moderate hemolyzed, icteric or lipemic plasma will not interfere with the assay.

Sampling: 2 mL citrate plasma, mix well, tube must be filled no less than 80% of the maximum volume. Separate plasma soon, plasma is stable for 5h at 4°C.

Reference Interval: For the functional, Clauss based method:
150-450 mg/dL

Fibrinopeptide A and B see Thrombin Time

FK- 506 see Tacrolimus (FK 506), Whole Blood

Folic Acid, Red Blood Cells

Related Information: Blood Count, Complete
Folic Acid, Serum
Homocysteine, Total, Plasma
Phenobarbital, Serum
Primidone, Serum
Vitamin B 12 , Plasma or Serum

Background: Red blood cell (RBC) folate is a more reliable parameter to assess folate deficiency than serum due to minor variations caused by diet. Celiac disease can be ruled out when RBC folate and D-xylose absorption is normal.

Megaloblastic anemia present, if due to folate deficiency, values < 100 ng/mL erythrocytes.

Sampling: 2 mL of EDTA blood, fasting sample preferred, stable for 2 days at room temperature.

Reference Interval: 150 – 600 ng/mL erythrocytes

Folic Acid, Serum

Related information: Blood Count, Complete
Folic Acid, Red Blood Cells
Homocysteine, Total, Plasma
Phenobarbital, Serum
Primidone, Serum
Vitamin B 12 , Plasma or Serum

Background: The reduced form of folic acid is essential for the synthesis of amino acids, purines and DNA. Clinically, anemia, congenital malformation in newborns and vascular diseases are seen in deficiency.

Folic acid is composed of p-aminobenzoic acid and glutamic acid. Dihydrofolate dehydrogenase catalyses the reduction reaction to dihydrofolic acid and to tetrahydrofolic acid, which are transformed to folate cofactors serving as donators of one carbon units for oxidation, particularly in purine and pyrimidine synthesis and amino acid conversions such as homocysteine to methionine (cobalamin also required). Elevated homocysteine levels are linked to vascular diseases. Nucleoside synthesis impairment, through decreased synthesis of precursors may cause megaloblastic anemia.

Daily 50-200 ug of folic acid is usually absorbed from an average intake of 500-700 ug (US). The richest sources are yeast, liver, kidney and green vegetables. In the human liver 2-20 mg are stored. Stores are sufficient for 1-6 month. Before absorption, alpha 1-glutamyl transferase within the intestinal mucosa must hydrolyze all but one glutamyl residues of the polyglutamate form of N-methyltetrahydrofolate. Excretion via urine and stool.

Limitations: Hemolysis increase falsely folic acid levels. Decreased by contraceptives. Significant fluctuations with diet.

Sampling: 1 mL serum, overnight fasting sample preferred. Avoid hemolysis and exposure to light. 20% loss per day at room temperature and light exposure.

Reference Interval:

Adult: 5.89 nmol/L - 33.08 nmol/L (2.6 - 14.6 ng/ml)
(convert: ng/ml x 2.266 = nmol/L)

Children: (nmol/L)

year	Male	Female
0-1	16.3-50.8	14.3-51.5
2-3	5.7-34.0	3.9-35.6
4-6	1.1-29.4	6.1-31.9
7-9	5.2-27.0	5.4-30.4
10-12	3.4-24.5	2.3-23.1
13-18	2.7-19.9	2.7-16.3

Follicle Stimulating Hormone (FSH), Serum, Urine

Related information: Estradiol, Serum
Estrone, Serum
Luteinizing Hormone (LH)

Background: Please see Luteinizing Hormone (LH), Serum.

Limitation: FSH increases with age and is increased in smokers.

Sampling: Serum: 2 mL of serum. Avoid hemolysis. FSH is stable for 4h at room temperature, 2 weeks at -20°C. Avoid freezing thawing cycles.
Urine: 10 mL of urine. Since FSH is less pulsatile, a less than 24h collection period is suitable. Note total quantity and length of collection period.

Reference Interval:

Serum:	Male		1.0 - 8.0 IU/L
	Female	follicular phase:	2 - 8 IU/L
		ovulatory peak:	5 - 25 IU/L
		luteal phase:	2 - 8 IU/L
		post menopausal:	30 - 100 IU/L
	Children		1.5 - 8.0 IU/L
Urine:	Male > 8 years		< 20 IU/24h
	Female	9-15 years	< 22 IU/24h
		> 15 years	< 30 IU/24h
		post menopausal:	< 60-90 IU/24h
	Children		< 5 IU/24h

Free Light Chains Structure (FLC), Serum

Related Information: Albumin, Urine
Free Light Chains Structure, Urine
Immunoglobulin G (IgG), Serum, Urine, CSF
Protein Electrophoresis, Serum

Background: Monoclonal gammopathies are characterized by the clonal expansion of plasma cells. The disorders can be diagnosed and monitored by monoclonal immunoglobulins secreted by plasma cells. Monoclonal gammopathies include multiple myeloma (MM), light chain myeloma, Waldenstroem macroglobulinemia, nonsecretory myeloma (NSMM), smoldering multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis (AL) and light chain deposition disease (LCDD). AL, LCDD and NSMM display low concentrations of serum monoclonal light chains which cannot be detected by protein electrophoreses or immunofixation techniques but by more sensitive techniques detecting light chains not bound to immunoglobulins (free light chains). Sensitivity (referred to the reference interval) for detecting polyclonal hypergamma globulinemia, AL, LCDD, MM is 90%-100 % for a 95% confidence interval, specificity 92%-98%.

The ratio may be used for discrimination between monoclonal gammopathy of undetermined significance (MGUS) and MM. Kappa/ lambda ratio between 0.6 and 4.2 increase the probability of MGUS in asymptomatic patients. For AL an abnormal ratio in 90% of the patients has been reported.

Sampling: 1 mL Serum

Reference Interval:

	95% reference interval	diagnostic range
Kappa free light chain	3.3-19.4 mg/L	
Lambda free light chain	5.7-26.3 mg/L	
Ratio kappa/lambda free light chain	0.3-1.2	0.26-1.65

Free Light Chains Structure, Urine

Related Information: Immunoglobulin G (IgG), Serum, Urine, CSF
Albumin, Urine
Protein Electrophoresis, Serum

Synonyms: Bence Jones Protein, Urine

Background: Normal renal function renders protein excretion < 150 mg per day. 70% of filtered protein are albumin; transferrin, low molecular weight protein and immunoglobulins. An excretion rate of the fraction of light chains of more than 50 mg/24h favors a diagnosis of maligne monoclonal gammopathy.

Sampling: Aliquot 5 mL of a 24h urine, collected in a sterile container without preservatives, keep refrigerated. Note total quantity.

Reference Interval: Type kappa: < 22 mg/L
Type lambda: < 12 mg/L

Gamma-Glutamyl Transferase (Gamma-GT), Serum

Related Information: Alanine Aminotransferase (ALT), Serum
Alkine Phosphatase, Serum
Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Leucine Aminopeptidase (LAP), Serum

Synonyms: Gamma Glutamyl Transpeptidase; GGT; GGTP;
Glutamyl Transpeptidase; GT; GTP

Background: The enzyme, excreted by the biliary system, it is a sensitive indicator for obstructive hepatobiliary diseases such as intrahepatic cholestasis, hepatitis or pancreatitis. It is more specific for the hepato-biliary tract than alkaline phosphatase and independent from bone diseases or pregnancy whereas alkaline phosphatase is. It is independent from age beyond infancy. GGT values are independent also, in contrast to aspartate aminotransferase, from skeletal muscle diseases. Renal function does not influence GGT levels.

GGT is more sensitive to obstructive diseases than aspartate aminotransferase (AST) or alanine aminotransferase (ALT). Increase of GGT in obstructive diseases is about 5-50 times, in infectious hepatitis no more than 5 times.

Used in the diagnosis and monitoring treatment of hepatomas, carcinomas of the pancreas and in liver metastasis. There is a good correlation with tumor progression.

In the diagnosis of chronic alcohol liver diseases a 2 fold increase above normal levels and an AST:ALT ratio > 2:1 suggests ethanol abuses.

GGT correlates with body mass index,

Moderate increased in infectious mononucleoses and in systemic lupus erythematosus. Very high concentrations are found in primary biliary cirrhosis and in infants with biliary atresia. Increased in hyperthyroidism, decreased in hypothyroidism.

Drugs: Decrease: azathioprine clofibrate, estrogens, methotrexate, ursodiol.

Increase: acetaminophen, aminoglutethimide, phenytoin, barbiturates, carbamazepine, diphenylhydantoin, estrogens, interferon alpha, medroxyprogesterone, contraceptives, phenothiazine, valproic acid.

Sampling: 1 mL serum, EDTA or heparin plasma. Avoid hemolysis. Fasting sample is optimal.

Reference Interval:

Male:	< 66 U/L
Female:	< 39 U/L
Children:	< 45 U/L

Higher in newborns 3-6 month of age

Gastrin, Serum

Related Information: Helicobacter Pylori
Vitamin B 12, Plasma or Serum

Background: Gastrin a polypeptide hormone is secreted by neuroendocrine G cells of the gastric antrum and primary function as a acid secretagogue and is tropic for histamine secreting enterochromaffin cells of the gastric mucosa and weekly stimulates secretion of pancreatic enzymes and gallbladder contractions.

Useful in the diagnosis of gastrin secreting carcinoid tumors, most commonly (90%) located in the duodenum or pancreas or peripancreatic lymph nodes and are associated with the Zollinger Ellison syndrome (ZES) and with chronic atrophic gastritis.

A diagnosis of ZES can be made on low fasting gastric ph <2.5 and high fasting gastrin values >1000 ng/L. A secretin test can be applied in patients not fulfilling theses criteria. In healthy persons, secretin application decreases serum gastrin levels, in patients with gastrinomas levels raise >200 ng/L.

Limitation: Gastrin cell hyperplasia is also characterized by elevated gastrin values and gastric hyperacidity. Gastrin is also elevated in atrophic gastritis, pernicious anemia, retained antrum, after surgical small bowl resection, renal failure and cirrhosis.

Sampling: 2 mL serum or 2 mL EDTA plasma, (no heparin !), separate in refrigerated centrifuge soon and transport to laboratory at 4°C within 4h or freeze at -20°C and ship frozen.

To obtain basal levels, a 12h (overnight) fasting period is required.

For secretin stimulating test: Stimulate with an injection of 2 units/kg body weight of porcine secretin and obtain samples before stimulation, at 2 min, 5 min, 10 min, 15 min, 20 min and 30 min.

Reference Interval: Fasting sample:

Newborn 0-4 days	120-183 ng/L
Children	10-125 ng/L
15-60 years	25-90 ng/L
> 60 years	< 100 ng/L

Gentamycin, Serum

Related Information: Creatinine Clearance
Creatinine, Serum or Plasma
Creatinine, Urine

Synonyms: Refobacin®

Background: Gentamycin, an aminoglycoside antibiotic, is a bactericidal, concentration dependent protein synthesis inhibitor, used in treatment of aerobic gram negative bacteria.

Good activity in Pseudomonas aeruginosa, methicillin sensitive Staphylococci, Enterobacter aerogenes, Klebsiella pneumoniae, E.coli, Proteus vulgaris, Serratia sp., Yersinia sp., Pasteurella sp, Brucella sp, Campylobacter fetus.

Moderate activity against Gonococci sp., Listeria sp, Haemophilus influenza, Proteus mirabilis, Salmonella sp.

Half life time: newborns: 5h; Children and adults: 1.5-2h. No protein binding.

Indicated in urinary tract infections, in pneumonias, meningitis, peritonitis.

Aminoglycosides are excreted nearly entirely by glomerular filtration and dose has to be adjusted to renal function:

creatinine clearance mL/min	% of maximum daily dose (5.5 mg/kg body weight)	frequency
100	100	every 24 h
75	75	every 24 h
50	50	every 24 h
25	25	every 24 h
20	80	every 48 h
10	60	every 48 h
<10	40	every 48 h

Sampling: 2 mL serum.

Reference Interval: Therapeutic values: 4.0 – 10.0 µg/mL
Toxic values may start at: > 12.0 µg/mL

Germanium (Ge), Serum

Background: Low concentrations of the non-essential trace element germanium occur in nearly all soils, plants and animal life.

General toxicity to men of germanium is low (except for the tetrahydride germane).

However, low numbers of human cases linked to prolonged intake of germanium products with renal failure and even death have been reported, characterized by kidney dysfunction, kidney tubular degeneration, and germanium accumulation as well as other adverse effects such as anemia, muscle weakness, and peripheral neuropathy. Recovery of renal function is slow and incomplete even long after withdraw from germanium. The total dose of ingested germanium (as dioxide, carboxyethyl, germanium sesquioxide, germanium-lactate-citrate, or others) to reach toxicity is reported to be 15g - 300g over 2 month to 3 years.

High doses of germanium may result in an increased embryonic resorption, but possible malformations have been reported only after administration of dimethyl germanium oxide to pregnant animals.

Germanium is seems not to be carcinogenic and even appears to inhibit cancer.

Germanium oxide has been shown to be effective in vitro for inhibiting effects of mutagenic substances.

Possible anticancer effects of the organogermanium compound bis (2-carboxyethylgermanium) sesquioxide, which is not naturally occurring, may be due to induction of interferon-gamma, the enhancement of natural killer cell activity, and inhibition of tumor and metastatic growth.

In patients with premenstrual syndrome lower levels of the toxic metals lead, arsenic, and germanium were found to be significantly elevated (lowered levels of calcium, chromium, copper, and manganese).

In children with Kashin-Beck disease have lowered hair concentrations of germanium (and selenium boron).

It may be useful to monitor trace metals in patients undergoing hemodialysis. In uremic patients an important factor affecting trace element concentration is the degree of renal failure and modality of replacement. Several trace elements have been implicated in the decline of renal function including germanium, arsenic, cadmium, copper, lead and mercury. In uremic patients, aluminium, cadmium, chromium, lanthanum, strontium and zinc have been shown to accumulate in bone.

Sampling: 5 mL serum

Reference Interval: < 1.4 µg/L

Giardia lamblia, Microscopy

Related Information: Amoeba Antibody, Serology
Amoeba direct Examination, Stool

Synonyms: Giardia intestinalis; Lamblia intestinalis

Background: G. lamblia has a two stage life cycle, the trophozoite and cyst. The trophozoite is pear shaped with two nuclei, four pairs of flagella. The cyst is oval with four nuclei.

Transmission occurs by ingestion of the cyst with contaminated water or food. After encystations in the duodenum the trophozoite does not invade the gut wall, but inflammation occurs and malabsorption develops.

The parasite occurs worldwide, outbreaks have been reported related to contaminated water, chlorination does not eradicate the cysts. Reservoirs are humans and other mammals. In male homosexuals the prevalence is increasing. Decreased gastric acid may predispose individuals to infection. Overall human infection rates vary between 5%-15%.

Clinically giardiasis presents with anorexia, nausea, abdominal cramps, persisting for weeks. Giardiasis is one of the common causes of traveler's diarrhea. 50% of the infected individuals are asymptomatic.

Therapy: Metronidazole or quinacrine hydrochloride

Sampling: fresh stool; There is a cyclical peak every 3-7 days.

Reference Interval: Direct detection of Giardia by stool microscopy

Gliadin IgG/IgA Antibodies

Related Information: Endomysial Antibodies
Immunoglobulin A

Background: In Western countries, Celiac disease or gluten-sensitive enteropathy is the major cause of sprue. Determination of IgA, and in approx. 10% of patients with IgA deficiency, of IgG antibodies to the gluten protein gliadin is helpful for the diagnosis. Endomysial IgA antibodies and transglutinase antibodies are useful in diagnosis of celiac disease.
Clinically, sprue is characterized by diarrhea, flatus, steatorrhea, anemia, delayed puberty, impaired growth, weight loss, and osteoporosis.
There is a close association of dermatitis herpetiformis with gluten sensitive enteropathy.
The most sensitive method to diagnose celiac disease is intestinal biopsy, followed by endomysial antibodies and IgA and IgG gliadin antibody evaluation.

Sampling: 1 mL serum

Reference Interval: Differentiation of immunoglobulin class

Adults:

IgA antibody negative: < 25 RE/mL, borderline 25-50 RE/mL, positive > 50 RE/mL
IgG antibody negative: < 25 RE/mL, borderline 25-50 RE/mL, positive > 50 RE/mL

Children < 4 years:

IgA antibody negative: < 50 RE/mL, borderline 50-100 RE/mL, positive > 100 RE/mL
IgG antibody negative: < 50 RE/mL, borderline 50-100 RE/mL, positive > 100 RE/mL

Glucagon, Plasma

Related Information: Adrenocorticotropic Hormone, ACTH, Plasma
Gastrin, Serum
Glucose, Blood, Urine, Liquor
5-Hydroxyindoleacetic Acid (5-HIAA), Quantitative, Urine
Insulin, Serum

Background: Glucagon is a polypeptide counteracting the effects of insulin. Glucagonoma, a rare neuroendocrine tumor of the pancreas, secretes glucagon levels of > 500 pg/mL, values of >1000 pg/mL are diagnostic. Clinically the patient presents with skin rash, impaired glucose tolerance, abdominal pain, diarrhea, peptic ulcer, and anemia.

Limitations: Increased values may occur in diabetic ketoacidosis, stress, uremia, Morbus Cushing, cirrhosis, hyperosmolality, pancreatitis, large burn wounds, trauma, surgery; decreased values develop in cystic fibrosis, chronic pancreatitis, post-pancreatectomy.

Sampling: 2 mL EDTA plasma supplemented with 0.1 mL (250-500 units) of the protease inhibitor Trasylol, snap-freeze, and ship frozen. 12h fasting sample for basal levels.

Reference Interval: 40 -130 pg/mL

Glucose

Related Information: Cerebrospinal Fluid (CSF, Liquor)
Glycosylated Hemoglobin A1c , Blood
Insulin, Serum
Insulin Resistance

Background: Diagnostic procedures in diabetes mellitus includes:
1) random plasma glucose
2) fasting plasma glucose
3) two hour post-glucose load glucose assays.

Gestational diabetes mellitus is in the first step screened by 1h plasma glucose post 50 g glucose load and in case of abnormal values a 100 g glucose load test is recommended.

1. Random Glucose Plasma

Background: Useful test in monitoring therapy of diabetes mellitus and one of the parameters to diagnose. Used in monitoring metabolic diseases such as ketosis, acidosis, and coma. Hypoglycemia should prompt investigation of C peptide and insulin.

Sampling: 1 mL blood in sodium fluoride tube

Reference Interval:

Newborns	<115 mg/dL (6.4 mmol/L)
Children and Adults	<200mg/dL (11.1 mmol/L)
Hypoglycemia:	47-60 mg/dL (2.6-3.3 mmol/L)
Critical:	
neonates	<40 mg/dL (2.2 mmol/L)
adult male	< 50 mg/dL (2.8 mmol/L) or > 400 mg/dl (22.2 mmol/L)
adult female	< 40 mg/dL (2.2 mmol/L) or > 400 mg/dl (22.2 mmol/L)

2. Fasting Glucose, Plasma

Synonyms: Blood Sugar Fasting, FBS; FPS;

Background: Causes of elevated fasting blood glucose levels are:
Non-fasting specimen
Stress
Cushing disease
Acromegaly
Pheochromocytoma
Glucamoma,
Liver disease
Pancreatitis,
Drugs such as thiazides, glucocorticoids, beta-blockers, estrogens etc.

Causes of hypoglycemia:
Islet cell tumors (measure C peptide and insulin as well)

Adrenal insufficiency
Adrenal hyperplasia
Hypopituitarism
Fructose intolerance, galactosemia, leucine sensitivity
Drugs salicylates, quinine etc.
Childhood

Glycogen storage diseases, galactosemias, fructose intolerance, ketotic hypoglycemia of infancy, fructose 1-6 diphosphatase deficiency, carnitine deficiency are causes of neonatal hypoglycemias.

Limitations: Hypoglycemia as an artifact is caused by leucocytosis, hemolysis or glycolysis in delayed non-separated specimens,

Sampling: Patient's preparation: 8h fasting prior to sampling, morning sampling preferred.

Draw 1 mL blood in sodium fluoride tube.

Glucose is decreasing by 5-10mg/dL (0.3-0.6 mmol/L) per hour if unseparated.

Reference Interval:

Premature infants	as low as 30mg/dL (1.6mmol/L)
Newborns	40-60 mg/dL (2.2-3.3mmol/L)
Children	60-100 mg/dL (3.3-5.6 mmol/L)
Adults	60-109 mg/dL (3.3-6.0 mmol/L)

3. Post-Glucose Load, Plasma

Synonyms: Oral Glucose Tolerance Test, Postprandial Glucose, PP.

Sampling:

Patient's preparation:

Patients fasting for 8h, test usually done in the morning

75 g load: Oral intake of a commercially available solution.

Gestational diabetes mellitus:

Fasting not required

50 g load: oral intake of a commercially available solution

100 g load: if the 50 g test result is equivocal or abnormal

Sampling time:

75 g load: 2 hours after glucose intake

50 g load: 1 hour after glucose intake

100 g load: fasting sample, 1h and 2h and 3h after intake. Label properly

Reference Interval:

Recommendations of the American Diabetes Association (ADA):

Diagnosis of diabetes mellitus: One out of the following 3 criteria is positive and has been confirmed by any of the following on a subsequent day

- Symptoms of diabetes plus random plasma glucose levels > or = 200 mg/dlL (11.1 mmol/L). Symptoms are polyuria, polydipsia, unexplained weight loss.

- Fasting plasma levels > = 126mg/dL (7mmol/L) after a minimum of 8 hour fasting period
- 2h post load glucose > = 200mg/dL (11.1 mmol/L) after a 75 g load

ADA criteria for gestational diabetes mellitus
first step: If plasma glucose >140 mg/dL (7.8 mmol/L) after 50 g glucose load proceed to step two second step of diagnosis of gestational diabetes mellitus: If two or more values in the 3h oral 100 g glucose load are abnormal

fasting:	> 105 mg/dL (5.8 mmol/L)
1 hour:	> 190 mg/dL (10.5 mmol/L)
2 hour:	> 165 mg/dL (9.2 mmol/L)
3 hour:	> 145 mg/dL (8.0 mmol/L)

WHO recommendations:
For impaired glucose tolerance defined as fasting glucose levels of 100-125 mg/dL (5.6-6.9 mmol/L) the WHO recommends to perform a 2h oral glucose tolerance test: overnight fasting, in the morning oral intake of 75 g glucose (for children 1.75 g glucose per kg body weight).
-Impaired fasting glucose category: preload fasting 100-125 mg/dL (5.6-6.9 mmol/L)
-Impaired glucose tolerance category: fasting <126 mg/dL (6.9 mmol/L) and 2h post load glucose level 140-199 mg/dL (7.8-11mmol/L)
-Diabetes mellitus: preload fasting >or= 126 mg/dL (7 mmol/L) and 2 hour >or= 200 mg/dL (11.1mmol/L)

4. Whole Blood Glucose

Background: Glucose concentrations differ: Plasma glucose levels are approx. 11% higher than those in whole blood.
Whole blood glucose is used in instruments for self-monitoring. To adjust results from theses devices to plasma glucose the following is recommended for readings > 75 mg/dL (4.2 mmol/L) the difference should be less than 20%, for readings below 75 mg/dL, the difference should be less than 15 mg/dL (0.83 mmol/L).
Limitations: Mannitol, hematocrit, drugs, instrument cleaning, pO2, low total protein concentration may alter the results.
Reference Interval: adults 65-95 mg/dL (3.5-5.3 mmol/L)

5. Urine Glucose

Background: Exceeding of renal tubular threshold leads glucose loss in the urine.
Useful test in immediate evaluation of a comatose patient by dipstick method and evaluation of newborns.
Sampling: 5 mL random urine
Reference Interval: < 25 mg/dL

Glucose, Liquor see Cerebrospinal Fluid (CSF, Liquor)

Glucose-6-Phosphate Dehydrogenase (G6PD), RBC

Background: G6PD is a red blood cell (RBC) enzyme maintaining proteins in a reduced state, is X linked and one or a combination of 60 known mutations within the encoding gene results in premature hemolysis.

The defect is the most common metabolic red blood cell defect with hemolysis.

Useful in the evaluation of G6PD deficiency, occurring in RBC stressful conditions such as bacterial and viral infections or acidosis. Screening is more likely to avoid false negative results if not performed in an acute hemolytic episode, recovery period should be preferred.

In 10%–15% of Afro-Americans mutations associated with G6PD are present; the G6PD A-variant for example is associated with acute intermittent hemolysis and primaquine sensitivity. Other mutations are linked to drug sensitivities such as aspirin, doxorubicin, furazolidone, nalidixic acid, niridazole, nitrofurantoin, pentaquine, phenylhydrazine, quinidine, quinine, sulfamethoxazole, sulfapyridine and others.

Sampling: 2 mL EDTA blood, do not freeze, stable at room temperature for 1 day, at 4°C for 6 days.

Reference Interval: 7.2–10.5 U/g hemoglobin
In newborns higher.

Glutamanic Acid Decarboxylase Antibody (GAD)

Related Information: Glucose
Islet Cell Antibody
Parietal Cell Antibody
Thyroglobulin Antibody
Thyroperoxidase Autoantibody

Background: The enzyme GAD is part of the neurotransmitter GABA production pathway in pancreas and CNS.

GDA antibodies are of IgG class.

Useful in the diagnosis of:

- GDA antibodies are present in up to 95% of Stiff Man syndrome patients. Stiff Man syndrome is a rare disease characterized by progressive stiffness of skeletal muscles, particularly legs and back, rigors, spasms, hyperlordosis of the spine. Women predominate. Clinically seen between third and seventh decade of life. Associated with diabetes mellitus, in up to 60% of the patients with autoimmune diseases such as thyroiditis, Graves disease, pernicious anemia, myasthenia gravis; in up to 5% in breast carcinoma, Hodgkin's disease, carcinoma of the colon, carcinoma of the lung

-Diabetes mellitus:

GDA antibodies are present in 70%-80% in type I diabetes in children and adults. Indicated parameter in pathologic or borderline glucose tolerance tests in children in combination with other autoantibodies tests and familiar history of diabetes. However, sensitivity is 60%-90% for adults and as low as 3%-20% for children to develop within 5-10 years diabetes type I if GAD antibodies are present.

Predictive value for adults with type II diabetes for developing insulin dependent diabetes within 6 years is 80%.

Sampling: 1 mL serum

Reference Interval: Negative : < 0.75 U/mL

Glutamate Oxaloacetic Transaminase (GOT) see Aspartate Aminotransferase, Serum

Glutamate Pyruvate Transaminase (GPT) see Alanine Aminotransferase (ALT), Serum

Glutamic Pyruvate Transaminase see Alanine Aminotransferase (ALT), Serum

Glycosylated Hemoglobin A1c , Blood

Related Information: Fetal Hemoglobin
Fructosamine, Serum
Glucose, Blood, Urine, Liquor
Triglycerides, Serum or Plasma

Synonyms: Fast Hemoglobins, GHb, Glycohemoglobin, HB A1, Hemoglobin A1a ,A1b ,A1c.

Background: GHb is composed of varies compounds formed by ligation of sugars and hemoglobin. The formation rate of GHb is proportional to blood glucose concentration.

Essential parameter in long term glucose control. GHb reflects blood glucose levels over the preceding 60-120 days. Goal should be values < 7%, diabetes mellitus treatment need to be reevaluated if GHb > 8%.

Sampling: 1 mL of EDTA or heparin blood. Stable 1 week at 4˚C.

It is recommended a three month interval testing for type I diabetes mellitus, for type II diabetes 6 month.

Reference Interval: 4.8%–6.2%

Gonococcus see Neisseria gonorrhoeae

GPT see Alanine Aminotransferase (ALT), Serum

Growth Hormone (HGH, STH) see Somatotropin

Haloperidol, Serum or Plasma

Related Information: Lithium (Li), Serum

Synonyms: Dozic®; Fortunan®; Haldol®; Haloneural®; Serenace®

Background: Antipsychotic drug, used in the therapy of Tourette syndrome, sedation of agitated or delirious patients.

Sign of overdose: cardiovascular alterations such as EKG changes (depressed T or ST waves), arrhythmias; hyperglycemia; exacerbation of myasthenia gravis.

Bioavaliability 40%-80%; urinary excretion 1%; plasma binding 90%-94% increased in cirrhosis; volume of distribution 11-25 L/kg; half life time 13-23h decreased in children; peak time im: 0.6h, oral: 1.5-5h; peak concentration im: 5-40 ng/mL after a 10 mg single dose, oral: 5-14 ng/mL after a single 20 mg dose.

Haloperidol undergoes reversible metabolism to the reduced, less active form with a half life time of 16-120h. Slow reconversion to the parent drug may be responsible for prolonged half life time in 7 days samples of 70h.

Sampling: 2 mL serum

Reference Interval:			
	Therapeutic values:		4-20 (-40) ng/mL
	Toxic values:	adult	> 50 ng/mL
		children:	> 10 ng/mL

Hantavirus, Serology see Bunyaviruses, Serology

Haptoglobin (Hp), Serum

Related Information: C-Reactive Protein, Serum
Blood Count, Complete
Myoglobin, Blood or Serum or Plasma
Myoglobin Qualitative, Urine

Background: Haptoglobin is a plasma glycoprotein with alpha electrophoretic mobility that binds irreversibly to free hemoglobin, which can be removed by the liver saving hemoglobin from

renal loss. Two major genetic variants Hp1 and Hp2 are known.

Haptoglobin is a sensitive marker for hemolysis which is decreasing haptoglobin levels. If the red blood cells half life is decreased from 26 days to less than 17 days haptoglobin plasma levels are undetectable. Disease causing ineffective erythropoiesis, soft tissue hemorrhage and drug induced hemolytic anemia decrease haptoglobin levels.

Increase may occur in acute inflammation (acute phase reactant) counteracting concurrent hemolysis. Corticosteroids and nephrotic syndrome may elevate haptoglobin levels.

Decreased levels occur in liver disease and during estrogen therapy.

Sampling: 2 mL serum

Reference Interval:			
	1-10 days		5- 48 mg/dL
	10 days – 60 years		26-185 mg/dL
	>60 years	male	35-164 mg/dL
		female	40-175 mg/dL

Helicobacter pylori

Background: Helicobacter organisms are gram negative, spirale shaped, terminal flagellated, microaerophilic, urease positive bacilli (Campylobacter in contrast is urease negative), first isolated in 1982. The natural habitat of H. pylori is the human stomach.

Epidemiology: The infection rate decreases with increasing socio-economic level. Infection occurs in childhood and is likely to persist life long. Due to poor sanitation; the rate of infection in developing countries is high. In western countries in young individuals prevalence is up to 20%. The mode of infection is uncertain but likely to be fecal-oral or oral-oral.

Helicobacter pylori cause chronic gastritis and peptic ulcer and is considered a risk factor for gastric carcinoma.

H. pylori is fragile, biopsies must be kept in transport medium and cultured within 24h. Cultures will be kept for up to 10 days.

Therapy: Clarithromycin plus amoxicillin or clarithromycin plus metronidazole.

Sampling: Serology: 2 mL serum
Antigen detection: approx. 2 g stool
Culture and resistance testing: Gastric biopsy in Portagerm pylori transport medium

Reference Interval:

Serology:	Antibody of the IgG class IgG antibody	negative	<15 U/mL
		borderline	15-20 U/mL
		positive	>20 U/mL
	Validation by immunoblot		

Antigen detection: Negative

Culture: Report on diagnostic finding

Helminths, Microscopy, Feces

Test includes:

Ancylostoma duodenale (old world hookworm)
Ascaris lumbricoides
Cestoda (tapeworms)
Clonorchis sinensis
Diphyllobothrium (fish tapeworm)
Enterobius vermicularis (pinworm)
Fasciolopsis buski
Fasciola hepatica (sheep liver fluke)
Heterophyes heterophyes
Hymenolepis nana (dwarf tapeworm)
Necator americanus (new world hookworm)
Nemathelminthes (Nematodes, roundworms)
Paragonimus westermani (lung fluke)
Schistosomia species
Taenia solium (pork tapeworm)
Taenia saginata (beef tapeworm)
Trematodes (flukes)
Trichuris trichiura (whipworm)
Strongyloides stercoralis (small roundworm)

Background: The multicellular metazoan or helminthes are subdivided in two phyla: the Platyhelminthes (flatworms) and the Nemathelminthes. The phylum Platyhelminthes contains two medical important classes: Cestoda (tapeworms) and Trematoda (flukes).

Cestoda (tapeworms)

The tapeworms consist of two parts, a scolex (head) and multiple proglottids, which replicate from the germinal center next to the scolex to grow worm, the distal end contain gravid proglottids, which are excreted with the feces. The intermitted hosts are pigs, cattle, and fish. Infection of the human is by larvae ingestion or in case of cysticercosis and hydatid disease by egg ingestion.

Taenia solium (pork tapeworm)

The adult worm causes taeniasis. The infection occurs after ingesting uncooked pork containing the larvae. The larvae take 3 months to grow into the adult worm measuring up to several meters. Cysticercosis occurs, if the egg is digested by the definitive host, the human, not by the pig as intermediate host. The egg hatches in the small intestine and the oncosphere disseminate by the circulation system especially into the eye and brain, where they encysted to form cysticerci.

Laboratory diagnosis is made by identifying gravid proglottids with 5-10 primary uterine

branches in the stool. T. saginata proglottides have 10-15 uterine branches. Cysticercosis is diagnosed by finding cysts in tissue after surgical removal. Treatment: Praziquantel, for cysticercosis in addition surgical.

Taenia saginata (beef tapeworm)

Infection is acquired by humans eating undercooked beef containing the larvae which attach in the small intestine and grow in 3 month to the adult, several meters long worm. Detached proglottides passed with the feces infect cattle. The oncosphere emerge from the egg and are carried to the muscle to develop in cysticerci.

Laboratory diagnosis: T. saginata has, in contrast to T. solium, no hooklets at the scolex but also 4 suckers. Treatment: Praziquantel

Diphyllobothrium latum (fish tapeworm)

After ingestion raw or undercooked fish containing the larvae (plerocercoid or sparganum), the larvae develop in the human gut to the adult worm, releasing eggs, which develop in fresh water into embryos to be ingested by copepod Crustacea's as the first intermediate host. When the copepod is eaten by the second intermediate host, (pike, trout, and perch) the larvae differentiate into plerocercoids in the fish muscle.

Laboratory diagnosis is made by demonstrating in feces the typical eggs or typical parts of the worm: 2 elongated sucking grooves with no hooks at the scolex, eggs are oval with an operculum at one end, proglottides are wider then long, which differentiates the organism from the other cestodes.

Hymenolepis nana (dwarf tapeworm)

The 3-5 cm long worm does not need an intermediate host and eggs can infect humans directly. In the duodenum, hatched eggs develop into cysticercoid larvae and into adult worms, reaching by autoinfection several hundreds of parasites in the gut.

Laboratory diagnosis is made by demonstrating eggs which 6 hooked larvae and 8-10 filaments lying between the membrane of the larvae and the outer shell.

Trematodes (flukes)

including Schistosomia species, Clonorchis sinensis and Paragonimus westermani, Fasciola hepatica, Fasciolopsis buski and Heterophyes heterophyes.

Schistosoma

Three species are known: S. mansoni and S. japonicum live in the mesenteric veins, S. haematobium in the veins of the urinary bladder. Infection occurs by free swimming cercariae, penetrating the skin. The larvae enter the circulation system, enter the liver for maturation into the fluke and migrate into the typical veins system thereafter. The female flukes produce eggs to enter the gut or bladder lumen and eggs can be diagnosed in stool or urine.

The egg hatches in fresh water to penetrate snails and develop into cercariae. S. mansoni is endemic in Africa and Latin America, S. haematobium in Africa and Middle East, S. japonicum in Asia.

Clinically, transient eosinophilia, gastrointestinal hemorrhage, liver granulomas may occur with fibrosis and hepatomegaly, portal hypertension with splenomegaly and esophageal varices. Liver function remains unaltered. In chronic S. haematobium infection, carcinoma of the bladder may occur.

Laboratory diagnosis is made according to the egg form: S. mansoni eggs have prominent lateral spine, S. japonicum small lateral spine and S. haematobium eggs have terminal spine.

Therapy: Praziquantel

Clonorchis sinensis (and closely related Opisthorchis viverrini, Opisthorchis felineus)

also named human liver flukes.

Aquatic snails are infected by human feces containing ova to differentiate to the rediae and further to free swimming cercaria are released from the snails encyst to the stage of metacercariae under the scales of freshwater fish and are capable to infect humans if eaten undercooked. Passing through the duodenum, the metacercariae encyst and enter the biliary ducts and differentiate to the adult hermaphroditic fluke producing eggs which are excreted by the feces. The geographical region is restricted to eastern Asia ans some areas in Siberia. Prevalence in endemic regions up to 35%.There is an association between O. viverrini and cholangiocarcinoma in high endemic areas.

Laboratory diagnosis is made by finding in the stool typical small, brown, operculated eggs.

Paragonimus westermani (lung fluke)

Infection occurs by eating undercooked metacercariae containing crab or crayfish. The larvae encysted in the small intestine and migrate through the mucosa and diaphragma into the lung to differentiate into hermaphroditic adult flukes. Eggs produced are either swallowed or coughed, reaching fresh water and hatch into miracidia, entering snails as the first intermediate host. There, first redia develops and then cercariae which encyst in freshwater crabs as the second intermediate host.

Paragonimiasis is endemic in eastern Asia and central and Western Africa and occasionally in other tropical areas.

Laboratory Diagnosis is made by finding typical operculated eggs in sputum or feces.

Treatment: Praziquantel

Fasciola Hepatica (sheep liver fluke)

causes diseases primary in sheep and other domestic animals. Humans are infected by watercress contaminated with the larvae, they excyst in the duodenum and reach the liver to mature into the adult. Eggs shed into the bile tract are shed by the feces, hatch in fresh

water and enter snails as an intermediate host, develop into cercariae which are shed and encyst on aquatic vegetation.

Laboratory diagnosis is made by identification of eggs in the feces.

Therapy: Praziquantel and bithionol

Fasciolopsis buski

is endemic in Asia and India. Aquatic vegetation is the source of infection when carrying eggs. Attached to the gut mucosa, the fluke differentiate into the adult. Eggs are shed with feces and a snail is necessary as an intermediate host.

Laboratory diagnosis is made by demonstrating characteristic eggs in the feces.

Heterophyes heterophyes

is endemic in Africa, Middle East, Asia. Infection occurs by eating raw fish containing cysts. Mucosa attached larvae produce eggs in the small intestine, passed in the feces and are ingested by snails in brackish water. Cercariae are produced that encyst in certain fish species.

Laboratory diagnosis is made by finding characteristic eggs in the feces.

Nemathelminthes (Nematodes, roundworms)

Nematodes have cylindrical bodies covered with a highly resistant cuticle. The male has a coiled tail, the female is usually larger. The intestinal nematodes include Enterobius (pinworm), Trichuris (whipworm), Ascaris (roundworm), Necator, Ancylostoma (hookworms), and Strongyloides (small roundworm). Diagnosis of Trichinella and Anisakiasis (infection with the third-stage larvae of the round worm Anisakis marinae) is not made by stool examination. Two larvae forms are known: the noninfectious rhabditiform larvae and the infectious filariform larvae.

Symptoms: Itching in the perianal skin area is caused by Enterobius infections, rectal prolapse may occur in Trichuris infection and migrating larvae of Ascaris may cause pneumonia. Anemia occurs in Ancylostoma and Necator infection, Strongyloides may disseminate in various tissues in immunocompromised patients.

Enterobius vermicularis (pinworm)

After ingestion, eggs hatch in the small intestine, differentiate into adult worms and migrate to the colon, where mating occurs releasing eggs which become infectious larvae within 6 h at the anus which may reinfect the host when carried to the mouth.

Enterobius is found worldwide and affects children most commonly.

Laboratory diagnosis is made by recovered eggs from the perianal skin by tape technique. They are not recovered from the feces.

Treatment: Mebendazole or pyrantel pamoate.

Trichuris trichiura

Humans are infected by ingesting eggs in contaminated water or food. Hatching in the small intestine the larvae differentiate in adults who migrate to the colon to mature and produce thousands of eggs daily. Eggs are passed with the feces and form embryos in moist warm soil. Ingestion of eggs completes the cycle.

Laboratory diagnosis is made by demonstrating barrel-shaped (lemon shaped) eggs with a plug at each end in the feces.

Treatment: Mebendazole.

Ascaris lumbricoides

Infection occurs via egg contaminated food or water. Eggs hatches in the small intestine and the larvae migrate through the intestinal mucosa and bloodstream into the lungs, passing through the trachea and are swallowed. In the intestine they develop into adult worms which are up to 25 cm long. Eggs are passed through the feces and form embryos in warm moist soil. Ascariasis is common in the tropics ans in the southeastern US states.

Lab. Diagnosis is made microscopically by detecting oval, irregular surfaced eggs.

Treatment: Mebendazole and pyrantel pamoate.

Ancylostoma duodenale (old world hookworm) and Necator americanus (new world hookworm)

Infection occurs when filariform larvae living in a moist soil penetrate the skin, and are carried to the lungs, migrate to the trachea and are swallowed. In the small intestine they develop into adult worms attached to the mucosa. Eggs are passed in the feces and develop first into feeding, rhabditiform larvae and then into infectious, non feeding filariform larvae.

Hookworms are distributed worldwide in tropical areas.

Laboratory diagnosis is made microscopically by observing typical eggs in the stool, frequently occult blood in the stool and eosinophilia.

Treatment: Mebendazole and pyrantel pamoate.

Strongyloides stercoralis

Infection occurs by penetration of the skin by infectious (filariform) larvae which migrate to the lung. After entering the trachea they are swallowed. In the small intestine the larvae differentiate to adult worms, enter the mucosa and produce eggs, which hatch within the mucosa forming rhabditiform larvae which are passed with the feces. Some larvae form filarial larvae which auto-infect the host by penetrating the mucosa and migrate to the lung. In immunocompromised patients, massive autoinfection may occur with dissemination into organs. The rhabditiform larvae passed with the stool, molt through stages in warm moist soil to form adult female and male worms. The entire life cycle can occur in the soil, but after several free living cycles filarial larvae are formed which are capable to enter the parasitic cycle in humans.

Strongyloidiasis is endemic in the tropics, particularly in south eastern Asia. Prevalence in the US: 0.4%-4%

Laboratory diagnosis is made by finding the larvae form in stool and massive eosinophilia.

Sampling: approx. 2 g of fresh stool.

Optimum for obtaining specimens:

Ascaris lumbricoides, hookworms, Trichuris trichiura occur are constantly in feces but Diphyllobothrium latum and Schistosomia species are seen on an irregular base.

Reference Interval: Report on diagnostic finding

Hemochromatosis DNA Testing

Related Information: Ferritin, Serum or Plasma
Transferrin and Total Iron Binding Capacity, Serum

Synonyms: Hereditary Hemochromatosis; HFE Genotyping

Test Includes: Detection of C282, H 63D, S65C mutation

Background: Hereditary hematochromatosis (HH) is an autosomal recessive disease. It is common in Europe and among Caucasians; the prevalence in Caucasians is 1:400 and 1:10 for carriers. Siblings have a 1:4 risk of developing the disease. Caucasian parents and offspring's have a 1:20 risk of being affected.

The HFE gene is located in the HLA region on chromosome 6p21, encoding a cell surface protein which is similar to HLA class I molecules. The normal heterodimer modulates the affinity of the transferrin receptor for transferrin, the mutation prevents expression of the protein at the position at the cell surface.

Clinically, patients in late stage HH present with arthropathy, cardiomyopathy, hypothyrosis, testicular atrophy, abnormalities of the anterior pituitary gland, pancreas, cirrhosis, diabetes mellitus and skin bronzing, which may be preventable by early diagnosis and treatment.

Useful test in the evaluation of patients with persistent elevated AST or ALT or elevated serum transferrin iron saturation in at least two fasting blood samples. Liver biopsy is a complementary procedure particularly in patients to develop cirrhosis. Used also in risk assessment in families with hemochromatosis. For northern Europe 90% of the patients have a mutation at C282Y in the HLA lined HFE gene, in 40%-60% of non C282Y cases a mutation at H63D occurs with lower penetrance. Only 2% of C282Y/H63D or homozygote H63D patients develop clinically significant signs.

Limitations: Expression of heterozygosis of C282Y mutation does not invariably indicate clinical signs of HH. Fibrosis usually does not occur before the age of 40 years.

The test is not diagnostic for neonatal and juvenile hemochromatosis since different genes are affected.

Sampling: 2 mL EDTA blood, do not freeze, ship to laboratory within 5 days. Please provide clinical diagnosis, ethic background, serum iron, ferritin level, family history of HH.

Reference Interval:

Normal:	absence of detectable mutation
Carrier status:	one mutation detected
Hereditary hemochromatosis or predisposition for disease:	two or more mutations

Hemoglobin Electrophoresis

Background: HbA is the predominant hemoglobin (Hb) in the human body, other normal Hb types are HbA_2, which is gene encoded and modified forms such as Hb A_{1a}, HbA_{1b}, HbA_{1c}. During week 5-8 of gestation, HbF replaces precursor Hb forms (HbGower and Portland), newborns still have 80% HbF, which is replaced by adult Hb during the first 12 month of life.

HbA and HbF are composed of four chains out of two classes (alpha, beta, delta, gamma globulin). For HbA the chains are $alpha_2$ and $beta_2$, for HbA_2 $alpha_2$ and $delta_2$, for HbF $alpha_2$ and $gamma_2$.

The electrophoresis method separates Hb into the normal forms HbA_2 or HbF and abnormal forms such as HbC, HbS, and others.

The parameter is used in the diagnosis of hemoglobinopathies (incidence worldwide 0.17%) such as thalassemia, sickling hemoglobulinemias and structural chain abnormalities and in the evaluation of hemolytic anemias. Cord blood is suitable to detect alpha chain variants (HbF, HbG) and HbS or HbC.

Thalassemia is caused by a deficient synthesis of alpha or beta or rarely delta or gamma chain. Patients present increased levels of HbA_2, HbF, HbH (four beta chains) or HbBarts (four gamma chains).

Other forms of hemoglobinopathies are due to abnormal structures of the alpha, beta delta or gamma globulin, there are approx 900 types known so far.

HbA_2 is elevated in beta thalassemia, sickle cell disease, megaloblastic anemias, and hyperthyroidism. HbA_2 is decreased in alpha thalassemia, beta delta thalassemia, delta thalassemia, iron deficiency, and sideroblastic anemias.

Limitations: Avoid test after blood transfusions.

Sampling: 3 mL EDTA whole blood

Reference Interval:

	Adult	Children 1-2 years	newborn
HbA	97-98.5%	95-98%	18%
HbA_2	1.5-3.2%	1.5-3%	0.25%
HbF	0.8-0.5%	0.5-2%	82%

Children HbF	< 2 months	<50%
	2-4 months	<15%
	5 months	<5%
	6 month-1 year	<2%

Hemopexin, Serum

Background: Hemopexin is a beta-migrating single chain polypeptide with a MW 70 kDa and with 20% carbohydrates. Hemopexin binds heme released by degeneration of hemoglobin, contributing by protecting the iron from escaping from the porphyrin molecule and preserving body iron stores.

Deceased to a lesser extend during decreased production in liver failure; a major decrease is caused by intravascular hemolysis, when the amount of free hemoglobin exceeds haptoglobin binding capacity. Heme-hemopexin complexes are cleared by hepatocytes, lowering hemopexin levels in the circulation. Heme subsequently binds to albumin but is redistributed to hemopexin which is newly synthesized by the liver. Therefore depressed levels of free hemopexin are a long term marker for previous hemolysis after haptoglobin levels have returned to normal.

Sampling: 1 mL serum

Reference Interval: 50-115 mg/dL

Hepatitis A Antibodies, IgG and IgM (IgG anti-HAV, IgM anti-HAV)

Related Information:
Alanine Aminotransferase (ALT), Serum
Alkaline Phosphatase, Serum
Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis C Genotyping
Hepatitis C Virus RNA Quantification (HCV-RNA)
Hepatitis D Serology
Hepatitis E Antibody (Anti-HEV
Prothrombin Time

Background: Transmission of hepatitis A virus occurs via the fecal oral route. Traveling in endemic areas or consumption of contaminated food are major risk factors. After an incubation period of 2-7 weeks the self limiting disease manifests with fever, jaundice, anorexia, and diarrhea. Fecal excretion peaks before the symptoms develop. Specific IgM antibodies appear in acute hepatitis A infection within a week of the clinical onset and persist for 3-6 month with a peak at 3 month and up to one year in 20% of the patients. IgG specific antibodies persist life long and 50% of the adult population of Western countries have IgG type antibodies. Hepatitis A does not become chronic, subclinical courses, particularly in children are common. Rarely, a fulminant Hepatitis A infection is seen. A vaccine is available.

Sampling: 1 mL serum, EDTA or citrate plasma

Reference Interval:
Hepatitis A IgG antibody (IgG anti-HAV):
IgG positive: Immunity protective for at least 5 years.
Hepatitis A IgM antibody (IgM anti-HAV): negative

Hepatitis B (HBV), Serology and Antigen Detection

Related Information:
Alanine Aminotransferase (ALT), Serum
Alkaline Phosphatase, Serum
Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Hepatitis A Antibodies, IgG and IgM (IgG anti-HAV, IgM anti-HAV)
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis C Genotyping
Hepatitis C Virus RNA Quantification (HCV-RNA)
Hepatitis D Serology
Hepatitis E Antibody (Anti-HEV)
Prothrombin Time

Background: HBV is a partially double stranded DNA, enveloped virus of the hepadnavirus family. The major proteins are: The surface antigen (HBsAg), which is part of the envelope, the core antigen (HBeAg) which is located together with the e antigen(HBeAg), a proteolytic product, in the nucleocapsid protein. There are four serologic subtypes of the HBsAg, adw, adr, ayw and ayr for epidemiological use.

The only natural hosts are humans. HBV is distributed worldwide with a high prevalence in Asia. Mode of transmission are via blood, sexual intercourse and perinatally. About 5% of HBV infected patients become chronic carriers defined as HBsAg persisting for more than 6 month. Chronic carriers are more likely to develop in newborns (up to 90%) than in adults, and subsequently with a high risk of developing hepatocellular carcinoma. Immunity lasts lifelong when antibodies directed against HBsAg are produced.

Clinically, many HBV infections are asymptomatic but fulminant courses may occur particularly in patients coinfected with HIV or with preexisting liver damage. The Incubation period varies between 1 and 6 month (usually 4-12 weeks)

Staging of HBV infection:

Test	Acute disease 2-12 weeks	Window phase 10-15 weeks	Recovery years	Chronic carrier
HBs Antigen	positive	negative	negative	positive
HBs Antibodies	negative	negative	positive	negative
HBc Antibodies				
-IGM	positive (early)	positive	negative	negative
-IgG	positive (late)	positive	positive	positive
HBe Antigen	positive	negative	negative	positive or negative
HBe Antibodies	negative	positive	positive	positive or negative

HBs Antigen can be detected 1-7 weeks before liver enzymes levels rise, 50% of the patients are positive 3 weeks after onset of the acute hepatitis, at week 17 only 10 % are still positive. Markers for infectivity are HBs Antigen and HBe Antigen. HBe Antigen usually convert to negative within 3-6 weeks,

persistence for more than 10 weeks suggests risk for development of chronic Hepatitis B. Infectivity is approx. 5 fold as high if HBe Antigen and HBs Antigen are co-present as compared to HBs Antigen alone. In chronic carriers HBeAg may become negative and HBe Antibodies may develop after more than 6 month, but HBs Antigen persists.

A quantification of HBs Antibodies is useful in the assessment of the immune status after vaccination.

Sampling: 1 mL serum citrate plasma or EDTA plasma for each test

Hepatitis B core Antibody (Anti-HBc)

Reference Interval: negative

Hepatitis B core IgM Antibody (IgM anti-HBc)

Reference Interval: negative

Hepatitis Be Antigen (HBeAg)

Reference Interval: negative

Hepatitis Be Antibody (Anti-HBe)

Reference Interval: negative

Hepatitis Bs (surface) Antigen (HbsAg)

Reference Interval: negative

Hepatitis Bs (surface) Antibody quantitative (Anti-HBs)

Reference Interval: negative < 10 IU/L

Quantification for immune status assessment:

Recommendations for vaccination:

< 20 IU/L	immunity not sufficient, immunization necessary	
Immunity present	20–50 IU/L	booster within weeks
	51–100 IU/L	check in 6 month
	101–1000 IU/L	check in 1 year
	1001–7500 IU/L	check in 2–3 years
	>7500 IU/L	check in 5 years

Hepatitis B Virus DNA Detection (HBV-DNA)

Related Information:

Alanine Aminotransferase (ALT), Serum
Alkaline Phosphatase, Serum
Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Hepatitis A Antibodies, IgG and IgM (IgG anti-HAV, IgM anti-HAV)
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis C Serology
Hepatitis C Virus RNA Quantification (HCV-RNA)
Hepatitis D Serology
Hepatitis E Antibody (Anti-HEV
Prothrombin Time

Background: Chronic viral hepatitis is caused by Hepatitis B virus (HBV) or Hepatitis C virus. In most of the HBV infected patients, antibody response to HBs Antigen occurs and persists lifelong. 10% of the HBV infections are characterized by the absence of HBs Antibodies and the presence of HBs Antigen and HBc Antigen. Determination of HBV DNA is a supplement test to determine carrier state and quantification provides information of the infectivity and is of prognostic relevance. It is useful for the measurement of the response to antiviral therapy.

Sampling: 2 mL serum or EDTA blood, (heparinized blood is not accepted)

Reference Interval: Determination of the HB virus load
DNA not detectable: < 1000 Virus particles (VP) / mL

Hepatitis C Antibody (Anti-HCV)

Related Information:
Alanine Aminotransferase (ALT), Serum
Alkaline Phosphatase, Serum
Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Hepatitis A Antibodies, IgG and IgM (IgG anti-HAV, IgM anti-HAV)
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis C Genotyping
Hepatitis C Virus RNA Quantification (HCV-RNA)
Hepatitis D Serology
Hepatitis E Antibody (Anti-HEV)
Prothrombin Time

Background: Hepatitis C is a single stranded RNA enveloped virus causing a slowly progressive and often asymptomatic hepatitis. Worldwide 180 million people are chronic carriers. About 30-50% of the patients recover; in 70-50% the infection becomes chronic. Cirrhosis develops in 20% of the patients after more than 20 years. HCV contribute to the prevalence of acute forms of hepatitis 20%, 60% to the cases of chronic hepatitis and 20-30% for cirrhosis of which 1-4% annually may develop hepatocellular carcinoma, whereas alcoholism enhances the rate of carcinoma. Antibody titer rises after 4-10 weeks post exposure. 80% of the infected become positive within 15 weeks post exposure.

Hepatitis C is transmitted by contact with human blood. There is no insect vector in opposite to the other flavivirus the yellow fever virus. 60% of HCV infections are due to shared needles in IV drug abusers and rarely by sexual contact. The risk of acquiring HCV by sexual contact however increase with coinfectoion with other sexual transmitted diseases. The risk of mother to child transmission is less than 5%, for needlestick infections less than 0.1%.

Limitations: False positive results may occur in pregnant women (0.2%), in recent immunized individuals against influenza virus, hypergammaglobulinemia, positive rheumatoid factor, connective tissue diseases. False negative results occur in patients with essential mixed cryoglobulinemias, hemodialysis, and immunodeficient patients.

Sampling: 1 mL serum EDTA or citrate plasma

Reference Interval: Antibody negative
Validation by Immunoblot

Hepatitis C Genotyping

Related Information:
Alanine Aminotransferase (ALT), Serum
Alkaline Phosphatase, Serum
Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Hepatitis A Antibodies, IgG and IgM (IgG anti-HAV, IgM anti-HAV)
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis C Serology
Hepatitis C Virus RNA Quantification (HCV-RNA)
Hepatitis D Serology
Hepatitis E Antibody (Anti-HEV)
Prothrombin Time

Background: There are 6 HCV genotypes and 50 subtypes known. The genotypes are based on differences of the genes that encode one of the two envelope proteins. Genotype 1,2,3 are found worldwide, genotype 4 mainly in Egypt and Zaire, genotype 5 in South Africa, genotype 6 in Asia. Subtypes are described with letters. There is an association between disease progression and genotype: Genotype 1 b and genotype 4 causes a more aggressive form of hepatitis,

Sampling: 5 mL EDTA blood kept at 4°C and ship as soon as possible or freeze to -20°C.

Reference Interval: Report on diagnostic findings:
Genotypes 1, 2, 3
Determination of subtype a, b

Hepatitis C Virus RNA Quantification (HCV-RNA)

Related Information:
Alanine Aminotransferase (ALT), Serum
Alkaline Phosphatase, Serum
Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Hepatitis A Antibodies, IgG and IgM (IgG anti-HAV, IgM anti-HAV)
Hepatitis B Virus DNA Detection (HBV-DNA)

Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis C Serology
Hepatitis C Genotyping
Hepatitis D Serology
Hepatitis E Antibody (Anti-HEV)
Prothrombin Time

Background: Hepatitis C is a member of the flavivirus family. It is an enveloped virus with a single stranded positive polarity RNA. The onset of Hepatitis C is usually slow; the mean incubation time is 8 weeks. Patients without receiving treatment remain in 80% chronic carriers for at least one year. Chronic active hepatitis occurs in 10% of theses patients. About 20% of the chronic carriers develop cirrhosis.

HCV–RNA assay becomes positive within days of exposure before ALT or AST becomes usually moderate elevated.

The assay is useful in early diagnosis and therapy monitoring.

Sampling: 3 mL EDTA blood kept at 4°C and ship as soon as possible or freeze to -20°C.

Reference Interval: PCR Report
RNA not detectable: < 100 VP/mL

Hepatitis D Antibody (Anti-Delta), Serology

Related Information: Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Hepatitis A Antibodies, IgG and IgM (IgG anti-HAV, IgM anti-HAV)
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis C Antibody (Anti-HCV)
Hepatitis C Genotyping
Hepatitis C Virus RNA Quantification (HCV-RNA)
Hepatitis E Antibody (Anti-HEV)

Background: Hepatitis delta agent (HDV), a RNA virus, occurs only in patients already infected with Hepatitis B virus. Coinfection increases the risk of fulminant and to develop chronic hepatitis with cirrhosis and carcinoma. Mode of transmission is more likely by i.v. drug use than sexual transmitted. Up to 20% of HBV positive individuals may carry in endemic areas HDV, in chronic liver disease patients up to 60%. Antibodies develop 5-7 weeks after infection.

Limitations: Patients with rheumatoid factors or lipemia may have false positive results.

Sampling: 1 mL serum or EDTA plasma

Reference Interval: Negative for IgG and IgM

Hepatitis E Antibody (Anti-HEV)

Related Information: Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis C Antibody (Anti-HCV)
Hepatitis C Genotyping
Hepatitis C Virus RNA Quantification (HCV-RNA)

Background: Hepatitis E is a self limiting hepatitis comparable to Hepatitis A. Route of transmission: Fecal-oral, particularly by contaminated water. The disease is endemic in India, Middle East, Southeast and Central Asia with seroprevalence between 2% and 30%. Acquisition of antibodies occurs predominantly during the first 2 decades of life. Incubation period is 15-60 days; no chronic infection has been described.
Serology: IgM antibodies are detectable 1-4 weeks after exposure, IgG can persist for 2 years. PCR is of limited use since no chronic state is known.

Sampling: 1 mL serum or EDTA plasma

Reference Interval: Negative for IgG

Herpes Simplex Virus Type 1, 2 (HSV), DNA Detection

Related Information: Herpes Simplex Virus Type 1, 2 (HSV), Serology

Background: The test detects nucleic acid of HSV-1 and HSV-2 in blood, CSF or swaps. In culture methods sensitivities are 40%-70% for genital ulcers and 40%-70% for neonatal encephalitis, the PCR improves the sensitivity substantially. PCR is considered as the test of choice for CNS HSV infection due the rapid and sensitive performance, however, a negative result cannot rule out HSV infection. HSV encephalitis is caused in most of the cases by HSV-1, HSV meningitis, which is more frequent, by HSV-2.

Sampling: Swap or vesicle fluid: Cytobrush in transport buffer
CSF/liquor: 2 mL
EDTA blood: 2 mL
Bronchial lavage fluid

Rapid transport to laboratory required, if more than 2h transit time expected, keep at 4°C, if 8h expected, freeze. Do not use heparinized tubes.

Reference Interval: HSV-1 or HSV-2 DNA not detected

Herpes Simplex Virus Type 1, 2 (HSV), Serology

Related Information: Herpes Simplex Virus Type 1, 2 (HSV), DNA Detection

Background: Herpes simplex virus (HSV)-1 and Herpes simplex virus (HSV)-2 also ICTV named as Human herpesvirus-1 and -2 are members of the subfamily Alphaherpesviridae in the genus Simplexvirus.

Herpesviridae have an icosahedral core surrounded by a lipoprotein obtained when budding from the nuclear membrane, a large seize of 120 – 200 nm, and a double stranded DNA.

HSV-1 peak incidence of primary infection occurs in childhood, for HSV-2 during adolescence. Adult seroprevalence in HSV-1 is 75% to 100%, for HSV-2 5%-95%. Main route of transmission for HSV are oral secretions, for HSV-2 genital secretions.

Herpes simplex virus types 1 and 2 and varicella viruses causes vesicular rash, HSV-1 causes lesion appears above the waist, HSV-2 below. HSV-1 causes acute gingivostomatitis, recurrent herpes labialis, keratoconjunctivitis, and temporal lobe encephalitis. HSV-2 causes neonatal disseminated disease, aseptic meningitis, recurrent genital herpes; HSV-1 is transmitted by respiratory secretions and saliva, HSV-2 via sexual contact and perinatal infection. Nearly all of the HSV-2 seropositive individuals shed virus intermittently from the mucosa.

Herpes simplex -1 or HSV-2 encephalitis, although rare with an incidence of 1 case per 250 000 population per year is the most common form of sporadic fatal encephalitis. 95% of HSV encephalitis is caused by HSV-1. One third of the adults developing herpes encephalitis have a primary infection, and those who have antibodies to HSV at the onset of encephalitis, 90% did not have had recurrent HSV-2 infection.

Neonatal herpes infection occurs if the mother has a primary infection during delivery. Infants born to seronegative mothers have an increased risk to acquire HSV-2 during delivery than infants born by seropositive mothers. More than 50% of the newborns become infected, mortality in disseminated infection in newborns exceed 70%. Prompt initiation of antiviral therapy may prevent development of neurologic impairment.

Therapy: For HSV -1 and-2 the DNA polymerase inhibitors acyclovir, valaciclovir, famciclovir, and in case of resistance foscarnet or cidofovir are available. Theses drugs have been shown to reduce duration of viral shedding, time of healing of lesions, duration of pain, complication rate. Intravenous administration of acyclovir is indicated even before laboratory confirmation in patients suspected systemic disease or herpes encephalitis.

Sampling: 1 mL serum

Reference Interval:	Differentiation of immunoglobulin classes	
IgA antibody	negative	< 0.9 COI
	borderline	0.9 – 1.0 COI
	positive	> 1.0 COI
IgG antibody	negative	< 20 RE/mL
IgM antibody	negative	< 0.9 COI
	borderline	0.9 – 1.0 COI
	positive	> 1.0 COI

IgG differentiation to IgG-HSV-1 and IgG-HSV-2 type

IgM antibodies are produced in primary infection and to a lesser extend during recurrent disease. Unspecific reactivity occurs. Increased IgA antibodies support the diagnosis of recent or recurrent infection.

Herpes-Zoster see Varicella-Zoster Virus, Serology

High Density Lipoprotein Cholesterol, Serum or Plasma

Related Information: Apolipoprotein A-1 and B-100, Serum
Cholesterol, Total, Serum or Plasma
Lipoprotein (a), Serum
Low Density Lipoprotein Cholesterol
Triglycerides, Serum or Plasma

Synonyms: Alpha1 Lipoprotein Cholesterol ; HDL ; HDLC ; HDL Cholesterol

Background: The HDL fraction summarizes a heterogenous class of lipoprotein particles. The level of HDL is considered as a major risk factor for coronary heart diseases (CHD) in an inverse related manner.

CHD risk increases 2%-3% for every 1 mg/dL decrease in HDL.

Increase in HDL is seen in physical exercise, weight loss, and moderate alcohol consumption as well in medications as niacin, fibrates, statins, resins, estrogens. A decrease is associated with smoking, obesity, pregnancy, stress, hospitalization, and medications as probucol, corticosteroids, androgens, progestins, diuretics, propanolol. Decrease also occurs during chronic renal failure, type II diabetes, myocardial infarction, thyroid dysfunction.

Hereditary defects of metabolism are: Familial hyperalphalipoproteinemia which is a deficiency of the cholesterol ester transfer protein, causing an increase in HDL and decrease in LDLC and triglycerides.

Tangier disease, apolipoprotein A-I deficiency, lecithin–cholesterol acyltransferase deficiency and fish eye disease are further types of genetic disorders affecting HDL.

Sampling: 1 mL serum or plasma. For optimal results, the patient should be on a stable diet for 2-3 weeks, stable body weight and fasting for 10h.

Reference Interval:	Male standard risk	30–50 mg/dL
	favorable or protective	> 50 mg/dL
	Female standard risk	40–60 mg/dL
	favorable or protective	> 60 mg/dL

Histamine, Urine or Plasma

Related Information: Immunoglobulin E

Background: Histamine is a mediator of anaphylaxis or other allergic states such as urticaria, flushing, asthma, and tachycardia. Histamine is released by basophil cells and mast cells via IgE receptor mediation. May also be elevated in myeloproliferative diseases and in carcinoid tumors (gastric origin).

Limitations: False positive during urinary tract infections.

Sampling: Plasma: 2 mL of EDTA plasma, freeze immediately and ship frozen.
Urine: ship a 10 ml aliquot of a 24h urine collected in a clean container. Keep cool. Note total quantity.

Reference Interval: Plasma: 0.3-1.0 ng/mL
Urine: 10-35 ng/mL or < 45 µg/g creatinine

Histone-Antibodies

Related Information: Antinuclear Antibody, Antibodies, dsDNA, Antibodies, ssDNA, Smith (Sm) Antibody

Background: Histones are tetrameric proteins located at the nucleolus. The tetramers are composed of H2A-H2B and H3-H4.

Useful test in drug induced systemic lupus erythematosus (SLE). Relevant antibodies are of the IgG and IgA type, IgM antibodies are present in healthy individuals and are directed against complexed DNA with H2A-H2B. In drug induced systemic lupus erythematosus antibodies directed against histones are present in 95% in high levels, and in 20%-70% in non-drug induced systemic lupus erythematosus. Absence of SLE antibodies such as Antinuclear Antibody, native ds-DNA Antibody, Smith (Sm) Antibody and high levels of Histone Antibodies favor the diagnosis of drug induced SLE. Clinically the drug induced SLE is characterized by skin and joint symptoms without renal involvement. Antibodies to ssDNA are present in 70%-90%, but no antibodies to dsDNA.

Felty syndrome is associated in up to 85% with high level histone antibodies, 5%-15% of patients with rheumatoid arthritis or primary biliary cirrhosis have elevated histone antibody levels as well as in autoimmune hepatitis, scleroderma, and neoplastic diseases.

Sampling: 1 mL serum

Reference Interval: Negative: < 20 U/mL

HIV-1/HIV-2 Serology

Test includes: HIV antibody detection by ELISA, confirmation of ELISA positives by Western Blotting, p-24 Antigen detection on request

Background: Human immunodeficiency virus (HIV) is the etiologic agent of AIDS. Acute infection is either symptome free or presents with flu-like disease. During the stage of acute infection at week 2-3 post infection virus can be detected in the plasma by p24 antigen assay or by PCR based viral DNA test. After 3 weeks, antibodies can be detected in serum or plasma.

Screening for HIV is performed by highly sensitive and specific ELISA (EIA) method; positive results have to be repeated by a second sample due to serious consequences of the diagnoses to rule out switched samples or contaminations and subsequently has to be confirmed by the Western blot method. HIV-2 is closely related to HIV-1, endemic in West Africa causing the same clinical disease, but time to develop AIDS may be longer.

Limitations: A positive HIV EIA must be confirmed by a second method that has to be based on an alternative principle of antibody detection. Cross reactivities in the screening EIA based test have been rarely described. Cross-reactions may be due to histocompatibility antigen mismatches or very rare in other viral diseases such as influenza.

Serology cannot be used in infants born to an HIV positive mother due to maternal antibody transfer by the placenta. Virus cultivation or DNA detection are more appropriate.

Sampling: 1 mL serum

Reference Interval: p-24 antigen detection: negative
HIV1/HIV-2 antibody detection: negative

HLA-B27

Related Information: C4Complement
Rheumatoid Factor, Serum or Body Fluid
Yersinia enterocolitica and Yersinia pseudotuberculosis, Culture and Serology

Background: HLA-B27 is an allele of the HLA-B locus. It is predictive marker for ankylosing spondylitis (AS). A patient tested positive has a 100 times greater like hood to develop AS than a negative patient.

Epidemiology: HLA B-27 allele is present in 3%-4% of African-Americans, in 6%-8% of Caucasians, and in 1% of Asians.

Sensitivity and specificity: 90% of patients with ankylosing spondylitis (AS) are positive. 10% of normal subjects are HLAB27 positive. Most of the HLAB27 subtypes are associated with AS.

The antigens is also associated, but to a lesser extend with Reiter syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, or post infectious arthritis as well as congenital deficiency of C4 and C2, adrenal hyperplasia.

Sampling: 3 mL EDTA or ACD blood

Reference Interval: Negative

Homocyst(e)ine Total, Plasma

Related Information: Cholesterol, Total, Serum or Plasma
Factor V Mutation (Leiden Mutation),
Folic Acid, Serum
Methylmalonic Acid, Serum, Plasma or Urine
Vitamin B 12 , Plasma or Serum

Background: 80%-90% of the homocysteine is protein bound in the plasma, 5%-10% circulates as homocysteine, 5%-10% is bound to mixed disulfides, 2% is unbound (free).

Metabolized from the essential amino acid methionine, it undergoes either remethylation to methionine, transsulfuration to cysteine and glutathione (vitamin B 6 and riboflavin needed) or oxidation to homocysteine and mixed disulfides.

Useful as an independent risk factor for atherosclerosis. An increased value is a marker for thrombophilic state on risk for thrombosis (arteria and venous).

When increased a marker for vitamin deficiency (B6, B12 riboflavin) and folic acid.

Raised levels in newborns may indicate inborn errors of cobalamin and folate metabolism and the rare autosomal recessive disorder of homocystinuria.

Elevated levels are found in patients with renal insufficiency and hypothyroidism.

Highly prevalent, in 10%-15% of the population, a thermolabile variant of 5,10-methylenetetra hydrofolate reductase present with raised blood homocysteine levels and require higher folic acid intake.

Sampling: Optimal is fasting 2 mL serum and immediately centrifuged.

10% increase per hour if not separated, slowed by placing on ice.

Reference Interval:

0-30 years		4.6-8.12 µmol/L
30-59 years	male	6.3-11.2 µmol/L
	female	4.5-7.9 µmol/L
> 59 years		5.8-11.9 µmol/L

Alternative: overall 95 th percentile 5-15 µmol/L

Homovanillic Acid (HVA), Urine

Related Information: Catecholamines, Fractionation, Plasma
Catecholamines, Fractionation, Urine
Vanillylmandelic Acid, Urine

Background: HVA is a major terminal metabolite of dopamine.

Patients with neuroblastoma excrete dopamine and vanillylmandelic acid. Neuroblastomas are third (7%-11%) among malignancies during childhood, behind leukemia and gliomas. Diagnostic sensitivity depends on the tumor stage, in early stages 60%-70% stage I/II and 80% for stage II increasing to 98% in stage IV.

In pheochromocytoma sensitivity of urinary excretion for tumor detection is 96% for catechol-

amines, 96% for metanephrine, and 89% for vanillylmandelic acid.

Sampling: Ship an aliquot of 10 mL of a 24h urine, collected in a container prefilled with of 10 ml of a 20% hydrochloric acid solution. Ph should be between 2 and 4. Note total quantity! Avoid aspirin, disulfiram, reserpine, pyridoxine 2 days prior to collection; avoid levodopa 2 weeks prior to the testing.

Reference Interval:

age in years	mg/g creatinine, 95% percentile
0-1	32.6
2-4	22
5-9	15.1
10-19	12.8
>19	7.6

Alternative value for adults: < 6.9 mg/24 h

Human Herpesvirus Typ 6, Serology

Synonyms: HHV-6; Herpesvirus-Typ 6

Background: HHV-6 is a member of the subfamily beta-Herpesviridae and in the genus Roseolovirus. HHV-6 was originally isolated from T cell cultures derived from the blood of patients with AIDS. In contrast to CD4 T cell infection with HIV, HHV-6 infection is rapidly controlled by the immune system. HHV-6 is closely related to cytomegalovirus and HHV-7 viruses. There are two HHV-6 variants; HHV-6 B is the primary etiologic agent of exanthema subitum, for HHV-6 A (and HHV-7) no single disease has been associated with. HHV-6 (and HHV-7) infection occurs early in life, virus is present in saliva of most adults. Virus replicate in CD4 and in CD8 T cells, in natural killer cells, monocytes, epithelial cells and in brain cells.

Exanthema subitum (roseola infantum) in young children is characterized by fever, sometimes associated with a mild respiratory illness and lymphadenopathy, followed by the appearance of a fine maculopapular rash spreading from the trunk to the extremities. High fever for 3-4 days and inflammation of the tympanic membranes may occur, but rash may be present in only 10% of the patients. It was estimated that up to 25% of all hospital admissions of children under the age of 3 years with acute febrile illness is due to HHV-6 infection. Primary HHV-6 infection may also cause seizures in infants which accounts for up to 30% of all febrile seizures under the age of 3 years. Rarely, serve courses have been described such as meningoencephalitis, fulminant hepatitis or pancytopenia. In adolescents, HHV-6 may cause mononucleosis like illness.

A definite role in Multiple sclerosis and lymphoproliferative disorders has not been established and is still under investigation.

In immunocompromised patients, HHV-6 has been associated with intestinal pneumonia and encephalitis.

Serology: IGM antibody is the first antibody to be produced in response to acute (primary) as well as in recurrent disease, although the amount of produced IgM is generally higher during primary infection. Paired samples 10-20 days apart are recommended for serological diagnosis.

Therapy: Some effect was seen with Foscarnet and Cidofovir

Sampling: 1 mL serum

Reference Interval: Differentiation of immunoglobulin class

IgG antibody negative:	< 0.9 COI
borderline:	0.9 – 1.1 COI
positive:	> 1.1 COI
IgM antibody negative:	< 0.9 COI
borderline:	0.9 – 1.1 COI
positive:	> 1.1 COI

Human Papillomavirus (HPV) DNA

Synonyms: HPV, HPV Test, HPV screen

Background: HPV primarily infects keratinizing mucosal squamous epithelium. HPV is a member of the family of Papovaviruses, which are double stranded, circular, supercoiled DNA viruses with an icosahedral nucleocapsid. Carcinogenesis by HPV involves two proteins encoded by gene E6 and E7, interfering with the tumor suppressor gene p53 and Rb. More than 100 types of papilloma viruses are known, some highly correlated to carcinoma of the cervix.

Although prevalence of HPV infection as a sexual transmitted disease (STD) among women is high, only a faction develops high grade squamous intraepithelial lesions with few progressions to cervical carcinoma. Co-risk factors are smoking, oral contraceptives, nullipara, and other STDs. Immunocompetent women are able to clear the infection within 1-2 years. The test is useful in monitoring patients demonstrating minor cytological abnormalities by Pap test or any abnormal cytologic results or clinical finding such as koilocytosis, condyloma acuminatum, low grade squamous intraepithelial lesions, high grade squamous intraepithelial lesions, invasive cervical squamous cell carcinomas and adenocarcinomas.

Of the 30 known anogenital HPV types, 13 types are implicated in the pathogeneses of cervical cancer: 16,18,31,33,35,39,45,52,58,59,68. The most common high risk types are: 16,18,31,33,35,45. Low risk types are: 6,11,42,43,44.

Sampling: Cytobrush in special transport medium on request to obtain from MEDLAB

Reference Interval: Report on diagnostic finding

Humoral Immunoglobulin Production, Liquor see Cerebrospinal Fluid (CSF, Liquor)

Hydantoins see Phenytoin, Serum

5-Hydroxyindoleacetic Acid (5-HIAA) Quantitative, Urine

Related Information: Serotonin, Blood

Background: 5-HIAA is a serotonin metabolite excreted in larger amounts by carcinoid neoplasms of the gastrointestinal tract or respiratory tract and other sites. Used in the diagnosis and monitoring of carcinoid tumors. Urinary excretion > 24 mg/24h favors the diagnosis, particularly if clinical signs are present as flushing, hepatomegaly, diarrhea, and bronchospasm.

Limitations: However, some tumors release non-hydroxylated indole acid which is not measured in the assay. Renal diseases may lower urinary secretion.

Increase in patients with malabsorption, (celiac disease, tropical sprue), chronic obstruction.

Urinary increase after ingestion of food rich in serotonin such as avocados, bananas, cantaloupe, chocolate, eggplants, dates, kiwi, melon, nuts, pineapples, plantain, plums, tomatoes.

Drugs increasing 5-HIAA are acetaminophen, salicylates, phenacetin, naproxen, methocarbamol, imipramine, isoniazid, MAO-inhibitors, methenamine, methyldopa, reserpine, phenothiazine.

Sampling: 10 mL aliquot of a 24h urine, collect in a prefilled container with 10 mL of 20% hydrochloric acid, note total quantity.

Reference Interval: 0.6 – 8.2 mg/24h

17-alpha-Hydroxyprogesterone (17-OHP)

Related Information: Adrenocorticotropic Hormone, ACTH, Plasma
Androstenedione, Serum
Cortisol, Serum or Plasma
Progesterone, Serum

Background: 17-OHP is a precursor of cortisol and synthesized by the adrenal cortex, ovaries, testes, and placenta.

It is a marker for patients with congenital adrenal hyperplasia (CAH), characterized as an autosomal recessive disorder by deficiency of cortisol due to 21 hydroxylase deficiency (90% of the cases) which leads to ACTH induced adrenal hyperplasia. Patients present with virilization and mineralocorticoid deficiency, increased 17-ketosteroid and pregnanetriol urine values.

The test is used

- In CAH newborn screening and diagnosis and therapy monitoring on cortisol medication.
- In the evaluation of hirsutism, infertility, hermaphroditism which may be caused by 17-hydrolase deficiency.
- In the diagnosis of endocrine active tumors.

Limitations: 17-OHP is elevated to a lesser extend in 11 beta hydroxylase deficiency. To differentiate both 11-deoxycortisol and desoxycorticosterone have to be determined.

Sampling: 2 mL serum or heparin plasma, peak level in the morning. Separate serum or plasma within 6h. Newborn screening at the age of 2-4 days recommended, not earlier than day 2.

Reference Interval:				(ng/mL)
	Infants	cord blood		7.4-18.7
		3 days to 60 days		0.1-9.4
		3 month to 11 years		< 0.9
		12-20 years		< 1.8
	Adult	male		0.4-3.3
		female	follicular	0.1-1.2
			luteal	0.4-4.8
			postmenopausal	0.1-0.6

Newborn screening (ng/dL) (dryed whole blood spot)

weight	borderline	congenital adrenal hyperplasia suggested
<1299 g	>13500	
1300-1699 g	11500-13400	>13500
1700-2199 g	6500-8900	>9000
>2200 g	4000-8900	>9000

Hydroxyproline, Total, Urine

Related Information: Alkaline Phosphatase, Serum
Alkaline Phosphatase, Liver-Intestine-Bone-Isoenzymes, Serum
Calcium (Ca), Total, Serum
Osteocalcin, Serum or Plasma
Pyridinolines

Test includes: Creatinine, Total, Urine

Background: A marker for bone metabolism and bone turnover. Elevated in Paget s disease, healing phase after fractures, primary and secondary hyperparathyroidism. The parameter is sensitive to diet, low dose gelatin were used for establishing reference intervals. For best results avoid foods containing gelatine (cooked collagen) and meat for 1-2 days prior to collection. Ice cream, candies, desserts may contain gelatine as well. Avoid aspirin.

Sampling: Ship to the laboratory a 10 ml aliquot of a 24h urine, collect in container pre filled with 1 mL glacial acetic acid. Note total quantity.

Reference Interval:	Children	up to 1 month	2000 µmol/g creatinine
		1-12 month	1500 µmol/g creatinine
		1-6 years	1000 µmol/g creatinine
		7-14 years	200 µmol/g creatinine
	Adults	> 15 years	30 µmol/g creatinine

Ident Card see Paternity Testing

Immunoelectrophoresis, Serum

Sampling: 1 ml serum

Reference Interval: Report on diagnostic findings
Including immunoglobulins

Immunoglobulin E (IgE)

Related Information: Aspergillus fumigatus, Serology
Eosinophil Count
Histamine, Urine or Plasma

Background: IgE is a monomeric immunoglobulin composed of epsilon heavy chains and two kappa or lambda chains with a MW of 190 kDa, carbohydrate is 12%, serum half life of 2 days. It does not fix complement nor does it cross the placenta. Plasma cells producing IgE are predominantly located along the respiratory and gastrointestinal membrane.

The Fc region binds to the high-affinity IgE receptor on the surface membrane of mast cells and basophils. Bound IgE serves as a receptor for antigens after crosslinking by allergens; mediators such as histamine, prostaglandin D2, kallikrein, leukotrienes C, D and E are released and an immediate type I hypersensitivity reaction occur, which may include urticaria, sneezing, rhinorrhea, conjunctival edema, attacks of asthma and possibly anaphylactic shock. The synthesis is controlled by interleukin-4 and interleukin-13.

Function: Main host defense mechanism against parasites such as Strongyloides, Trichinella, Ascaris, Hookworms. IgE specific for parasite proteins bind to receptors on eosinophils and trigger antibody dependent cellular cytotoxicity (ADCC) response.

In atopic disease levels exceed 400 IU/mL, very high levels > 1000 to 20000 IU/mL may be reached in bronchopulmonary aspergillosis, asthma, atopic eczema, IgE myeloma, and parasitism. The level of IgE does not strongly correlate with atopy; it may be in the upper normal range.

Elevated cord blood levels may predict atopy in later life.

Sampling: 2 mL serum.

Reference Interval: (1 IU =2.4 ng protein)

Adult:	< 100 IU/mL
Cord blood:	< 2.0 IU/mL
Newborn:	< 1.0 IU/mL
Children:	
up to 1 year:	< 16 IU/mL
1 – 2 years:	< 29 IU/mL
3 – 4 years:	< 58 IU/mL
5 – 7 years:	< 79 IU/mL

Immunoglobulin A (IgA), Serum, Saliva, CSF

Related Information: Cryoglobulin, Qualitative, Serum or Plasma
Endomysial Antibodies
Gliadin IgG/IgA Antibodies
Immunoglobulin G (IgG), Serum, Urine, CSF
Immunoglobulin G Subclasses (IgG subclasses)
Protein Electrophoresis, Serum and Protein, Total, Serum

Background: About 6% of the serum immunoglobulins are IgA class and play a major role in mucosal immunity. IgA class immunoglobulins are secreted with milk, colostrum, saliva, tears, and into the respiratory and intestinal system. The mechanism of action includes inhibition of adherence of microorganisms to the surface of mucosal cells. As a multivalent immunoglobulin with high avidity of binding to antigens it is relevant in neutralization of viruses and in combining with antigens in food, preventing absorption and allergic reactions.

IgA fixes complement in the alternative pathway, has opsonizing properties for phagocytosis through an Fc receptor on macrophages, it induces eosinophil degranulation, linking it to anti-parasitic response.

Half life 5 to 6.5 days; daily synthetic rate is 24 mg/kg/day; the placenta is not crossed. Useful in evaluation of humoral immune status. Used to evaluate lymphoproliferative diseases such as multiple myeloma and `Mediterranean` lymphoma with bowl involvement. IgA myelomas are characterized by IgA > 2g/L, hypercalcemia, hyperviscosity and 25% of the patients present a monoclonal IgA.

IgA may be decreased in chronic sinopulmonary diseases, ataxia telangiectasia in congenital IgA deficiency associated with autoimmune diseases and antibodies to IgA.

In Berger disease, an IgA glomerulonephritis, 50% of the patients present with elevated serum IgA.

IgA deficiency is associated with chronic diarrhoea, giardiasis, celiac disease, with autoimmune diseases such as rheumatoid arthritis.

Sampling: 2 mL serum, 1 mL saliva, 1 mL CSF. If cryoglobulinemia or macroglobulins are expected, sample should be kept at 37°C.

Reference Interval for Serum:

Children: (g/L)	male	female
1-30 days	0.01-0.22	0.01-0.19
1 month - 6 month	0.07-0.56	0.01-0.59
6 month - 1 year	0.09-1.07	0.015-0.9
1-3 years	0.18-1.71	0.25-1.41
4-6 years	0.60-2.31	0.47-2.06
7-9 years	0.77-2.52	0.41-2.18
10-12 years	0.61-2.69	0.73-2.39
13-15 years	0.42-3.04	0.82-2.96
16-18 years	0.89-3.14	0.90-3.22
Adults: (g/L)	0.7-3.8	

Alternative Reference Interval for Serum (g/L)

	mean white male	mean white female
20-24 years	1.32	1.28
25-29 years	1.4	1.35
30-34 years	1.5	1.42
35-39 years	1.59	1.49
40-44 years	1.7	1.59
45-49 years	1.81	1.65
50-54 years	1.3	1.74
55-59 years	2.06	1.83
60-64 years	2.2	1.93
65-69 years	2.34	2.03
70-74 years	2.49	2.14
>75 years	2.66	2.26

Reference Interval for Saliva: 20-200 mg/L

Reference Interval for CSF: 2-6 mg/L

Immunoglobulin G (IgG), Serum, Urine, CSF

Related Information: Immunoglobulin G Subclasses (IgG subclasses)
Protein, Total, Serum

Background: Heavy chain classification of immunoglobulins leads to five classes with IgG class displaying the highest plasma concentration. Polyclonal gammopathy is seen in chronic inflammatory or autoimmune diseases. Plasma cell myeloma, lymphoma or non malignant conditions may be related to monoclonal gammopathy. The quantitation is useful in monitoring IgG myeloma, evaluate humoral immunity, and follow up immunodeficiency states. The monoclonal IgG fraction is elevated to more than 3 g/dL in approx. 60% of the cases of multiple myeloma.

Sampling: Serum: 1 mL serum, stable for 5 days at 4˚C. CSF: 1 ml CSF.
Urine: A 10 ml aliquot of a 24 h urine collection is required, please note total quantity.
Suspected samples for macroglobulins or cryoglobulins should be held at 37˚C. Samples suspected for cold agglutinins serum should be separated prior to cooling to 4˚C.

Reference Interval for Serum: (mg/dL)

	age	male	female
Children:	1-30 days	260-980	220-1031
	31-182 days	195-643	390-794
	183-365 days	184-974	407-774
	1-6 years	550-1400	600-1500
	13-15 years	709-1860	891-1900

Adults: 564-1765 mg/dL

Reference Interval for Urine: < 15 mg/24 h
Reference Interval for CSF: < 4 mg/dL

Immunoglobulin G Subclasses (IgG subclasses)

Related Information: Immunoglobulin A (IgA), Serum, Saliva, CSF
Immunoglobulin G (IgG), Serum, Urine, CSF
Protein, Total, Serum

Background: IgG immunoglobulins account for 80% of all immunoglobulins. Selective deficiencies despite of normal overall IgG occur in patients presenting recurrent infections, antibody responses within certain subclasses are linked to certain types of pyogenic infections. IgG2 deficient patients present with recurrent respiratory infections. Selective IgG1 deficiency was reported to be associated with sino-respiratory diseases and caused by S. pneumoniae and Hemophilus sp. IGA together with IgG2 and IgG4 deficiencies were linked to phenytoin therapy. IgG4 was found to be increased in sclerosing pancreatitis.

IgG subclass	1	2	3	4
Percent of total IgG	65%	23%	8%	4%
Half life time (days)	21	21	8	21
Complement fixation	moderate	weak	strong	none

Sampling: 2 mL serum
Reference Interval: (mg/dL)

Age (years)	IgG1	IgG2	IgG3	IgG4
0-1	190-620	30-140	9-60	6-60
1-2	230-710	30-170	10-100	5-40
2-3	230-830	40-240	5-130	3-120
3-6	350-810	50-310	9-160	5-180
older than 6	270-1740	30-630	10-320	11-620

Immunoglobulin M (IgM)

Related Information: Cold Agglutinin Titer
Cryoglobulin, Qualitative, Serum or Plasma
Protein Electrophoresis, Serum
Protein, Total, Serum
Rheumatoid Factor, Serum

Background: IgM has a large molecular mass of 900 daltons, which limits the immunoglobulin to the vascular compartment. It is a pentamer of 7S gamma globulin. IgM accounts for 5-9% of the total immunoglobulins and account for cold agglutinins, isoagglutinins and most types

of rheumatoid factors. It binds complement and the initially produced antibody in immune response. IgM is the first antibody class produced by the fetus. It does not cross the placenta in contrast to the IgG type.

Low IgG, IgA and IgE levels with marked increased IgM occur in the hyper-IgM combined primary immunodeficiency syndrome. Patients develop infections with encapsulated bacteria and intracellular organisms such as Pneumocystis carinii, Cryptosporidium parvum and Leishmania species.

Waldenstrom's disease is characterized by weight loss, anemia, hyperviscosity, hepatosplenomegaly, lymphadenopathy, epitaxis and by IgM macroglobulins with IgM levels > 3g/mL.

In contrast myeloma derived immunoglobulins are monoclonal IgG or IgA type.

IgM is increased in primary biliary cirrhosis in addition to elevated alkaline phosphatase and antimitochondrial antibodies.

Decreased levels of IgM occur in congenital or acquired hypogammaglobulinemias.

Sampling: 1 mL serum, if cryoglobulins or macroglobulins are expected, keep sample at 37°C.

Reference Interval: (mg/dL)

	Age	male	female
Children:	1-30 days	12-117	19-104
	31-182 days	27-147	9-212
	183 d - 1 year	27-197	4-216
	1-6 years	63-240	70-298
	7-9 years	49-231	62-270
	10-12 years	58-249	81-340
	13-18 years	57-298	69-361

Adults: 53-375 mg/dL

Influenza Type A and B, Serology

Background: Influenza viruses are the only member of the small, 110 nm in diameter, segmented-single stranded RNA orthomyxoviruses. The envelope is covered with spikes of hemagglutinin and neuramidase. The hemagglutinin binds to the cell surface receptor and is also target for neutralizing antibodies.

Influenza A causes worldwide epidemics and pandemics every 10-20 years, influenza B causes major outbreaks. Transmission via respiratory droplets, incubation period 1-2 days. Complications: Bacterial pneumonia, Reye's syndrome, characterized by encephalopathy and liver degeneration in children following viral infections such as influenza and chickenpox.

There is no lifelong immunity, but vaccines.

Sampling: 1 mL serum, sample at onset and reconvalescent serum

Reference Interval: Differentiation of immunoglobulin class

IgA antibody	negative:	< 0.7 COI
	borderline:	0.7–1.0 COI
	positive:	> 1.0 COI
IgG antibody	negative:	< 20 RE/mL

Insulin, Serum

Related Information: Ammonia, Plasma
Glucose, Blood, Urine, Liquor
Insulin-Like Growth Factor Binding Protein 3 (IGF-BP3), Serum
Insulin Resistance
Albumin, Urine

Background: From the precursor protein preproinsulin three hormones are derived: proinsulin, insulin, and C-peptide.

Hypoglycemia may be caused by islet cell tumor, exogenous insulin, hypoglycemic drug, alcohol, pituitary or adrenal insufficiency, and severe hepatic impairment. In children, persistent hypoglycemia of infancy (PHHI) has to be considered.

Useful in hypoglycemic disorders:

- PHHI presenting without ketosis or acidosis during infancy. Serum glucose < 54 mg/dL, serum insulin >10 µU/mL, increased C-peptide and increased proinsulin. The most severe form presents immediately after delivery, the less severe form during childhood. A third form is characterized by hyperammonemia.
- tumor-induced hypoglycemia is caused by islet cell tumor, most of the tumors are benign.
- hypoglycemia as a secondary phenomenon in patients with carcinomas.

Sampling: Patient should be in a fasting state. 2 mL serum, freeze immediately, ship to laboratory frozen.

Reference Interval:	Infants	0-13 mU/L
	Adults	6-25 mU/L

Insulin Auto-Antibody Human (IAAb), Serum

Related Information: Insulin, Serum

Background: Preceding or manifestation of diabetes mellitus type I, antibodies to insulin occur age dependent. In children < 5 years IAAb prevalence is 90%-100% whereas > 12 years prevalence decrease to 40%.

Useful in the predictive diagnostic marker for diabetes mellitus type I.

IAAb is tested positive in 2% of first degree relatives of diabetes type I patients. In combination with tyrosine phosphatase IA-2 autoantibody, pancreatic isle cell autoantibody, glutamic acid decarboxylase (GAD65) autoantibody, the predictive value increases to 80%-100% for type I diabetes

mellitus if at least three of the autoantibodies are tested positive. If 2 autoantibodies are tested positive, 25% develop a diabetes mellitus within 10 years, if one antibody is present, 10%.

Sampling: 1 mL serum

Reference Interval: < 1.0 U/mL

Insulin-Like Growth Factor-1 (IGF-1), Serum or Plasma see Somatomedin C, Serum or Plasma (IGF-1)

Insulin-Like Growth Factor Binding Protein 3 (IGF-BP3), Serum

Related Information: Insulin, Serum
Somatotropin
Somatomedin C

Synonyms: Somatomedins

Background: At least 10 different IGFBPs are known. The serum concentrations are proportional to the amount of circulating growth hormone. IGFBP-3 has a long half life time and binds 95% of IGF in the blood. Besides transporting IGFs, it plays a role in apoptosis.

Sampling: 1 ml serum, stable for 2 days at 4°C.

Reference Interval:

Children	0.9–4.2 µg/ml
Male	1.7–6.7 µg/ml
Female	2.0–7.3 µg/ml

Insulin Resistance

Related Information: Glucose, Blood, Urine, CSF
Insulin, Serum

Background: The HOMA model for insulin sensitivity allows to calculate the degree of beta cell function and the degree of peripheral insulin response. Therapeutic approaches may be adjusted to the major cause either to decreased insulin secretion or to impaired peripheral insulin sensitivity.

There are more than 500 studies using the HOMA formula for assessing insulin resistance or sensitivity (IR or IS).

Studies include the investigation of longitudinal changes in beta cell function and IR in patients with diabetes to evaluate the natural history of the disease or treatment regimes (sulfonylureas, metformin, and diet). Large scale epidemiological studies have been done to evaluate various ethnic groups with glucose intolerance. The large scale Bruneck Study concluded HOMA as a predictor for true insulin sensitivity comparable to the intravenous tolerance test.

Useful parameter:
- for individuals with abnormal glucose tolerance to track changes in insulin sensitivity and beta cell function.
- in individuals with abnormal glucose tolerance to assess the balance of insulin sensitivity and beta cell function, indicating whether reduced insulin sensitivity or beta cell failure predominates.
- in collecting longitudinal data in subjects who may develop abnormal glucose tolerance.
- if used with a careful interpretation in individuals on insulin secretagogues.

An initial increase in beta cell function in subjects on sulfonylurea may be followed by a decline, reflecting the secretagogue mechanism without amelioration of the rate of beta cell failure.
Limitations: HOMA can not be used in patients taking exogenous insulin. A clinical view always has to be taken into consideration, that for example a thin and fit individual with an overshooting high sensitivity of 200% to insulin may display a beta cell function of only 50%.
The model is validated within a range of 1-2000 pmol/L insulin or 1-25 mmol/L glucose.

Sampling: 2 mL serum for insulin level (freeze immediately, ship to laboratory frozen) and 1 mL blood in sodium fluoride tube for blood glucose level.

Reference Interval: There are no standardized reference ranges

HOMA % Beta cells function (HOMA % B)	110% - 90%
HOMA % Insulin Sensitivity (HOMA % IS)	90% -110%

Interleukin 6 (IL-6)

Related Information: C-Reactive Protein, Serum
Fibrinogen, Functional
Plasminogen, Plasma

Background: IL-6 is an immune, hematopoietic and proinflammatory cytokine, secreted as a 184 amino acid peptide of 21 kDa, mapped on chromosome 7 and synthesized by T and B cells, monocytes, as well as by macrophages, fibroblasts, keratinocytes, synoviocytes, chondrocytes and endothelial cells. IL-6 acts receptor mediated on T cells, hepatocytes, hematopoietic progenitor cells and neuronal cells. It stimulates B cells to differentiate, stimulates osteoclast formation, proliferation of vascular smooth muscle cells induces platelet derived growth factor production, induce fever by affecting the hypothalamus and induces as one of the proinflammatory cytokine IL-1, IL-6 and TNF the production of acute phase proteins by the liver. IL-6 acts synergistically with IL-1, IL-3, IL-5, IL-9, IL-11, GM-CSF, G-CSF on Burst Forming Unit-Erythrocyte and on Colony Forming Unit-Erythrocyte-Granulocyte-Macrophage. IL-6 acts also on Colony Forming Unit-Megacaryocyte to increase platelet production. IL-6 stimulates human myeloma cells to proliferate. In the CNS IL-6 supports survival of cholinergic neurons, in the reproductive system, it induces secretion of human chorionic gonadotropin from trophoblasts.
IL-6 may be used in patients with rheumatoid arthritis, with a significant correlation synovial fluid

concentration of IL-6 and IgG. It may play a role in development of membranoproliferative glomerulonephritis fond in patients with systemic lupus erythematosus. It may pal a role in diabetes type I and in plasmocytomas. It is helpful in differentiation between septic cause of fever or drug induced fever in patients on chemotherapy.

Sampling: 2 mL serum, separate immediately in refrigerated centrifuge, freeze and ship frozen.

Reference Interval: < 5.4 pg/mL

Intrinsic Factor Antibody (IFA)

Related Information: Folic Acid, Serum
Homocysteine, Plasma
Methylmalonic Acid, Serum or Plasma or Urine
Vitamin B_{12}, Plasma or Serum

Background: Intrinsic Factor (IF) is a 62 KD glycoprotein secreted at a rate of 50-100nmol per liter of gastric juices. Pernicious anemia is a common cause of vitamin B_{12} deficiency and is associated with antibodies to parietal cells and intrinsic factor autoantibodies. There are 2 types of autoantibodies against IF known:

A) Type I or blocking antibody which binds competitively to the vitamin B_{12} binding site of the IF. The antibody in the serum is of class IgG, the antibody is directly secreted into the gastric juice is of IgA class inhibiting the uptake of vitamin B_{12} in the ileum. 70% of the patients suffering from pernicious anemia develop type I antibodies.

B) Type II which binds to the vitamin B_{12}–IF complex. Type II antibodies are not pathogenic, but are associated with pernicious anemia in 35% of the patients and in 50% of the patients when type I antibodies are present.

False positive results are rarely reported in Graves' disease and atropic gastritis. Parietal cell antibodies are less specific for pernicious anemia although present in up to 90% of the patients.

Sampling: 1 mL serum, stop vitamin B_{12} medication 3 days prior to blood collection.

Reference Interval: Antibodies Typ I: not detectable

Iron (Fe), Serum

Related information: Copper, Serum or Urine
Erythropoietin (EPO), Serum
Ferritin, Serum or Plasma
Occult Blood in Stool (Hemoccult)
Porphyrins, Quantitative, Urine or Stool
Transferrin and Total Iron Binding Capacity, Serum

Background: Please see also Transferrin, Serum.

Iron is essential for oxygen and electron transport ($Fe2^+/Fe3^+$) and as a metal cofactor for enzymes. Hemoproteins are involved in oxygen binding and metabolism (peroxidase, catalase,

oxidase, cytochrome); nonheme proteins (iron cofactor function) are involved in mitochondrial actionase, DNA synthesis (ribonucleotide reductase), required for collagen, tyrosinase and catecholamine metabolism. Iron has effects on cell mediated immunity.
Distribution: Overall iron is estimated to be 40-50 mg per kg body weight. 30 mg exists in the form of hemoglobin. 5-6 mg in women and 10-12 mg in men exists in iron stores (ferritin, hemosiderin), 6-7 mg in tissue, in myoglobin, heme-enzymes and non-heme-enzymes. < 0.2 mg is bound to transferrin.
Regulation: Iron is not excreted by the body, besides small amounts in bile, urine, sweat, occult loss into the gastrointestinal tract or uterine loss. Daily loss is less than 1 mg in men, in women 1.5 mg. Recommended daily intake for men 10 mg, for woman 18 mg. Absorption only in the $Fe2^+$ form mainly in the duodenum with an absorption rate of 5%-10% of dietary iron which can be increased up to 20%-30% in a deficient state.
After absorption, iron is bound to transferrin. Cells acquire iron from transferrin by the transferrin receptor (TfR), a transmembrane glycoprotein that is predominant in all cells and particularly in placenta, liver and erythroid precursor cells.
The average value for plasma iron is 18 µmol/L, total iron binding capacity 56 µmol/L, transferrin saturation 35%. Total plasma pool of iron is estimated to 3 mg, iron stores to 350–900 mg. (man at the upper and woman at the lower limit)

Overview on iron status indicators changes:

Status	Ferritin	Transferrin	Serum Iron	Iron Saturation
Iron deficiency	down	up	down	down or normal
Anemia in chronic diseases	up or normal	down or normal	down	down or normal
Sideroblastic anemia	up	down or normal	up or normal	up
Hemolytic anemia	up	down or normal	up	up
Hemochromatosis	up	normal or down	up	up
Acute liver impairment	up	variable	up	up
Protein deficiency	down	down or normal	down or normal	

Iron deficient states are caused by inadequate absorption due to celiac disease, inflammatory bowl disease, bowl resection, dietary, intrinsic red cell defects or to increased iron loss due to tumors, varices, gastritis, ulcer, and parasites.
Overload occurs either in a state were erythropoiesis is normal but iron binding capacity of transferrin is exceeded and iron is deposited in the liver and into other organs or when iron is overloaded by transfusions and macrophages take up the excess of iron.
Limitations: In infectious, inflammatory or malignant disease transferrin saturation and iron concentrations may be decreased but are not indicating a deficient state. Total iron binding capacity (TIBC) and transferrin are increased with normal saturation in patients on oral contraceptives
Deferoxamine interferes with TIBC. TIBC is falsely overestimated during highly free iron levels.

Sampling: 1 mL serum, EDTA plasma not accepted. Avoid hemolysis. Fasting sample is preferred in the morning, there is a circadian rhythm, low in the evening, up to 30% higher in the morning. Stable for 1 week at 4˚C.

Reference Interval: 48–152 µg/dL for adult males
5-10% lower for adult females

Iron (Fe), Urine

Related Information: Hemolysins
Glucose-6-Phosphate Dehydrogenase (G6PD), RBC
Hemoglobin Electrophoresis
Hemoglobin, Qualitative, Urine
Iron and Iron Binding Capacity/Transferrin, Serum
Lactate Dehydrogenase (LDH), Serum

Background: In case of intravascular destruction of blood, free hemoglobin alpha-beta dimers are bound to haptoglobin and removed from the circulation by the live parenchymal cells if plasma hemoglobin levels exceeds 50-200 mg/dL (the binding capacity of haptoglobin for hemoglobin). The dimers of hemoglobin are filtrated by the glomeruli and a portion is reabsorbed by the tubular cells. The tubular cells convert hemoglobin to hemosiderin. If the tubular cells are shed into the urine, hemosiderinuria occurs. Hemoglobinuria occurs if the tubular reabsorption capacity is exceeded. Hemoglobin not bound to haptoglobin or not excreted by the kidney is oxidized to hemiglobin and the oxidized heme groups are bound to hemopexin, a beta globulin. The complex is cleared by hepatic parenchymal cells. If hemopexin is depleted, hemin groups bind to albumin, forming methemalbumin.
Useful in the assessment of intravascular hemolysis, hemochromatosis, hemolytic anemia, nephrotic syndrome, paroxysmal nocturnal hemoglobulinuria, multiple transfusions.
Limitations: Hemosiderin is shed in the urine several days after onset of hemolysis with slow decline, which may take weeks to month after heart valve replacement.

Sampling: A 5 mL aliquot of a 24h urine collection. Note total quantity.

Reference Interval: 3–99 µg/24h

Iron Total Binding Capacity see Transferrin and Total Iron Binding Capacity, Serum

Jo-1 Antibody

Related Information: Antinuclear Antibody
Scl-70 Antibody
SS-A/Ro and SS-B/La Antibodies

Synonyms: Antihistidyl Transfer tRNA Synthetase

Background: Aminoacyl-tRNA synthetases are a group of 20 enzymes to catalyze the reaction of amino acids with t-RNA. Jo-1 antigen resides on the enzyme histidyl-tRNA synthetases and is located in the cytoplasma.

Jo-1 antibodies account for 75% of all antibodies directed against synthetases and Jo-1 antibodies occur in 20%-35% of patients with inflammatory myositis, dermatomyositis, polymyositis, in overlap syndromes, and cancer associated myositis, as well as in fibrosing alveolitis.

Sampling: 1 mL serum

Reference Interval: Negative: < 20 U/mL

Kalium Serum or Plasma see Potassium, Serum, Plasma

Kalium, Urine see Potassium, Urine

Knee Punctate see Synovial Fluid Analysis

Lactic Acid, Whole Blood, Plasma or CSF

Related Information: Ammonia, Plasma
Ethanol, Blood, Serum or Urine
Ibuprofen, Serum
Salicylate, Serum or Plasma

Synonyms: Blood Lactate, Lactate

Background: Derived from pyruvate in glycolysis, levels rise sharply during exercises. Lowest values occur during fasting and upper values during postprandial state.

Increased in lactic acidosis caused by carbon monoxide intoxication, anemia, methemoglobulinemia, respiratory failure, shock hypotension.

Increased in drug mediated lactic acidosis by ethanol, methanol, ethylene glycol, cyanide, nitroprusside, salicylate, nalidixic acid, catecholamines. Increased during therapy with biguanides (phenformin), particularly in patients >60 years.

Increased in inborn errors of metabolism such as diabetes mellitus; mitochondrial myopathy; glycogen storage diseases Type I,II,III,V,VIII; fructose1-6-biphosphatase deficiency; deficiency of pyruvate carboxylation.

Increased in liver and renal failure, infections, malignancies.

Useful as a prognostic parameter for mortality and admission to the emergency unit: Patients with values >36 mg/dL need emergency care.

Sampling: 2 mL sodium fluoride plasma. For most precise results, arterial blood is required. Separate plasma immediately and transport to the laboratory soon. Temperature independent increase per hour in sodium fluoride stabilized plasma probe is 1.8 mg/dL.

Reference Interval: (mg/dL)

Neonates (capillary blood)	2.4-20
Plasma, Venous	4.5-20
Arterial	4.5-14
Plasma, CSF	11-19

Lactate Dehydrogenase (LDH), Serum

Related Information: Alanine Aminotransferase (ALT), Serum
Aspartate Aminotransferase (AST), Serum
Creatine Kinase (CK, NAC-activated)
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis C Antibody (Anti-HCV)
Hepatitis C Genotyping
Hepatitis C Virus RNA Quantification (HCV-RNA)
Lactate Dehydrogenase Isoenzymes, Serum
Myoglobin, Blood or Serum or Plasma

Background: LDH is a zinc containing enzyme of the glycolytic pathway and is present in the cytoplasm of all cells. LDH is a tetramer of two active subunits, H (heart) and M (muscle), MW 134 kDa. Combination of the subunits produces 5 isoenzymes LDH 1 (HHHH) to LDH 5 (MMMM). The activity of LDH in various tissues varies only about 1.5 fold. In plasma, most LDH comes from breakdown of erythrocytes and platelets.

Percentage of Isoenzymes in tissues:

	LDH1 (HHHH)	LDH2 (HHHM)	LDH3 (HHMM)	LDH4 (HMMM)	LDH5 (MMMM)
Serum	25	35	20	15	5
Heart	45	40	10	5	0
Red Cells	40	35	15	10	0
Lung	10	15	40	30	5
Skeletal muscle	0	0	10	30	60
Liver	0	5	1o	15	70

Causes for elevated levels:

A wide variety of neoplasms, particularly LDH5 elevation, combined with elevated with serum alkaline phosphatase.

Hypoxia with cardiorespiratory disease: Cardiac failure, myocarditis. After myocardial infarction, LDH starts to rise after 12h and stays elevated during 1-2 weeks. In contrast during pericarditis

and angina, LDH is not substantially elevated.
Elevated levels occur in hemolytic anemia; in megaloblastic anemias, such as pernicious anemia; in infectious mononucleosis (LDH is more elevated than AST); in inflammatory diseases; in hypothyroidism.
Pancreatitis: LDH to AST ratio > 18 in patients with biliary pancreatitis may indicate pancreatic necrosis.
Raised levels in pulmonary infarct and in lung diseases.
Viral Hepatitis: AST and ALT are more increased than LDH and LDH5 is high. Usually only moderate increase in liver disease and cirrhosis.
Elevated in renal infarct, seizures, CNS diseases, pancreatitis, collagen diseases, fractures and traumas with excessive cell death, muscular dystrophy, shock, hypotension,
Not useful in screening for cancer but selectively in Hodkgin and non Hodgkin lymphomas used as an additional staging marker.
Sampling: 1 mL of serum or plasma. Avoid any, even little hemolysis! Heparin or oxalate plasma is not accepted. Stable 3 days room temperature

Reference Interval:		
	Adult	135 – 220 U/L
	Newborn 4–20 days	225 – 600 U/L
	Children 2–15 years	120 – 300 U/L

Lactate Dehydrogenase Isoenzymes, Serum

Related Information:
Alanine Aminotransferase (ALT), Serum
Aspartate Aminotransferase (AST), Serum
Creatine Kinase (CK, NAC-activated)
Epstein Barr Virus (EBV), Serology
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis C Antibody (Anti-HCV)
Hepatitis C Genotyping
Hepatitis C Virus RNA Quantification (HCV-RNA)
Lactate Dehydrogenase Isoenzymes, Serum
Myoglobin, Blood or Serum or Plasma

Background: See also Lactate Dehydrogenase (LDH), Serum
The troponins have replaced LDH isoenzyme tests in the diagnosis of myocardial infarction, but LDH is useful in combination with the troponins and in the evaluation of other disease.
LDH1 may be a marker in testicular seminoma resp. in dysgerminoma, but there is also a relation to nonseminomatous tumors.
Sampling: 1 mL of serum or plasma. Avoid any, even little hemolysis! Heparin or oxalate plasma is not accepted. Stable 3 days room temperature

Reference Interval: main origin

LDH 1:	20–33%	red blood cells, heart
LDH 2:	21–40%	red blood cells, heart
LDH 3:	16–32%	
LDH 4:	5–13%	liver, skeletal muscle
LDH 5:	3–9%	liver, skeletal muscle

LDH1 to LDH2 ratio normally 0.5-0.8, in myocardial damage and in hemolytic anemias LDH1 becomes greater than LDH2.

Lactate, Liquor see Cerebrospinal Fluid (CSF, Liquor)

Lamotrigine, Serum

Synonyms: Lamictal®

Background: As phenytoin, lamotrigine suppresses rapid firing of neurons and inactivates sodium channels. It is used in focal epilepsy and primary and secondary generalized tonic clonic seizures. It is efficient in myoclonic seizures, absences, atonic and tonic seizures, and in Lennox-Gastaut syndrome.

Adverse effects are headache, diplopia, nausea, somnolence and rash. Life threatening dermatitis develops in 1%-2% of pediatric patients.

Bioavailability 93%-100%; urinary excretion 10%; plasma binding 56%; volume of distribution 0.9-1.2 L/kg; half life time 24-35h increased in liver disease and serve renal disease; peak time 1-3.4h, peak concentration 2.1-2.9 µg/mL after a single 200 mg oral dose.

Lamotrigine undergoes glucoronidation to 2-N-glucoronide as the primary elimination pathway. Valpronate increases half life twofold.

Sampling: 2 mL serum

Reference Interval: Therapeutic 2.0-10 µg/mL

Legionella Pneumophila

Background: Legionellae are gram negative rods, staining faintly and requiring a highly enriched iron and cystein medium for culture. Approx 90% of pneumonias caused by legionellae are due to L. pneumophila, 9% to L. micdadei and L. bozemanii, 1% to the other approx. 30 species.

Main source for infection is environmental water in air conditioners and water tapes. Airborne transmission does not occur. Immunocompromised patients are on high risk for acquiring Legionella infection. Legionellae account for 5%-15% of adults and 1% of children's pneumonia.

Named after the outbreak of pneumonia during a convention of the American Legion in Philadelphia in 1976, Legionellae causes atypical pneumonia (also atypical: Mycoplasma, viral, psit-

tacosis, Q fever). Incubation period is 2-14 days. Clinically mild forms are characterized by pneumonias accompanied by influenza like illness (Pontiac Fever), serve forms by non-bloody diarrhea, proteinuria, and hematuria.

Laboratory Diagnosis: Sputum gram strain usually is negative for bacteria. Culture need a special supplemented media, the laboratory should be notified if an atypical pneumonia is expected.

Legionella antigen may be detected in lung tissue and in the urine.

Raise in antibody titer in convalescent serum 2 weeks apart is a reliable test for Legionella infection.

Treatment: Erythromycin in combination with rifampicin. Alternative: Levofloxacin or moxifloxacin

Sampling: Serology: 2 mL serum each at the beginning and after 3-8 weeks.
Culture: Sputum, bronchial lavage, tracheal secret, blood.
For environmental screening: 200 mL water

Reference Interval: Serology: Antibody titer negative < 1:100
Culture: Report on diagnostic finding: Growth of Legionellae

Leishmaniasis, Serology

Related information: Chagas Disease and Protein Electrophoresis, Serum

Test includes: L. donovani

Background: The four major pathogens of the genus Leishmania are L. donovani, L. tropica, L. mexicana, L. brasiliensis. Other species are L. major, L. aethiopica, L. peruviana.

L. donovani causes kala-azar or visceral leishmaniasis. The life cycle involves the sand fly species Phlebotomus in the old world and Lutzomyia in S. America. Dogs and rodents, foxes are reservoirs. The sandfly ingests macrophages from an infected host containing amastigotes, differentiating into promastigotes within 10 days in the gut, multiplying and are transmitted during the next bite. Affected organs are part of the reticuloendothelial system (liver, spleen, bone marrow) resulting in normocytic normochromic anemia, leukopenia, polyclonal gammopathy and thrombocytopenia. Symptoms are intermittent fever, weakness weight loss, enlarged spleen, gastrointestinal bleedings which are persisting for month to years.

Treatment: Sodium stibogluconate.

Leishmania tropica L. mexicana, L. braziliensis: L. tropica and L. mexicana cause the cutaneous form of leishmaniasis. L braziliensis is the cause of a mucocutaneous form. Endemic in Central and South America.

Clinically the initial cutaneus lesions is a re papule at the bite site, enlarging and forming satellite nodules that ulcerate. In immunocompetent patients a single lesion heals spontaneously.

In the mucocutaneous form metastatic lesions are formed frequently developing disfiguring granulomatous ulcerating lesions at the nasal cartilage, with a slow healing tendency.

Limitations: Serology is helpful in epidemiology studies, for clinical diagnosis serology is of limited help. Cross reaction with Chagas disease and malaria.

Sampling: 1 mL serum

Reference Interval: Antibody detection: negative

Leptospira, Serology

Related information: Leptospira Culture, Blood or Urine or Liquor

Background: Please see Leptospira Culture, Blood or Urine or CSF.

Human leptospirosis is usually caused by L. interrogans with approx. 200 serologic variants.

Sampling: 1 mL serum. Acute and convalescent sera drawn 2 weeks apart.

Reference Interval: Test includes Leptospira interrogans serovar autumnalis, -australis, -canicola, - hebdomalis, -icterohemorrhagica

A single titer is of very limited value, titer < 1:160 are considered as negative.

A four fold increase in titer in paired samples is positive.

Peak of antibody titer at week 3 to 6, slow decline afterwards.

Leptospira Culture, Blood or Urine or Liquor

Related Information: Leptospira, Serology

Background: Three genera of spirochetes cause human infections: Treponema, Borrelia, and Leptospira. Leptospira are fine, spirale shaped bacteria, which are not stained with dyes but are seen by dark field microscopy and can be cultured in rabbit serum or albumin with fatty acids containing media. Leptospira species. infects rats and other rodents, domestic livestock and dogs. Animals excrete the bacterium in urine. Leptospira infection is acquired by contact with contaminated mud, freshwater or soil through ingestion, entry through mucous membranes, conjunctiva or broken skin, putting miners, farmers, veterinarians, dairymen, swineherds, abattoir workers, miners, fish and poultry processors, outdoor adventures (canoeing, rafting, swimming), on risk. Person to person transmission is rare.

The disease is typically biphasic with fever, chills, headache, and aseptic meningitis first and followed by a short period of resolution. A second phase is characterized by aseptic meningitis, liver dysfunction and impaired kidney function. Clinically leptospirosis can vary from a mild, self limiting disease to fulminant, fatal hepatorenal failure (Weil syndrome).

Sampling: Avoid for bacterial culture of urine contamination with skin flora. Best to use is the mid portion of the urine stream (avoid first and final portion), catheter or suprabubic puncture urine. Blood or cerebrospinal fluid is suitable, too. The first septicemic phase lasts from day 4 to 7 post infection, when cultural results may be positive. Within the followed 1-3 days, culture is negative. During the last phase and up to several months, low numbers of leptospira are intermittent released in the urine. Frequent sampling is necessary.

Avoid blood collection in citrate solutions. Transport specimen into the laboratory within one hour. Do not refrigerate.

Report on diagnostic findings: No Leptospira species isolated
Incubation time 4-6 weeks.

Leucine Aminopeptidase (LAP), Serum

Related Information: Alkaline Phosphatase, Serum
Bilirubin, Fractionated, Serum
Gamma-Glutamyl Transferase (Gamma-GT), Serum

Synonyms: Arylamidase; Arylamidase-Naphthylamidase; LAP

Background: LAP is present in all tissues; it hydrolyzes amino acids from the terminal end of peptides, with highest activity at leucine terminal sites. In serum most of LAP is of liver origin where it is membrane bound similar to GGT and ALP.

Used to differentiate in patients with increased alkaline phosphatase levels between liver and biliary tract (increased) versus bone diseases (no increase). Increased in cholestasis.

May be useful to detect early renal tubular injuries in diabetes mellitus patients.

Increased in the third trimester of pregnancy, produced by the placenta.

In the majority of patients with systemic lupus erythematosus LAP is increased.

Elevated levels, even without liver metastases, occur in malignancies such as breast, endometrial and ovarian carcinomas, in germ cell tumors of ovary and testis.

Sampling: 1 mL serum (EDTA -, Oxalate-, Citrate-, plasma not accepted)

Reference Interval: Male 19-35 U/L
Female 18-33 U/L

Light Chain see Free Light Chains Structure (FLC), Serum
see Free Light Chains Structure, Urine

Lipase, Serum

Related Information: Amylase, Total, Serum
Amylase, Total, Urine
Bilirubin, Fractionated, Serum

Synonyms: Triacylglycerol Acylhydrolase

Background: Pancreatic lipase is a glycoprotein with a molecular weight of 45 kDa. It hydrolyses glycerol esters of long fatty acid chains at the 1 and 3 ester bonds. Lack of bile salts with a lack of emulsification and absence of co-lipase renders lipase activity ineffective.

Pancreatic lipase activity is sensitive marker in the evaluation of pancreatitis. In contrast to amylase it does not occur in saliva and lipase returns to normal later than amylase.

Lipase may be elevated in patients with obstruction of the pancreatic duct, in renal diseases acute cholecystitis, intestinal obstruction or infarction, duodenal ulcer, liver diseases, alcoholism, diabetic ketoacidosis. Patients with abdominal trauma have elevated amylase and lipase levels; in patients with mumps elevated lipase indicates an involvement of the pancreas.

Drugs capable to increase serum lipase are: acetaminophen, valproic acid, oral contraceptives, codeine, meperidine, methacholine, morphine, pentazocine, secretin, calcitriol, cerivastatin,

chlorothiazide, clozapine, diazoxide, didanosine, dideoxyinosine, estropipate, felbamate, hydrocortisone, mercaptopurine, metolazone, metronidazole minocycline, nitrofurantoin, pegaspargase, prednisolone, sulfamethoxazole.

Sampling: 1 mL serum (EDTA plasma not accepted), stable for 1 week at room temperature.

Reference Interval: < 60 U/L

Lipoprotein (a), Serum

Related Information: Apolipoprotein A I and B-100, Serum
Low Density Lipoprotein Cholesterol

Synonyms: Lp(a)

Background: Lp(a) has been shown in studies to be a risk factor for coronary heart disease and cerebrovascular diseases. However, other studies failed to demonstrate the correlation.
There is a wide range for values across populations. For individuals of African origin the median values are three times higher than the median in whites. Reference intervals have to be adjusted to ethnic group the patient belongs to.

Sampling: 1ml serum, stable for one week refrigerated.

Reference Interval: MEDLAB suggests for the German white population a cut off at 30 mg/dL

Liquiprin® see Acetaminophen, Serum

Liquor see Cerebrospinal Fluid (CSF, Liquor)

Listeria monocytogenes, Serology

Background: Listeria monocytogenes is a short, motile, Gram-positive, non-spore-forming bacillus causing gastroenteritis, invasive infections particularly in immunocompromised and elderly patients. In sheep and cattle it is associated with encephalitis and abortion. Listeria monocytogenes is widespread in natural environment particularly in soil, decayed matter, wood. Human cases are due to ingestion of contaminated food such as inadequate pasteurized dairy products and contaminated processed meats. Incidences in Europe and US are 0.7 cases per 100 000 population, mortality 40%, neonatal incidences in the US and Europe are 13 per 100 000 live birth.
Listeriosis during pregnancy is characterized by influenza like illness with fever and chills, fatigue, muscle pain headache and often precedes delivery by 2-14 days. Premature labor is common, 70% deliver newborns at less than 35 weeks of gestation. Mortality including stillbirth and abortion rate of 40%-50%. In neonates there is an early (within 2 days of life) and a late onset form after 7 days of life. The late onset form presents in 95% with meningitis, whereas the early on-

set form presents with pneumonia (60%), cyanosis, apnea, respiratory distress, anemia (62%), thrombocytopenia (35%) and meningitis (21%). Isolation rates from blood is 73% in early onset cases, from CSF 94% in late onset cases.

Sampling: 1 mL serum

Reference Interval: Differentiation of immunoglobulin class

IgG antibody	negative:	< 1:1000
IgM antibody	negative:	< 1:1000

Liver Kidney Microsomal Antibodies (LKM Antibodies)

Related Information:
Antimitochondrial Antibodies
Antinuclear Antibody
Bilirubin, Fractionated, Serum
Smooth Muscle Antibodies
Soluble Liver Antigen (SLA)-Antibody (Anti-SLA)
Thyroglobulin Antibody
Thyroperoxidase Autoantibody

Background: LKM antibodies bind to three microsomal proteins:

- LKM-1: LKM -1 bind predominantly to the cytochrome P450 2D6 (MW 50kD). LKM-1 antibodies are characteristic for autoimmune hepatitis type 2. Two subsets are known:
  The subset type 2a is characterized in addition to by the presence of anti-liver cytosol 1 antibodies. Types 2a patients are mainly HCV negative, female children with higher levels of LKM-1.
  The type 2b subset patients are positive for HCV but less often positive for LKM-1.
  Limitation: In 2% of patients with viral hepatitis C LKM-1 antibodies are present. LKM-1 antibodies may be present in thyroiditis, diabetes mellitus, hemolytic anemia, arthritis, and colitis ulcerosa.
- LKM-2: In Drug induces hepatitis (by Ticrynafen) LKM-2 may be elevated.
- LKM-3: Antibodies are present in 10%-20% of the chronic hepatitis D patients
  For classification of autoimmune hepatitis please also see Soluble Liver Antigen (SLA)-Antibody (Anti-SLA)

Sampling: 1 mL serum

Reference Interval: Negative

Low Density Lipoprotein Cholesterol

Related Information:
Apolipoprotein A-1 and B100, Serum
Cholesterol, Total, Serum or Plasma
High Density Lipoprotein Cholesterol, Serum or Plasma
Triglycerides, Plasma or Serum

Synonyms: Beta Lipoproteins, LDL Cholesterol, LDLC

Background: LDLC concentration is considered a major risk factor for coronary artery disease.

Limitations: LDLC may be increased by thiazides, beta blockers, and estrogens; decreased by fish oils, niacin, and fibrates.

Sampling: 1 mL serum (no EDTA plasma)

To obtain best results patients should be on a stable diet for 3 weeks and fasting for 10 h before sample drawing.

Reference Interval:		
	Optimal	less than 100 mg/dL
	Good	100-129 mg/dL
	Borderline	130-159 mg/dL
	Elevated	160-189 mg/dL
	Very high	above 190 mg/dL

Lupus Anticoagulants / Lupus Inhibitors, Serum or Plasma

Related Information: Activated Partial Thromboplastin Time
Cardiolipin Antibody
HIV Type 1 and Type 2, Serology
Platelet Count
Treponema pallidum (TPAH Serology)

Background: Lupus anticoagulants (LA) and anticardiolipin antibodies (ACA) are antiphospholipid antibodies. LA are mainly IgG and IgM class immunoglobulins forming complexes with prothrombin and beta-2 glycoprotein-I, which subsequently react with phospholipids of the clotting system.

Clinically, LA is highly correlated with venous and arterial thrombosis, and to a lesser extend with thrombocytopenia, systemic lupus erythematodes, abortion and other autoimmune diseases.

LA or ACA may be associated with drugs such as procainamide, phenytoin, chlorpromazine as well as with infections (EBV, varicella, malaria, tuberculosis, borreliosis, HIV), with malignancies and with Sneddon syndrome, Guillain Barre and Behçet-syndrome.

Limitations: 5% of the healthy population has low titers of LA or ACA, increasing with age.

Sampling: 3 mL citrate plasma, snap-freeze immediately, ship frozen. Avoid traumatizing the vessel during puncture, the vessel membranes and thrombocytes contain neutralizing phospholipids. High concentration of heparin may give false positive results.

Reference Interval: Negative: 14–40 seconds

Luteinizing Hormone (LH)

Related Information: Estradiol, Serum
Follicle Stimulating Hormone (FSH), Serum
Progesterone, Serum
Prolactin, Serum
Testosterone, Serum

Synonyms: Follitropin, ICSH, LH

Background: The decapeptide, with carbohydrate side chains, gonadotropin releasing hormone (GnRH) secreted by the hypothalamus stimulates release of Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) from the pituitary gland. The alpha subunit of the glucohormones (TSH, hCG, LH, FSH) are nearly identical, the beta subunit confers hormone specificity.
In children, both gonadotropins are constant and low, FSH is higher than LH. Both hormones increase in puberty, LH increase first during non REM sleep, later in puberty sleep and wake pattern are equivalent.
In men LH and FSH pattern is pulsatile, LH with 9-14 secretory surges per day with 2-3 fold increases, FSH with low magnitudes of 25% increases over mean.
In women the menstrual cycle is divided in a follicular phase and a luteal phase by the midcycle peak of LH and FSH. FSH and LH are higher in the follicular phase than during the luteal phase, FSH in addition is falling during the preovulatory period.
In postmenopausal women, gonadotropins are secreted in a more episodic fashion. FSH levels are higher due to lack of granulosa cell produced inhibin. This negative feed back mechanism for FSH is not affected by administration of estrogens. LH levels are similar or higher.
In men there is an increase in LH and FSH, in part due to lack of negative feed back by decreased testosterone.
Diagnostic use: Elevated FSH and LH values occur in anorchia, gonadal failure, testicular feminization syndrome and in menopause.
Low serum levels occur in primary pituitary or hypothalamic failure.
High LH, a LH to FSH ratio > 2, increased ovarian androgens, and non ovulatoryrhythem has a 75% diagnostic sensitivity for Stein-Leventhal Syndrome. High LH during the follicular phase in polycystic ovary syndrome may interfere with conception.
Limitations: LH secretion is pulsatile and can vary by 60% from the daily mean in the course of the day, whereas FSH can vary by 20%.

Sampling: Serum: 1 mL serum. To obtain highly reliable results, up 6 samples during a six hour period are recommended. LH in serum is stable 2 weeks at room temperature.
Urine: 24h urine, collect in a container prefilled with boric acid. Urine collection over a 24h period LH minimizes pulsatility error. The LH serum ovulatory peak occurs 24h-36h delayed in urine.

Reference Range:

		Serum	Urine
Female:	follicular phase	2.0–16.0 IU/L	< 5 IU/24h
	ovulatory peak	20.0–60.0 IU/L	
	luteal phase	2.0–16.0 IU/L	< 5 IU/24h
	menopausal	20.0–60.0 IU/L	> 5 IU/24h
Male:	< 70 years	1.0–6.0 IU/L	< 0.2-5 IU/24h
	> 70 years	3.1–35.0 IU/L	
Children:	prepupertal	0.5–4.0 IU/L	< 0.2 IU/24h

Lyme Disease see Borrelia, Serology

Lymphocyte Immunophenotyping

Related Information: Beta-2-Microglobulin, Serum or Urine
Complete Blood Count
HIV Type 1 and 2, Serology

Background: Mature T cells ($CD3^+$) express either CD4 or CD8 antigen, defining T helper cells as $CD4^+$ and suppressor/cytotoxic as $CD8^+$ cells.

General imbalances of the immune system occur in Fas deficiency. Fas is a surface marker (CD95, of group TNF) normally interacting with Fas-L leading to apoptosis. Fas deficiency leads to a non malignant proliferation of $CD4^-$ $CD8^-$ T-cells known as autoimmune lymphoproliferative syndrome (ALPS) or Canale Smith syndrome.

Enumeration is useful in monitoring HIV positive patients. $CD4^+$ cell number usually fall by 30%, $CD8^+$ increase by 40% during 6-12 month after infection and the ratio $CD4^+$ / $CD8^+$ falls below 1. Absolute $CD4^+$ count falling below 400 cells/µl indicates disease progression.

$CD8^+$ T-cell count also increase during other viral infections and after vaccination, therefore absolute numbers are useful to determine.

Splenectomy increases absolute lymphocyte count.

Idiopathic $CD4^+$ lymphocytopenia (ICL) is a rare cause of low $CD4^+$ count and is often associated with a decreased $CD8^+$, NK and B-cells count.

Limitations: Abnormal values are reported from patients under steroid therapy, immunosuppressive therapy, recent surgery with general anesthesia, and in patients with lymphomas.

Asian population display a lower mean percentage of CD4 values, a lower ratio, and a lower absolute CD4 lymphocyte count.

Sampling: 3 mL EDTA blood. Sample is stable for 24h at room temperature, do not refrigerate, do not freeze

Reference Interval:

	percent	absolute
T-lymphocytes		
T-lymphocytes, total	75–93%	800-2500/µL
T-helper lymphocytes ($CD4^+$)	35–60%	650-1200/µL
T-suppressor lymphocytes ($CD8^+$)	30–38%	500-800/µL
B-lymphocytes		
B-lymphocyte count, total	7–17%	70-350/µL
Natural killer cells (NK)	5–15%	50-300/µL
Ratio $CD4^+$/$CD8^+$	1.1–2.3%	

Lyphocin® see Vancomycin, Serum

Lysozyme, Blood or Urine or CSF

Synonyms: Muramidase

Background: Lysozyme is present in neutrophil granules, in leukemic and normal eosinophils. The test is used in the differentiation of leukemia. Lysozyme is present in the M4 type of acute myeloid leukemia, occasionally in the M1, M2, and M6 type. It has been found to correlate with the degree of differentiation of monocytes in leukemia.

Also used as a marker in monitoring sarcoidosis, and it may be elevated in tuberculosis.

Sampling: Serum: 1 mL, separate serum or plasma and freeze immediately.

Urine: 5 mL aliquot of a 24h collected urine shipped frozen and collected on ice.

A random urine sample is suitable, too.

CSF (Cerebrospinal fluid): 0.5 mL

Reference Interval:

Serum:	4-15.6 µg/mL
Urine:	0-1.4µg/mL
CSF:	< 1.5 µg/mL

M2 – PK, Feces

Related Information: CA 19-9, Serum (Gastrointestinal)

Background: M2-PK is an isoenzyme of pyruvate kinase (PK), expressed in proliferating and in tumor cells. PK occurs in a tetrameric form and in a dimeric form. In tumor cells, the dimeric form (tumor M2-PK) is predominant. Since tumors of the gastrointestinal tract grow into the lumen, tumor M2-PK is detectable in the feces of patients with GI malignancies.

Colorectal cancer: Sensitivity for detection of colorectal cancer or polyps was shown to be 27% and 10% for the occult blood (Guajak), 91% and 19% for the immunological test for occult blood and 73%-77% and 48% for the M2-PK-test, respectively. Specificity was 89%, 94% and 72%, respectively, indicating that M2-PK display a lower specificity in diagnosing cancer.

TNM and Dukes' classification of the tumors correlates strongly with faecale M2-PK levels.

Gastric cancer: Compared to controls, samples of patients with inflammatory bowel disease or different types of gastrointestinal tumors did not show significant differences, but up to 80% of patients with gastric cancer present elevated M2-PK.

Sampling: approx. 2 g stool

Reference Interval: < 4 U/mL

Magnesium (Mg), Serum

Related Information: Calcium (Ca), Total, Serum or Urine
Digoxin, Serum
Magnesium, Urine
Potassium, Urine
Vancomycin, Serum

Background: Magnesium is the fourth most abundant cation in the body with an amount of approx. 22 g behind sodium, potassium and calcium and the second most prevalent intracellular cation. Half of the amount is located in the bone, the other half in soft tissue. Extracellular Mg accounts only for 1% of total body Mg (TBMg). In the serum, approx 55% is unbound, 30% is albumin associated and 15% is complexed with phosphate, citrate or other anions.

Magnesium is essential for the function of approx. 300 enzymes, in DNA replication, mRNA translation. Mg is necessary in membrane stabilization, energy metabolism (ATP), and maintaining potassium balance.

TBMg depends on gastrointestinal absorption and renal excretion. Dietary intake is estimated to 300-350 mg/day, the renal excretion 120-140 mg/day by glomerular filtration of 70%-80%.

Useful in: Acute myocardial infarct, cardiac arrhythmias, hypokalemia, hyponatremia, during diuretic therapy, digoxin therapy, diarrhea, in the diagnosis of neuromuscular symptoms such as spasm, fasciculations, weakness, dizziness, tetany, convulsions.

Sampling: 1 mL serum or plasma, EDTA plasma is not acceptable. Avoid hemolysis, since erythrocytes contain threefold the concentration as compared to serum.

Reference Interval: 1.7-2.5 mg/dL

Since a fraction of Mg is bound to albumin, patients with hypalbuminemia may have values at the lower reference limit.

Magnesium (Mg), Urine

Related Information:
Calcium (Ca), Total, Serum
Calcium (Ca), Urine
Cyclosporine A (monoclonal)
Digoxin, Serum
Magnesium, Serum
Oxalate, Urine
Potassium, Serum or Plasma
Vitamin D, Serum

Background: Urinary magnesium may serve as an early indicator for developing serum magnesium deficiency leading to hypocalcemia with cardiac arrhythmias.

Useful in the assessment of Mg deficiency in patients with gastrointestinal disorders such as Crohn disease or gut failure, in patients suffering from calcium oxalate kidney stones, since oxalate stone formation is related to urinary concentrations of oxalate and calcium but inversely related to urinary citrate and magnesium.

Elevated urinary excretion occurs in patients with elevated blood alcohol levels, diuretics, Bartter syndrome, Gitelman syndrome, aldosterone therapy or corticosteroids; in renal transplant patients on cyclosporine and prednisone.

Drugs reducing magnesium storage with high magnesium excretion: aminoglycosides, cyclosporine, pentamidine, foscarnet, amphotericin B.

Sampling: 5 mL aliquot of a 24h urine collection recommended, due to circadian rhythm. Use a clean plastic container for collection, avoid strictly contact of the urine with metals. Keep cool. Note total quantity.

Reference Interval: 73–122 mg/24h

Malaria

Related Information: Myoglobulin Qualitative, Urine
Blood Count Complete

Test includes: Microscopic examination of thick and thin smears; antibodies to P. falciparum and P. vivax.

Background: Malaria is the most common infectious disease now due international travel frequently coming to attendance in non endemic areas.

Malaria is caused by four members of the species Plasmodium: P. vivax, P. falciparum, P. malariae, and P. ovale, transmitted by the insect vector of the genus Anopheles.

P. vivax causes tertian malaria with an incubation time of 10-14 days and a cycle length of 45h.

P. falciparum causes malignant tertian, tropical malaria with an incubation time of 10-14 days and a cycle length of 48h.

P. ovale causes malaria ovale with a cycle length of 48 h.

P. malariae causes quartan malaria with an incubation time of 18-42 days and a cycle length of 72 h.

Sampling:

Microscopy: 2 to 3 thin and 2-3 thick air dried smears made at bedside on oil free clean slides. To prepare a thick smear, spread a drop of blood without anticoagulants on 2-5 fold the area of the original drop on a slide using a corner of another slide. To prepare a thin slide, smear the drop over the entire area of the slide. Specimens should be prepared immediately before or during the start of a fever spike. Thick films have an increased sensitivity, but are more difficult to read. Optimal circumstances allow a sensitivity of 10 parasites per ul blood.

Serology: 3 mL serum for antibody test available for Plasmodium falciparum and P. vivax.

Important: Please note travel history and countries visited by the patient.

Reference Interval: Microscopy: Plasmodium not detectable
Limitations: Negative result does not rule out malaria.
Serology: Antibody negative for Plasmodium falciparum and P. vivax.

Marijuana see Cannabinoids (Marijuana Metabolites) Immunological Drug Screen, Urine

Measles (Morbilli), Serology

Background: Measles, a paramyxovirus, causes infection of the lymphoreticular system and the respiratory tract. Clinically measles infection present with maculopapular eruption, starting on the face and descending to the extremities including palms and soles, Koplik's spots, lymphadenopathy and cough. Measles are near elimination in countries with childhood vaccination programs. Due to maternal neutralizing antibodies vaccination not is performed after 15 month of age. Booster vaccination is strongly recommended.

Measles are transmitted by respiratory droplets, produced during the prodromal period and some days after the rash appears. The measles virus is highly infectious with an incubation time of 10-14 days. The rash is caused by cytotoxic T cells targeted to virus infected vascular endothelial cells in the skin. There is a 0.1% incidence of encephalitis with 40% permanent sequelae. Also measles and bacterial pneumonia and bacterial otitis media may occur.

Measles in pregnant women increases the risk of stillbirth.

Immunity lasts life long, is mainly cell-mediated, but IgG antibody levels indicate immunity. Maternal immunity is transferred to the fetus and lasts for the first 6 month of life. Measles infection may depress cell mediated immunity, particularly against Mycobacteria sp.

Sampling: 2 mL serum

Reference Interval:	IgG antibody negative	< 250 mIE/mL
	IgM antibody negative	< 1.0 COI

Melanin, Urine

Background: Melanocytes metabolize tyrosine by tyrosinase to dihydroxyphenylalanine (DOPA) further to dopaquinone and by oxidation to melanin. The fist step catalyzed by tyrosinase takes place in melanosomes and under the control of melanin stimulating hormone. Melanosomes are transferred to skin or mucosa cells.

Urinary increase of melanin metabolites such as indole, catechols and catecholamines occur in malignant melanoma in the stage of metastasis.

Sampling: 10 mL of random urine; transport to laboratory soon.

Reference Interval: Not detectable

Melatonin, Serum

Background: Melatonin is produced by the pineal gland and is derived from serotonin. It is involved in regulating sleep cycles and is released with darkness and suppressed by daylight. Melatonin is used to soften jet lag symptoms. Melatonin has been shown to be effective in sleep disorders, improving onset of sleep, duration and quality of sleep and increasing REM phases. Particularly patients older than 65 years with low melatonin levels show improvement of the sleep onset time but not an improved sleep or total sleeping time. Melatonin may be associated with midcycle suppression of luteinizing hormone, resulting in inhibition of ovulation. It also may suppress prolactin release.

Sampling: 1 mL serum

Reference Interval:	Daylight values	< 30 pg/mL
	Night values at approx. 9 pm to 4 am	< 150 pg/mL

Metanephrines, Urine

Related Information: Catecholamines, Fractionation, Plasma
Catecholamines, Fractionation, Urine
Homovanillic Acid (HVA), Urine
Vanillylmandelic Acid, Urine

Test includes: Normetanephrine and Metanephrine

Background: The catecholamines epinephrine and norepinephrine are secreted by the adrenal medulla and small amounts are secreted unchanged in the urine, most are metabolized by monamine oxidase and catechol-o-methyltransferase (COMT) producing the major urinary metabolites vanillylmandelic acid (VMA), metanephrine, and normetanephrine. Homovanillic acid, the final product of dopamine metabolism, is excreted in the urine too.

Useful to assay in the diagnosis of catecholamine secreting neoplasms from the adrenal medulla such as pheochromocytomas, paragangliomas and neuroblastomas.

Limitations: Drugs or substances which increase values: Benzodiazepines, diuretics, exogenic catecholamines (nose drops, appetite suppressants), amphetamines, methyldopa, cigarette smoking, caffeine ingestion, alcohol, nitrates, phenothiazine, and tricyclic antidepressants.

Drugs decreasing values: Bromocriptine, clonidine, dexamethasone, monoamine oxidase inhibitors.

Sampling: A 10 mL aliquot of a 24h urine, collected in a prefilled container with 10 mL of 20% hydrochloric acid (not boric acid), note total quantity. Keep cool.

Reference Interval:	Total:	< 850 µg/24h
	Normetanephrine:	< 450 µg/24h
	Metanephrine:	< 400 µg/24h
	(Conversion into SI: µmol/ 24h = µg/24h x 5.46)	

Methadone, Urine

Related information: Antidiuretic Hormone, Plasma
Opiates, Quantitative, Urine

Synonyms: Dolophine®; Eptadone®; Metasedin®; Methadose®; Physeptone®; Symoron®

Background: A modified diphenylheptane analgesic, similar properties as morphine, but orally more effective and with a longer half life time. Methadone is metabolized by the liver and excreted in bile and urine.

As a morphine substitute, it does not cause euphoria or serve somnolence and it blocks the action of other co-administered opiates.

Bioavailability 80%-100%; urinary excretion 14%-34%; plasma binding 86%-92% with a blood to plasma concentration ratio of 0.75; volume of distribution 2.4-4.8 L/kg; serum half life 15-39h correlates to urine ph and decreased in burn patients and children; serum peak time 3h, serum peak concentration IV: 450-550 ng/mL after a 10mg dose or oral: 70-980 ng/mL after 0.12 -1.9 mg/kg for 2 month.

Onset of action 0.5-1h after oral dose.

Adverse effects: sedation, CNS and respiratory depression, nausea, vomiting, bradycardia, hypotension, miosis, antidiuretic hormone release. Overdose treatment with Naloxone.

Sampling: 10 mL of random urine, refrigerate if not transported to the laboratory within 8h .

Reference Interval: Negative for urine < 250 ng/mL
Serum levels >100 ng/mL prevent withdrawal symptoms, pain relief in cancer patients requires serum levels of 170-530 ng/mL.

Methemoglobin (MetHb), Whole Blood

Related Information: Carboxyhemoglobin, Blood

Background: A form of hemoglobin with oxidized Fe^{+++} state, unable to bind oxygen.

Slight cyanosis occur if values exceed 15% to 30% of total hemoglobin, symptoms such as fatigue, dizziness, dyspnea, headache, tachycardia and severe cyanosis above 40%-50%.

Lethal >70%.

Most common causes are drug or chemically induced, particularly by aniline, nitrites, nitroglycerin, nitrate, flutamide, metoclopramide, phenazopyridine, dapsone, phenacetin, acetophenetidin, prilocaine, sulfonamides, sulfones, chlorates, primaquine, quinones, local anesthetics such as benzocaine, lidocaine, and procaine.

A rare form of hereditary metHb is a deficiency of cytochrome b5 reductase (or red cell NADH-methemoglobin reductase), as a recessive autosomal trait. Met Hb levels in homozygotes are 15%-20%, in heterozygotes MetHb is not increased.

Newborns may react more sensitive to metHb inducing drugs or nitrate in drinking water, since cytochrome b5 reductase is less active.

Sampling: 5 mL of EDTA whole blood. After sample drawing, keep on ice. Process soon. 10% decrease within 4h, 16% within 8h if kept on ice.

Reference Interval: < 1% of total hemoglobin
Clinical symptoms > 15%, lethal >70%

Methylmalonic Acid, Serum or Plasma or Urine

Related Information: Vitamin B 12, Plasma or Serum
Folic Acid, Serum
Homocysteine, Plasma

Background: Cobalamin is required for isomerization of methylmalonic acid to succinic acid.

An increase in methylmalonic acid in urine or serum indicates a cobalamin deficiency, and may be used for vitamin B12 therapy monitoring. Folate deficiency does not influence methylmalonic acid values. (Serum homocysteine concentrations are increased in folate and cobalamin deficiency).

Methylmalonic acid is a diagnostic marker in rare inherent disorders presenting with metabolic ketoacidosis, methylmalonic acidemia and aciduria.

Limitation: Renal failure and decreased plasma volume my increase methylmalonic acid and folate levels.

Patients with impaired gut flora due to antibiotic treatment may have decreased cobalamin levels and subsequently elevated methylmalonic acid values.

Sampling: 2 mL serum; 10 mL urine

Reference Interval: Serum: 9-32 µg/L
Urine: < 10 mg/g of creatinine
(Conversion into SI: µmol/L = µg/L x 0.0085)

Metyrapone Stimulation Test, Serum

Related Information: Adrenocorticotropic Hormone, (ACTH), Plasma
Cortisol, Serum or Plasma
Cortisol free, Urine
Applies to: 11-Desoxycortisol, Serum

Background: The metyrapone stimulation test (MST) is used to assess the adrenal function in adrenal insufficiency (AI) or Cushing syndrome (CS). Metyrapone inhibits the conversion of 11-deoxycortisol to cortisol and thereby produces decrease in serum cortisol which increases the pituitary release and serum levels of ACTH. In the overnight MST, metyrapone is administered at midnight and cortisol, 11-deoxycortisol and ACTH is measured at 8 AM the following morning. The MST is useful in patients suspected for secondary AI (pituitary or hypothalamic), which display decreased 11-deoxycortisol and ACTH levels in the MST. In Cushing syndrome, the MST is used to distinguish pituitary caused CS from adrenal based CS. In CS patients meeting or exceeding the criteria, the CS is of pituitary origin; patients not meeting the criteria, diagnosis are either an adrenal tumor or ectopic corticotrophin syndrome. Adrenal tumor usually leads to low ACTH levels; ECS patients have normal or elevated ACTH levels.

Dosage of metyrapone (overnight protocol): Patients < 70 kg: 2 g orally
70-90 kg: 2.5 g orally
> 90 kg: 3 g orally

Drugs inducing metabolism of metyrapone such as phenytoin, rifampin, phenobarbital, mitotane, corticosteroids should be discontinued before the test.

Sampling: 2 mL heparin plasma

Reference Interval: 11-desoxycortisol, unstimulated, basal

Premature newborn	< 1.4 µg/dL
Children 0–12 years	0.02–0.25 µg/dL
Adult	0.05–0.3 µg/dL

Overnight MST protocol: Morning (8 AM) levels should be < 3 µg/dL. If levels are higher, results can not be interpreted and may be due to failure to take the metyrapone or a rapid clearance due to enzyme induced by other drugs. Approx 5% of normal population exceed 3 µg/dL.

If the cortisol level is < 3ug/dL the thresholds are:

for 11-deoxycortisol serum: > 7 µg/dL

for ACTH serum: > 75 pg/mL

Microglobulin β-2- , Serum or Urine

Related Information: HIV-1/HIV2 Serology
Vancomycin, Serum

Background: Beta-2-Microglobulin is a low molecular weight, membrane derived light chain component of class I human leucocyte antigen (HLA). It is filtered in the glomerulus and reabsorbed in the tubules.

A broad range of diseases lead to elevated levels such as renal failure, lymphomas, neoplasms, inflammatory state (Crohn's disease, hepatitis, sarcoidosis, vasculitis), amyloidosis, immunodeficiency states, hyperthyroidism, viral infections,

It correlates with seize, growth rate and renal function in multiple myeloma and prognosis.

Used as a predictive marker in therapy of patients with low grade lymphomas. Early marker in aminoglycoside renal toxicity. Progression marker in HIV patients.

Sampling: 1 mL of serum. A 5 mL aliquot of a 24 urine; urine ph should not decrease below 5.5 since stability of the compound is lost. Note total quantity.

Reference Interval:

Serum:	Averages:	Neonates	0.30 mg/dL
		0-59 years	0.19 mg/dL
		60-69 years	0.21 mg/dL
		>69 years	0.24 mg/dL
Urine:			< 120 µg/24 h

Molybdenum (Mo), Serum or Urine

Related Information: Uric Acid, Serum

Background: Mo is essential for at last 3 enzymes: xanthine oxidase (purine metabolism), aldehyde oxidase (ethanol metabolism) and sulfite oxidase (amino acid metabolism). A body-total of 8-10 mg of Mo is distributed in the skeletal muscle (60%, the liver (20%) and other organs. The recommended daily intake is around 75-250 µg, in children 2 µg/kg body weight. Rich in Mo are diary products, liver, coconuts, and vegetables. Deficiency may develop after bowel resection.

Mo is bound to alpha$_2$ globulin during circulation.

Dietary sulfides interact with copper and Mo to form insoluble copperthiomolybdenates in the gut, influencing the resorption.

Diseases associated with Mo:

Dysfunction of xanthine oxidase causes xanthinuria, a hereditary disease.

During the initial phase of acute virus hepatitis, circulating Mo is increased. Increased Mo values occur in cirrhosis, alcohol abuses, drug induced liver toxicity, liver metastasis, occlusion of the bile tact, which is due to release of Mo from hepatocytes or impaired uptake into the liver.

Failure to synthesize molybdopterin, a recessive inherent error of metabolism, is characterized by xanthine oxidase deficiency (serum uric acid < 1 mg/dL with increased urine hypoxanthine and xanthine) in combination with sulfite oxidase deficiency (increased urine sulfite, absent inorganic urinary sulfate, increased urinary S-sulfo cysteine) and presents clinically with neurologic abnormalities, (seizures, opisthotonos, and impaired myelin synthesis resulting in early death). Histopathology shows the absence of Mo in the liver, indicating molybdopterin as an essential tissue storage factor.

Patients with chronic renal failure may accumulate Mo up to toxic levels.

Sampling: 2 mL serum. 10 mL random urine

Reference interval:

	Serum:	0.5- 3 ng/mL
		70% of US population have < 5 ng/mL
		toxicity may start at 170 ng/mL
	Urine:	10-16 µg/L

Mononucleosis, infectious see Epstein Barr virus

Morphine see Opiates, Quantitative, Urine

Mumps Virus, Serology

Background: Mumps virus belong to the paramyxoviruses typically with a RNA genome and two types of envelope spikes, one with hemagglutinin and neuroamidase activities and the other with cell-fusing and hemolytic activities. There is only one serotype. Neutralizing antibodies are directed against the hemagglutinin. The internal nucleocapsid protein S antigen is used in the complement fixation test.

Mumps virus is limited to humans as the host. It is transmitted by respiratory droplets. It occurs worldwide with a peak in winter. 30% are inapparent. Virus is excreted approx. between 10 days before and 1 week after onset. Following the recommendations of vaccinating at the age of 12-15 month (measles, mumps, and rubella) and a second vaccination at 4-6 years or 11-12 years, the incidence of mumps has fallen to 308 cases in 1999 in the US. Immunity lasts life

long. During the first 6 months (approx.) maternal antibodies are protective.

Clinic: After an incubation of 18-21 days a prodromal stage with fever malaise anorexia is followed by the tender swelling of the parotid glands unilateral or bilateral, resolving after 1 week. The disease may be complicated by orchitis in postpubertal males, and meningitis, which is usually benign.

Sampling: 1 mL serum, draw acute and convalescent sera 10-20 days apart.

Reference Interval: Differentiation of immunoglobulin classes

IgG antibody	negative:	< 20 RE/mL
IgM antibody	negative:	< 1.0 COI

Mycobacteria

Background: The major pathogens are Mycobacterium tuberculosis and to a minor extend M. bovis, the cause of tuberculosis and M. leprae, the cause of leprosy. Atypical mycobacteria (M. avium-intracellulare complex and M. kansasii) cause tuberculosis-like disease. Members of the rapid growing Mycobacterium fortuitum-chelonei complex cause disease in immunocompromised patients or are associated with implants.

Transmission occurs in M. tuberculosis by respiratory droplets, in M. bovis by non-pasteurized milk from infected animals, mainly cows, in M. leprae by long term close contact to patients, in atypical mycobacteria (M. kansasii, M, marinum, M. avium-intracellulare complex, M. fortuitum-chelonei complex) by contaminated soil and water. Patients with smear negative sputum sample may transmit M. tuberculosis in up to 20%. On multidrug therapy, which lasts for 6-12 month, patient's sputum becomes non-infectious after 3-4 weeks.

Sampling: 3-5 mL sputum
50 mL of morning urine
20 mL of gastric juice

Reference Interval: Culture: Report on diagnostic finding
For M. tuberculosis: direct detection by PCR assay for DNA:
negative: M. tuberculosis DNA not detectable

Mycoplasma hominis

Background: The small organism lacking a cell wall has been implicated in an infrequent cause of pelvic inflammatory disease. Ureaplasma urealyticum however causes approx. 20% of non-gonococcal urethritis.

Sampling: urethral, vaginal or cervical swab; urine.

Reference Interval: Culture result: not detectable

Mycoplasma pneumoniae, Serology

Background: The fastidious free-living organism is known to account for up to 20% of hospitalized adults with community acquired pneumonia.

Mycoplasma pneumoniae causes primary atypical pneumonia. Infections are transmitted by respiratory droplets, occurs worldwide with a peak in winter. Outbreaks are reported in young adults and in groups with close contact. Approx. 10% of infected develop pneumonia. Immunity is incomplete, further episodes may occur.

Classification: Mycoplasma organisms belong to the genus Mycoplasma (class Mollicutes) and are described as the simplest and smallest self-replicating bacteria because of their total lack of cell wall, the paucity of their metabolic pathways, and the small size of their genome. In the 1980s, they were shown to have evolved from more classical bacteria of the firmicutes taxon by a so-called regressive evolution that resulted in massive genome reduction but are considered successful pathogens of man and animal.

Sampling: 1 mL serum, convalescent serum 2-4 weeks apart recommended for definitive diagnosis.

Reference Interval:

Differentiation of immunoglobulin class	
IgA antibody negative:	< 9 RE/mL
borderline:	9–11 RE/mL
positive:	> 11 RE/mL
IgG antibody negative:	< 9 RE/mL
borderline:	9–11 RE/mL
positive:	> 11 RE/mL
IgM antibody negative:	< 9 RE/mL
borderline:	9–11 RE/mL
positive:	> 11 RE/mL

Myeloperoxidase Antibody (MPO) see Antineutrophil Cytoplasmatic Antibody (ANCA)

Myoglobin, Blood or Serum or Plasma

Related Information:
Carboxyhemoglobin, Blood
Creatine Kinase (CK, NAC-activated)
Creatinine Kinase Isoenzymes, Serum
Haptoglobin (Hp), Serum
Lactate Dehydrogenase (LDH), Serum
Myoglobin, Qualitative, Urine
Troponin T, Serum

Background: Myoglobin is a small 17.8 KDa oxygen binding protein of the cytoplasm of the skeletal and heart muscle cells, released through traumatization with a plasma half life of

10-20 min (CK: 15 h, CKMB:12h). Myoglobin is not specific for a distinct tissue. Most of urine myoglobin is derived from skeletal muscle.

Myoglobin is an early and highly sensitive marker to confirm acute myocardial infarction.

Indicated: Acute myocardial infarction (AMI): serum myoglobin increases 2-4 h after onset of pain, whereas CK starts to increase after 4-6 h. Predictive marker for AMI: to rule out: negative predictive value 98%; to confirm: positive predictive value 64%. Myoglobin peaks within 4-12 h and decreases into reference interval with in 24-36 h.

Monitoring thrombolytic therapy of AMI: An initially rapid myoglobin increases > 150 µg/L/h, and a decrease into reference interval within 10-20 h is correlated with successful thrombolysis.

Monitoring diseases of the skeletal muscle

Sampling: 2 mL serum, plasma, blood;
Urine: 5 mL

Reference Interval:

	Serum	< 64 ng/mL
	Urine	< 30 ng/mL

Myoglobin, Qualitative, Urine

Related Information: Carboxyhemoglobin, Blood
Creatine Kinase (CK, NAC-activated)
Creatinine Kinase Isoenzymes, Serum
Haptoglobin (Hp), Serum
Lactate Dehydrogenase (LDH), Serum
Myoglobin, Blood or Serum or Plasma
Troponin T, Serum

Background: Please see also Myoglobin Blood, Serum or Plasma. Most of the myoglobin detected in urine is of skeletal muscle origin. The assay is used in the investigation of myositis, rhabdomyolysis and muscle traumatization. Elevated accompanying parameters are serum creatine kinase, serum myoglobin.

Myoglobinuria may occur after viral diseases caused by Influenza-, Herpes simplex,-Epstein-Barr, -Enteroviruses; during bacterial diseases; in primary muscle diseases such as muscle dystrophy, polymyositis, dermatomyositis, particularly under steroid therapy; by drug toxicity (alcohol, carbon monoxide, amphetamine abuse, by animal poisons; during ischemia (compression, thromboembolism, myocardial infarction) and by trauma of the muscles (caused by epilepsia, injuries, high voltage shock).

Sampling: 5 mL random urine

Reference Interval: < 17 µg/g of creatinine

Myositis Antibody see Jo-1 Antibody

Neisseria gonorrhoeae

Background: Neisseria gonorrhoeae is a gram negative oxidase positive bacteria producing a lipooligosaccharide endotoxin which contains lipid A without long repeating sugar side chains. Pili for attachment to mucosal cell surfaces and antiphagocytic action and IgA proteases are further important virulence factors. Antigen and outer membrane protein changes enable N. gonorrhoeae to cause repeated infection. Disseminated infection is due in part to porin A protein, which inactivate the C3b component of the complement system and to the host immune system, particularly individuals with deficiency in complement C6-C9 function such as women during menses and pregnancy. Disseminated infections occur particularly in cases of asymptomatic infections.

Clinical sides include the endocervix, ascending to the uterine tubes (salpingitis, PID), anorectal areas, throat and eyes. During disseminated courses arthritis, tenosynovitis and pustules of the skin occur.

Since the growth of the organism is inhibited by metals and fatty acids, it can only be cultured on absorbing media such as agar containing heated blood. Cultivation is successful only in 50% whereas DNA detection is more sensitive (90%-95%)

Treatment: Ceftriaxone, ciprofloxacin. Resistance to penicillin is rising. Since co-infection with C. trachomatis is common, tetracyclines should be co administered.

Sampling: Culture: Swab (special transport media) to be transported to the laboratory immediately or to plate at bedside on special agar media to obtain optimal results.
DNA Probe: Swab in special transport medium

Reference Interval: Culture: Report on diagnostic finding
DNA Probe: Report on DNA detection

Neopterin, Serum

Background: Neopterin (D-erythro-6-trihydroxypropyl-pterin), synthesized by GTP-cyclohydroxylase-1, may be elevated in serum or urine during stimulation of the cellular immuno functions such as stimulation of macrophages by interferon–gamma or stimulation of monocytes derived dendritic cells.

Clinical conditions associated with increased neopterin production: Viral infections, parasites or intracellular bacterial infections, inflammatory states including rheumatoid arthritis, systemic lupus erythematodes, Morbus Crohn and other autoimmune diseases. The parameter is prognostic for malignancies and in HIV infections. It is useful in the follow up of transplant patients, in patients undergoing immunomodulatory therapy with cytokines, as well as during antibiotic or antiviral therapy. It may be helpful in differentiation of rheumatoid arthritis from osteoporosis.

Sampling: 2 mL serum

Reference Interval: 19-75 years:
0.65-2 ng/mL (2.6-8 nmol/L) or given as 95% 2.17 ng/mL (8.7 nmol/L)
Older than 75 years:
1.17-3.67 ng/mL (4.7-14.7 nmol/L) or given as 95% 4.75ng/mL (19 nmol/L)

Neurone-specific Enolase (NSE), Serum

Synonyms: Phosphopyruvate Hydratase

Background: NSE is a marker for neuroendocrine neoplasms and cerebral injury. NSE is one out of 11 enzymes of the glycolytic pathway, catalytic active to convert 2-phospho glucerate to phosphoenolpyruvate. NSE has a MW of 100 kDa composed as a dimer out of 3 subunits (alpha, beta, gamma). NSE is named the enzyme containing at least one gamma subunit.

Gamma subunit composed NSE: Synthesized in neuronal cells and neuroendocrine APUD-cells of the intestine, lung, pancreas, and thyroid gland.

Alpha-alpha subunit composed: Synthesized in glia cells and other cell types, named as a non-neuronal enolase enzyme. Beta subunit composed: synthesized in the muscle (beta-beta) and heart muscle (alpha-beta)

Small cell lung carcinoma: NSE diagnostic sensitivity 60%-93%, (CEA: 29%-69%).

Specificity against benign diseases 91%-95% (CEA: 82%-93%). In non-small cell lung carcinoma, specificity is 58%-93% (CEA 25%-68%). NSE may be the most sensitive marker in small cell lung carcinoma with 77%, followed by CYFRA21-1 with 36%; SCC 32%; CEA 28%. There is a good correlation with clinical staging, but no correlation with metastasis. NSE is a useful marker in monitoring with a predictive value of 92%.

Neuroblastoma: Values >30 µg/L of NSE are detected in 62% of children with neuroblastoma. Wilms tumor values are lower, only 20% of the patients present with >30ug/L. Good correlation with staging.

APUD cell carcinoma: Levels >12.5 ug/L are present in 11%-56% of the patients, depending on the localization of the tumor.

Seminoma: A median serum concentration of 40 µg/L in 70% of the patients has been reported.

Other malignancies: 22% of other carcinomas present levels >12.5 µg/L, usually a higher percentage in cases of metastasis.

Limitations: Increased also in benign lung diseases, in 5% of patients values > 12µg/L were reported. Increased in CNS diseases (meningitis, encephalitis, cerebral hematomas, Guillain Barré syndrome). Values > 25 µg/L occur in 2% of patients with non malignant diseases (levels >12.5 µg/L in 14% of patients). In cases of fetal brain defects up to 50% of the pregnant women presented increased NSE levels.

Sampling: 1 mL serum, strictly! Avoid hemolysis, since red blood cells contain gamma enolase causing false positive results.

Reference Interval:			
	Adults		< 12.5 µg/L
		borderline	13-25 µg/L
	Children	< 1 year	< 25 µg/L
		1-8 years	< 20 µg/L

Newborn Screen

Test Includes:
Acylcarnitine disorders
Amino acid metabolism disorders
Branched chain organic acids (leucine, isoleucine, valine) metabolism disorders
Congenital Adrenogenital Syndrome
Fatty acid oxidation disorders
Galactosemia
Glutaric aciduria type I and II
Organic acids metabolism disorders
Phenylketonuria
Thyroid function disorders

Background: General: The combined incidence of all disorders given in the test panel is about 1:4000 excluding hypothyreoses, phenylketonuria, adrenogenital syndrome, if including all parameters, the combined incidence is approx. 1:2000. Figures are evaluated in Germany.
For most of the disorders, therapies are available, but early identification is essential.
However, screening earlier than 36 hours after birth may not give valid results, screening earlier than 36 hours after birth is therefore indicated only
- if the newborn is discharged and no screening will be possible later on,
- if blood transfusion is indicated (screening has to be done before)
- if treatment with cortisone or dopamine is necessary (screen before initiation of therapy)

A re-screening has to be considered in theses cases.
For preterm or sick newborns same rules apply.
For highly preterm (less than 32 weeks of pregnancy) newborns, a second screening after corrected age of 32 weeks of pregnancy is strongly recommended.
Screening is recommended on day three of life, as standardized.

Information essentially required for the screening procedure:

- Name of the mother
- Name address of the hospital/doctor
- Date and time of specimen drawn
- Age of gestation

- Weight of the newborn
- Clear identification in case of siblings
- Parenteral nutrition of the newborn (yes or no)
- Period (hours) sample taken after birth

Sampling: is done at bed-side on a NEWBORN SCREENING TEST CARD which only can be obtained from the laboratory in advance.

The marked circles on the TEST CARD must be completely covered with the newborns blood sample. Do use native blood only (no EDTA or heparinized blood), either capillary blood or venous blood. Do not use umbilical blood. Screening has to be done before starting therapeutic use of catecholamine or corticosteroids. The blood drops are allowed to dry at room temperature, which usually takes one hour and applying heat is under no circumstances allowed for accelerating the drying!

The parameter description below serves as an overview. Not all parameters may be part of the test panel and are subject to change. New parameters may be included and may replace others. Cut off values and thresholds for pathologic values are constantly reviewed and are subject to change. The markers for diseases and cut off values are subject to change and interpretation. The laboratory provides an indication whether parameters are pathologic or borderline and may recommend a re-screening, follow ups or further, focused investigation in doubtful cases.

1. Congenital Adrenogenital Syndrome
(adrenogenital syndrome, AGS, congenitale adrenal hyperplasia)

Background: AGS an autosomal recessive disorder caused by 21 hydroxylase deficiency which is coded on chromosome 6 (6p21.3). More than 90% of AGS is caused by 21-hydroxylase deficiency. Due to altered syntheses of cortisol, more androgens are synthesized. AGS presents clinically with failure to thrive, salt-loss syndrome, atypical genitalia and a family history. The incidence in screened newborns is 1: 5 000 to 1:11 000.

Due to the lacking conversion pathway of 17-hydroxyprogesterone to 11-desoxycortisol by the enzyme 21-hydroxylase, 17 hydroxyprogesterone is accumulating to serum levels >100 µg/L (300mmol/L). Elevation of androgens such as DHEA or DHEAS are, however, not specific for AGS.

Reference Interval: Negative for AGS: Mature newborns older than 3 days:
< 60 µg/L (18.2 nmol/L)
Values are higher prior to day 3 and in preterm newborns or newborns with diseases.

2. Galactosemia

Background: Primary source of galactose is lactose, provided with milk. Three different disorders are known: galactokinase deficiency, galactose-1-phosphate uridyl transferase deficiency (GALT), and uridine-diphosphate-galactose-4 epimerase-deficiency. Overall incidence of all galactosemias are in Germany 1:55 000 and worldwide 1:18 000-1:200 000.

The majority is due to GALT.

Clinically the autosomal recessive disease present in 70 % of the cases as an acute illness at the end of the first week after birth with vomiting, icterus, rejection of feeding , hypoglycemia, ammoaciduria, and in more chronic forms with cataract (due to reduction of galactose to galactide), failure to thrive, liver enlargement, mental retardation, lethargica. Into the urine, high levels of galactose, the reduced form galactide or the oxidized form are excreted. Lactose free feeding improves within 1-3 days the situation dramatically.

Sampling: Brest feeding (milk) must have been started prior to testing. Test to be performed ideally within the first 3 days of life.

Reference Interval:

Serum: Galactose assay in serum: 0-2 mg/dL (SI: 0-1.11 mol/L)

False negative tests have been very rarely reported.

Assay for GALT: blood: 18-26 units/g of Hb

Up to 4 month after transfusions, positive test results were more frequently reported when assys are performed for GALT deficiency

Urine (not part of the test panel): Normal newborns may have physiologic elevated levels of galactose (up to 60 mg/dL) within the first days of live, in premature newborns the period may be extended to 2 weeks.

High milk intake may cause false positive levels.

3. Phenylketonuria

Background: 97% of the cases of the autosomal recessive aminoacidopathies are due to phenylalanine hydroxylase deficiency. The incidence varies by region between 1:10 000 and 1:50 000. To prevent mental retardation, early screen is necessary to initiate appropriate therapy through low phenylalanine intake below 200-300 mg per day. Hyperphenylalaninemia in mothers may result in fetal damage (microcephaly, growth retardation, heart disease), genetic counseling before pregnancy is indicated.

Sampling: Ideally, prior to testing, newborns should have a protein feed (milk).

Reference Interval:

Screening: During the first 12 hours of life >2 mg/dL (false negative 3%)
After 24 hours of life 4 mg/dL (false negative 10%-0.1%, percentage rate decreases with lifetime). If screened within the first day of life, a re-screen is indicated after 1-2 weeks.

Confirmation: >10 mg/dL suggests phenylketonuria
<10 mg/dL mild variant of phenylketonuria
Serum tyrosine, urinary pteridines and blood dihydropteridine may be tested as well.

4. Thyroxine T4 and Thyroid Stimulating Hormone (TSH)

Background: Fetal Thyroid Stimulating Hormone (TSH), T4 and T3 production starts at week 12 of gestation. Conversion of T4 to T3 is very low until week 30 of gestation, increasing to normal within the first month of life. Newborns with abnormal thyroid function show problems in mental and neurological development 4 times more often than normal newborns. Incidence of hypothyroidism is about 1:3 600.

Mature newborns: Within 24 h of life TSH increase rapidly, however values of >40 mU/L are observed in less than 1% of the newborns. TSH usually is less than 5 mU/L.

Premature newborns achieve thyroid status of adults after 4-8 weeks. A transient low level of T4 may be seen in 85% of prematures.

Sampling: Optimal collection time not earlier than 3 days after birth

Reference Interval: **T4**

Preterm newborn	
< 27 week of gestation	0.5-3.5 µg/dL
27-29 week of gestation	3.0-5.8 µg/dL
30-32 week of gestation	2.8-5.6 µg/dL
33-37 week of gestation	1.9-8.8 µg/dL

Mature newborn	Free T4	Total T4
cord blood	10-18 ng/L	60-130 µg/L
day 1 and 2	16-38 ng/L	105-260 µg/L
3-30 days	15-30 ng/L	80-200 µg/L
30-360 days	11-18 ng/L	55-140 µg/L

TSH

Preterm newborn	
19-27 week of gestation	2.6-5.5 mU/L
28-38 week of gestation	4.5-9.3 mU/L
39-42 week of gestation	2.7-5.7 mU/L

Mature newborn	
1-3 days	< 2.5-13.3 mU/L
1-4 weeks	0.6-10.0 mU/L
1-12 month	0.6-6.3 mU/L

5. Amino acid (AA) metabolism disorders

5.1 Argininemia (ARG), argininosuccinic aciduria (ASS) and citrullinemia (CIT)

Characterized by deficiency of arginase, arginosuccinate lyase (ASL) and argininosuccinate synthase (ASS) within the urea cycle. Clinically presenting with confusion, impaired speech, Reye s syndrome, mental impairment, ataxia and stupor. Laboratory abnormalities are in-

creased serum ammonia, glutamine, AST and AST and decreased urea. In argininemia, in addition orotic acid is increased.
AA markers:
For ASL and ASS: Citrate; cut off for positive >100 µmol/L (13SD)
For ARG: Arginine; cut off >132 mol/L (9SD)

5.2 Homocystinuria (HCU)
Deficiency in either cystathione-beta-synthase or deficiency in 5,10 methylenetetrahydrofolate reductase or in cobalamin or cobalamin metabolism. Clinically presents as mental or developmental retardation, thromboembolic episodes, or ectopia lentis. Defects in cobalamin metabolism results in addition in macrocytic anemia and methylmalonic aciduria.
AA marker: Methionine; cut off >67µmol/L (6SD)

5.3 Tyrosinemia (TYR)
Characterized by p-hydroxy phenyl acetic acid hydroxylase deficiency and resulting clinically in hepatic cirrhosis, renal tubular dysfunction and presenting increased plasma tyrosine. Incidence 1:155 000
AA marker: Tyrosine; cut off > 442 µmol/L (9SD)

5.4 Maple Syrup urine disease (MSUD)
A branched chain aminoacidemia characterized by a deficiency in brached chain amino acid oxidase. Clinically presenting with seizures, ketosis, and mental retardation. Laboratory results are increased urine and plasma branched chain amino acids. Incidence about 1:140 000 for Germany or 1:260 000 for the US
AA marker: Leucine; cut off >373 µmol/L.

5.5 Hypermethioninemia
AA marker: Methionine (Met) ; cut off >67 µmol/L (6SD), incidence 1:280 000. Also a marker for Homocystinuria (HCU)

5.6 Hyperornithinemia, -hyperammonemia,-hypercitrullinuria (HHH) Syndrome
AA marker: Ornithine (Orn) ; cut off >300 µmol/L (11SD)

6. Fatty acid oxidation disorders

Approximately 12 defects in fatty acid oxidation are known. Clinically presenting with hypoketotic, hypoglycemic coma induced by fasting. The most common defect is medium chain acyl CoA dehydrogenase deficiency, resulting in Reye's like syndrome with sudden infant death.

6.1 Short chain acyl CoA dehydrogenase (SCAD)
Incidence 1:33 000 and isobutyl-CoA dehydrogenase deficiency. Butyrylcarnitine (C4) or the

isomer isobutyrylcarnitine are primary markers; cut off >1.9 µmol/L (10SD)

6.2 Medium chain acyl CoA Dehydrogenase deficiency (MCAD)
Incidence 1:9 000
Marker: C8; cut off > 0.5 µmol/L (11SD)

6.3 Long chain hydroxyacyl CoA dehydrogenase deficiency (LCHAD)
Incidence 1: 220 000
Marker: C16OH (hydroxypalmitoylcarnitine); cut off > 0.1 umol/L (7SD)

6.4 Very long chain acyl CoA Dehydrogenase deficiency (VLCAD)
Incidence 1:135 000
Marker: Tetradecenoylcarnitine; cut off >0.9 µmol/L (12SD)

6.5 Carnitine palmitoyl-transferase type II deficiency (CPTII) and carnitine acylcarnitine translocase deficiency
Marker: C 16 (palmitoylcarnitine); cut off >12 µmol/L (7SD)

6.6 Glutaric aciduria type II (GA II)
Marker: C 8; cut off 0.5 µmol/L (11SD)
Further fatty acid oxidation disorders are:
multiple acyl CoA dehydrogenase deficiency, mitochondrial trifunctional protein deficiency and 2,4 dienoyl-CoA reductase deficiency

7. Organic acids metabolism disorders

7.1 Glutaric aciduria type I (GA I)
A defect in glutaryl-CoA dehydrogenase triggers clinical signs of dystonia, and encephalopathy. Laboratory tests results are metabolic acidosis, hypoglycemia, ketosis, elevated liver tests. Incidence 1:90 000.
Marker: Glutarylcarnitine (C5-DC) is the primary marker for GA I and secondary for GA II cut off: 0.21 µmol/L (8SD)

7.2 Branched chain organic acids (leucine, isoleucine, valine) metabolism disorders
Including Isovaleric academia (incidence 1:100 000), and 2-methylbutyrylCoA dehydrogenase deficiency.
Isovalerylcarnitine (C5) or its geometric Isomer, 2–methylbutyrylcarnitine is the primary marker for isovaleric academia (IVA) and 2-methylbutyrylCoA dehydrogenase (2-MBCD) deficiency.
Further organic acids metabolism disorders are:
methylmalonic acidemia, propionic acidemia and deficiencies of 3-methylglutaconyl-CoA hydratase

8. Acylcarnitine disorders

Clinically presenting with acidosis, increased anion gap, hypoglycemia, hyperammonemia.
The disorders include:
3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG)
3-ketothiolase deficiency
3-methylcrotonyl-CoA hydratase (carboxylase) (MCC) deficiency. Incidence 1:100 000
multiple-CoA carboxylase deficiency

Marker: 3-hydroxyisovalerylcarnitine (C5OH) (cut off at 0.8 µmol/L (12SD)) or its isomers, additional markers are tiglylcarnitine (cut off at 0.08 µmol/L (6SD)) and 3-methylglutarylcarnitine (cut off at 0.12 µmol/L (SD11)).

Norepinephrine, Plasma see Catecholamines, Plasma

Norepinephrine, Urine see Catecholamines, Urine

Normetanephrine see Metanephrines, Urine

Norwalk Virus, Antigen

Synonyms: Norovirus

Background: Named after the outbreak in a school in Norwalk, Ohio in 1969, the virus classified in the family Calicivirus together with the hepatitis E virus as a small, non-enveloped, positive single stranded RNA virus. It is the most common cause of viral gastroenteritis worldwide. It is transmitted predominantly by the fecal oral route, involving often contaminated seafood and water, but person to person transmission may occur. The animal pathogenic caliciviruses are, so far, not pathogenic to humans. Due to low dose of infection, virus excretion for several weeks after recovery in the feces and a high resistance to environmental factors, the virus spread efficiently. The infection is limited to the mucosal cells of the intestinal tract, causing watery diarrheas without bleeding, vomiting, low grade fever and abdominal pain, but a high number of infections are asymptomatic. Immunity is of short duration.

Sampling: approx. 2 g of stool

Reference Interval: Report of diagnostic finding
Antigen detectable

Occult Blood in Stool (Hemoccult)

Related Information: Carcinoembryonic Antigen (CEA), Serum
Ferritin, Serum or Plasma
Iron (Fe), Serum
Iron (Fe), Urine
Transferrin and Total Iron Binding Capacity, Serum

Background: In developing countries most common cause of blood loss in the stool is during hookworm infection, in industrialized countries colorectal adenocarcinoma. Other sources of bleeding are upper gastrointestinal tract or small intestine bleeding or other colorectal causes.
Used in screening particularly for colorectal adenocarcinoma, which is the second most common cause of death from cancer, but less than 30% sensitivity, and even in carcinomas >2 cm sensitivity if low.
Used in the diagnosis of upper gastrointestinal bleeding, celiac disease, Meckel diverticulum, vascular ectasias, polyposis.

Sampling: Patient should avoid vitamin C intake 5 days prior to sampling as well as alcohol, aspirin, halogens, cimetidine.
2 g stool, contact to toilet sanitizers or other disinfectants must be avoided. Ship to laboratory within one day.

Reference interval:		
	Negative	< 2 mg total hemoglobin per g feces
	Borderline	2-3 mg
	Positive	> 3 mg

Opiates Quantitative, Urine

Test includes: Morphine, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone.

Background: Opioids are the most effective analgesics with high potential for addiction.
Half life 2-4h, but 5-13h in neonates, volume of distribution 2-4 L/kg, protein binding 35%
False positive results are caused by poppy seeds; interpretation must be carefully if test is used for forensic purposes.

Sampling: 10 mL random urine

Reference Interval:		
	Therapeutic range	< 300 ng/mL
	Immunological drug screen: negative	< 300 ng/mL

Osmolality, Serum

Related Information: Antidiuretic Hormone, Plasma
Carbohydrate Deficient Transferrin (CDT)
Ethanol, Blood or Urine
Osmolarity, Urine
Sodium, Serum or Plasma

Background: Osmolality is a measurement of the number of particles in a solution independent of particle seize, weight, and charge.
Useful parameter in evaluation of electrolyte and water balance, hydration or dehydration status, antidiuretic hormone function, liver diseases, hyperosmolar coma.
High serum osmolality occurs in hypernatremia, dehydration, hypovolemia, hyperglycemia, azotemia and ethanol or methanol or ethylene glycol intoxication.
Low serum osmolality may be secondary to overhydration, hyponatremia, and alteration in antidiuretic hormone secretion.
Urine to serum ratio after 12h dehydration is usually > 3, in case of diabetes insipidus the ratio drops to 0.2-0.7.
During dehydration, the ratio serum sodium to serum osmolality remains normal
Sampling: 2 mL serum, ship to laboratory within 2h or refrigerate at 4°C.

Reference Interval:
275-295 mOsm/kg H_2O
Borderline 265-320 mOsm/kg H_2O
> 380 mOsm/kg H_2O may reflect hyperglycemia
> 400 mOsm/kg H_2O may be associated with grand mal seizures
> 420 mOsm/kg H_2O may be lethal
Urine to serum osmolality ratio: 1-1.3
Sodium in serum to serum osmolality ratio: 0.43-0.50

Osmolality, Urine

Related Information:
Antidiuretic Hormone, Plasma
Osmolality, Serum
Sodium, Serum or Plasma

Background: The parameter is used to evaluate the concentration ability of the kidney, antidiuretic hormone secretion, diabetes insipidus, dehydration and overhydration. Values < 400 mOsm/kg H_2O suggests renal impairment, < 100 mOsm/kg H_2O overhydration, > 800 mOsm/kg H_2O dehydration. To facilitate interpretation, serum osmolality should be measured.
Urine to plasma ratio is normally within 0.2-4.7. Low concentration ability is reflected by a low ratio slightly above 1.0, overnight fluid restriction gives values normally > 3.
Sampling: 2 mL of random urine

Reference Interval:

Neonates	75-300 mOsm/kg H_2O
Children and adults	250-900 mOsm/kg H_2O
Concentration ability after 14h fluid restriction:	> 800 mOsm/kg H_2O

Osmotic Fragility of Erythrocytes

Related Information: Bilirubin, Fractionated, Serum
Reticulocyte Count

Background: In hereditary spherocytosis (HS) an increase of osmotic fragility of RBC occur. HS patients present chronic hemolysis clinically asymptomatic up to severe uncompensated hemolytic forms. A number of inherent defects of the erythrocyte membrane are known. Vertical stabilization of the membrane is given by interactions between the spectrin ankyrin band-3 and protein 4.1 glycophorin C linkage, horizontal stabilization is achieved by spectrin heterodimer and actin and protein 4.1 interactions. HS affects vertical stability; the lipid bilayer is not stable, loosing lipids. The most common forms are spectrin and ankyrin deficiencies, others are band -3 and protein 4.2 deficiencies.

HS may lead to reticulocytosis, elevation of indirect bilirubin, MHC may be elevated, decreased or normal, and MCHC is elevated.

Increased fragility is observed in heriditary pyropoikilocytosis (HPP) caused by alpha-spectrin deficiency (defective vertical interactions) or caused by altered spectrin with alteration of the horizontal interaction, leading to spherocytes, elliptocytes and poikilocytes forms, decreased MCV, increased MCHC.

Osmotic fragility is increased in hereditary stomatocytosis characterized by elevated MCV, decreased MCHC

A higher resistance to osmotic lysis is seen in hereditary xerocytosis (HX) with normal or elevated MCV and increased MCHC. Normal osmotic resistance is observed in hereditary elliptocytosis (HE) with normal to elevated MCV and normal MCHC.

HE and HPP erythrocytes show increased thermal sensitivity.

Other conditions altering osmotic stability: Patients with malaria display osmotic fragility in infected and non infected RBC. Decreased osmotic fragility is observed in hypochromic RBC hemoglobin C disease and in thalassemia.

Sampling: 5 mL of EDTA whole blood, avoid hemolysis and clotting, transport to laboratory within 1h. Severe anemia causes abnormal results.

Reference Interval: Hemolysis begins at 0.44% and ends at 0.32% NaCl.
In 10% of all HS patients false negative are obtained. Incubation for 24h at 37°C will rule out the false negative results.

Osteocalcin, Serum or Plasma

Related Information: Alkaline Phosphatase Isoenzymes, Serum
Alkaline Phosphatase, Serum
Calcium, Serum or Urine
Hydroxyproline, Total, Urine
Parathyroid Hormone, Intact, Serum
Pyridinolines or Vitamin D, Serum

Synonyms: Bone-Gamma-Carboxyglutamic-Acid-Containing-Protein; BGP; Bone-GLA-Protein

Background: Osteocalcin is synthesized vitamin K dependent by osteoblasts and odontoblasts. It is the major noncollagen protein of the bone matrix 80% of the 49 amino acid, 5800 D protein is released into the bone matrix with a high affinity to hydroxyapatite. A small amount enters the circulation with a half life of 4 min and is cleared by the kidney, a glomerular filtration rate < 30 mL/min results in plasma levels above the reference range.

Serum levels are high in childhood, and a peak occurs in early puberty and in the menopause.

Useful in the diagnosis of primary hyperparathyroidism presenting with elevated values, in most cases also elevation of serum alkaline phosphatase.

In patients with secondary hyperparathyroidism values are elevated, in part due to decreased glomerular filtration rate.

Used as a marker for bone metastasis.

Used in monitoring osteoporosis, but not as a sole diagnostic tool.

In patients with rheumatoid arthritis values are in most cases decreased, but sometimes elevated. Usually, alkaline phosphatase values are moderate elevated.

Limitations: In patients with vitamin K deficiency, an osteocalcin with decreased activity, due to lacking decarboxylation is synthesized. The test does, however, not discriminate between functional and impaired osteocalcin.

Sampling: 1 mL serum, separate from red cells immediately since sensitive to proteolytic enzymes and freeze immediately. Ship frozen. Circadian rhythm with a peak in late afternoon, low in the morning.

Reference Interval:

Male	< 30 years	24–70 ng/mL
	30-49 years	14–42 ng/mL
	50-70 years	14–46 ng/mL
Female	Pre-menopausal (> 20 years)	11–43 ng/mL
	Post menopausal	15–46 ng/mL
	Osteoporosis patient	> 43 ng/mL

Oxalate, Urine

Related Information: Magnesium, Serum or Urine
Urine Analysis, Microscopic
Urinanalysis, Chemical, Screening

Synonyms: Calcium Oxalate, Urine

Background: Oxalate excretion is a predictor for calcium oxalate stones as hyperoxaluria is found in one third of the patients with oxalate nephrolithiasis. Hyperoxaluria is more common in patients with malabsorption (surgical bowl resection, in inflammatory bowl diseases 3-10% incidence of nephrolithiasis). Patients forming oxalate stones absorb higher fractions from the gut

and excrete more oxalate in the urine as non-stone formers. Oral calcium co-intake decreases urinary excretion in patients with ileal diseases.

High oxalate excretion at levels above 140 mg/day may be due to two types of genetic disorders: Type I (autosomal recessive), which may lead to renal failure, is a defect in glyoxalate metabolism with increased oxalate synthesis with high urinary glyoxylic acid and glycolic acid excretion. Type II displays a high urinary oxalic acid and L-glyceric acid with normal levels of urinary glycolic acid.

Limitations: Ascorbic acid urine concentrations higher than 10 µg/dL may give false positive elevated levels. Oxalate levels are increased during methoflurane, gelatin, strawberries, pepper, rhubarb, beans beets, spinach, tomatoes, chocolate, tea, pecans intake.

Sampling: Aliquot 10 mL of a 24 h urine collection, add approx. 0.5 mL 25% hydrochloric acid and mix well, note total quantity of the 24 h urine collection. If a 24 h urine collection is not possible, the concentration of oxalate in the first morning urine may give a rough estimation of the urine oxalate concentration; daily urine output must be estimated as well. Avoid vitamin C one day prior to sampling.

Reference Interval:		
	Female:	4–31 mg/24h
	Male:	7–44 mg/24h
	Children:	13–38 mg/24h

Oxcarbazepine, Serum

Synonyms: Trilepta®

Background: Oxcarbazepine (O) is indicated as monotherapy or as adjuvant treatment of partial seizures with or without secondary generalized tonic-clonic seizures. There is less hepatic enzyme induction as compared to carbamazepine and fewer hypersensitivity reactions, but hyponatremia occurs with the same frequency. Other side effects are dizziness, diplopia, and ataxia. O undergoes first pass metabolism to the active 10-hydroxy –oxcarbazepine (HC). Excretion in the glucuronide form of the 10 hydroxy metabolite.

Urinary excretion O: 1%, HC: 30% ; plasma binding HC: 45%; half life O: 2h, HC: 8-15h increase in renal disease and age; peak time 2-4h; peak concentration HC: 7-10 µg/mL after 300 mg orally.

Sampling: 2 mL serum

Reference Interval:	Therapeutic values:	
	Oxcarbazepine	< 3.0 µg/mL
	Oxcarbazepine-10-OH-Metabolite	5.0–30.0 µg/mL

P- ANCA see Antineutrophil Cytoplasmatic Antibody (ANCA)

P- 53 Antibody, Serum

Background: Mutations in the suppressor gene p53 are thought to be essential for cancer development. This gene is one of the important regulators of transcription, cellular cycle, DNA repair and apoptosis.

Inactivation of gene p53 leads to uncontrolled cell division, and further to transformation of normal cells into the carcinous cells. Observations that mutations in gene p53 appear under conditions of occupational and environmental exposures to chemical and physical carcinogens, such as vinyl chloride, radon, or aflatoxin B1, have proved to be of importance for the occupational and environmental health.

Because p53 mutations and subsequent changes in the protein encoded can induce an immune response occurring early in the carcinogenic process for some tumors that p53 autoantibodies may be a useful biomarker for risk of development of cancer. The prevalence of anti-p53 antibodies correlate with the degree of cancer malignancy. The increased incidence of anti-p53 antibodies statistically is also associated with higher frequency of mutations in gene p53.

-Asbestosis

There is statistically evidence for the relationship between p53 autoantibodies and the subsequent development of malignancy with a positive predictive value and an average lead-time to diagnosis up to 4 years.

-Prostate cancer

patients with prostate cancer have significantly higher total prostate specific antigen and p53-Abs than patients with benign prostatic disease (BPD), but serum p53-antibodies may not be related to clinical stage

-Ovarian

There is only low sensitivity for serum p53 antibodies in ovarian carcinomas alone, and no major additional effect of the detection rate of CA125 reported (but CA125 correlates with serum p53 antibodies). No associations are reported between p53 antibodies and clinical stage, age, and histology.

- Carcinoma of the uterus

Up to 23% of patients with carcinoma of the uterus have been reported with serum p53 antibody

- Breast cancer

Between 8% and 11% are positive for p 53 antibodies in screening assays.

- Pleural mesotheliomas

Up to 7% of patients with pleural malignant mesothelioma are positive for p53 antibodies, for lung cancer the sensitivity is 15%-17%.

- Esophageal squamous cell carcinoma

Up to 27%-30% of the patients are positive for serum p53 antibodies. A high concentration after tumor resection is a predictive marker for recurrence. A high concentration of p53 is an independent prognostic factor, a high concentration also indicates an advanced stage of esophageal carcinoma. The positive rate for serum-p53 antibodies may be higher as

compared to CEA in patients with squamous cell carcinoma.

- Adenocarcinoma

  Serum p53 antibodies are detected in up to 18%-63% of patients with adenocarcinoma and but only in 3% of patients with adenoma. As compared to the two other markers for adenocarcinoma, carcinoembryonic antigen (CEA) and carbohydrate antigen CA19-9, which showed no significant difference between superficial colorectal adenocarcinoma and adenoma, p53 can differentiate between the two dysplasias.

False positive in normal human serum: 0%-1.1% and up to 3.6% in respiratory diseases. No false positives in SLE or Sjoegren's syndrome or during pregnancy so far reported.

Sampling: 2 mL serum

Reference Interval: Negative:
median value of serum-p53 antibodies in healthy control individuals: 0.33 U/mL (range: 0.0-4.39 U/mL)
Positive: > 1.3 U/mL
High positive: > 10 U/mL

Pacerone® see Amiodarone, Serum

Pancreatic Amylase, Serum see Amylase, Isoenzymes, Serum

Pancreatic Elastase see Fecal Pancreatic Elastase 1

Papillomavirus (HPV) DNA see Human Papillomavirus (HPV) DNA

Paracetamol see Acetaminophen, Serum

Parainfluenza Virus, Serology

Background: Laryngotracheitis (croup), characterized by barking cough, inspiratory stridor and hoarseness is the most common disease in children caused by parainfluenza virus types 1, 2 or 3. Parainfluenza viruses also cause otitis media, conjunctivitis and common cold. Respiratory syncytial virus is the predominant cause of serve acute respiratory illness in children, followed by parainfluenza viruses. There is no protective immunity after parainfluenza infection.

Limitations: Cross reactivity with other viruses such as mumps may occur. Antibody production particularly in infants may be low.

Sampling: 1 mL serum during the acute phase and reconvalescent serum required. 3 fold rise in titer is diagnostic for infection.

Reference Interval: Antibody titer for types 1, 2, 3 and 4: negative < 1:40

Parasites Microscopy, Feces

Overview: please see

Amebas
Giardia lamblia (cyst form)
Helminth (eggs)

Sampling: Approx. 2 g stool in sterile tube

Parathyroid Hormone Intact, Serum

Related Information: Calcium (Ca), Total, Serum or Urine
Creatinine, Serum or Plasma
Osteocalcin, Serum or Plasma
Phosphate Inorganic, Serum
Vitamin D, Serum

Synonyms: Parathormone; PTH; PTH 1-84

Background: PTH is synthesized and secreted by the parathyroid gland. Intact PTH is a single chain polypeptide of 84 amino acids and a MW of 9500kDa. The secretion is regulated in a negative feed back loop by ionized calcium and by ionized magnesium, which is required for appropriate PTH release, and negatively by 1,25 Dihydroxyvitamin D3.

Function: Maintaining calcium levels in the extracellular fluid (ECF) by up regulating bone resorption and release of calcium and phosphate, by stimulation of calcium reabsorption from the renal tubulus and by stimulation of renal synthesis of 1,25 (OH_2) vitamin D3, increasing intestinal calcium and phosphate absorption, thus increasing serum calcium levels and decrease serum phosphate levels.

PTH has a half life of < 4 min and is cleared by the kidney and liver. In the liver, the PTH is cleaved into fragments, the inactive carboxy terminal fragments circulate approx. 30 min, since they are cleared by glomerular filtration.

Diagnostic used in patients with

Hypercalcemia: More than 90% of the patients with hypercalcemia are diagnosed with primary hyperparathyroidism (PHP) and humoral hypercalcemia of malignancy (HHM). Other, rare causes are familial hypocalciuric hypercalcemia (FHH), granulomatous diseases, thyrotoxicosis, vitamin D intoxication, lithium and thiazides medication, Addison disease, hypothyroidism, and PTH receptor defects.

FHH, an autosomal dominant disease caused by a defect in the calcium sensing receptor, is characterized by low urine calcium levels with the urine calcium: creatinine ratio usually <0.01

and with an elevated serum PTH.

HHM is characterized by appropriate PTH levels and caused either by a parathyroid hormone related protein with similar biological activity as PTH, which is synthesized by tumors, a or by cytokines released by tumors (particularly from myeloma) stimulationg osteolytic hypercalcemia.

Hypocalcemia: May be caused by hypoparathyroidism, rickets, low serum albumin, acute pancreatitis, sepsis, tumor lysis, renal insufficiency, and magnesium deficiency.

Hypoparathyroidism is a risk in thyroid surgery, in conditions leading to organ destruction as iron overload, autoimmunity, granulomatous diseases, metastasis and retardation in development (Di George syndrome).

Hypocalcemia can be drug induced by calcitonin, mithramycin, phosphates, phenytoin in combination with phenobarbital, foscarnet.

Sampling: 1 mL serum, centrifuge and freeze soon.

Reference Interval: 15-65 pg/mL

Parietal Cell Antibody

Related Information: Vitamin B 12, Plasma or Serum
Folic Acid, Serum
Glutamic Acid Decarboxylase Antibody
Intrinsic Factor Antibody (IFA)
Liver Kidney Microsomal Antibodies (LKM Antibodies)

Background: Gastric parietal cells secrete intrinsic factor which binds to vitamin B 12 thus allowing absorption in the ileum. Parietal cells also secrete hydrochloric acid, cathepsin and other proteins, resulting in case of autoimmune gastritis in atrophic gastritis with achlorhydria and vitamin B 12 deficiencies (pernicious anemia).

Useful parameter in the diagnosis, through not very specific, in pernicious anemia (50%-95% of the patients have antibodies). There is no correlation with the degree of malabsorption of vitamin B 12. In 20%-30% of the patients cross reactivity of the antibodies in thyroiditis and diabetes mellitus was observed.

Limitations: Parietal cell antibodies are detectable in 30%-60% of patients with chronic atrophic gastritis, in 20% with gastric ulcers, in 30% with Sjoegren syndrome, in 30% of first degree relatives of patients with pernicious anemia and in healthy adults, increasing with age from 2% in young adults to 10% in 80 years old individuals.

Sampling: 1 mL serum

Reference Interval: Negative (titers < 1:40)

Partial Thromboplastin Time (PTT) see Activated Partial Thromboplastin Time

Parvovirus B19, Serology

Background: Parvovirus, a non-enveloped, small (22 nm), single negative stranded DNA virus with icosahedral symmetry, causes a wide variety of symptoms.

Transmission occurs by respiratory droplets, transplacental and blood transfusions. In the US 50% of the adult population are seropositive for antibodies. There are no animal reservoirs known.

Infection of erythroblasts causes transient aplastic anemia, particularly in patients with sickle cell anemia, thalassemia, and spherocytosis. Immune complexes causes rash, together with infection of endothelial cells of the blood vessels the erythema infectiosum or slapped cheek syndrome or fifth disease may be explained, as well as arthritis.(The other four maculopapular rash diseases during childhood are measles, rubella, scarlet fever, roseola).

Infection of the fetus during the first trimester may cause fetal death, during the second trimester hydrops fetalis. Third trimester infection usually does not cause clinical alterations.

Detection of specific IgM during the second week post infection to up to 6 month. IgG titers rise shortly after IgM rise and lasts for years. Absence of antibodies cannot exclude infection, particularly in immunocompromised patients.

Usually, a lifelong immunity results from infection.

Sampling: 1 mL serum

Reference Interval: Differentiation of immunoglobulin class

IgG antibody	
negative:	< 20 U/mL
borderline:	20–24 U/mL
positive:	> 24 U/mL
IgM antibody	
negative:	< 20 U/mL
borderline:	20–24 U/mL
positive:	> 24 U/mL

Validation test is performed by immunoblot

Paternity Testing

Background: Parentage testing now applying the DNA profiling method allows direct investigation of the genetic material inherited from the parents to the child. Using recent PCR technology DNA analysis enables the determination of paternity or maternity with an accuracy of 99,99% and higher.

To determine suspected paternity, the examination of the child, the mother and the putative father(s) is required. If it is not possible to include the child's mother, paternity still can be determined with the child and the father, though at a lower level of certainty. This also applies to cases where the putative father can not be examined as in case of death. Descent can be clarified by testing the paternal grand parents or siblings of the putative father.

More complex family relationships may be confirmed or excludes by means of DNA analysis.

As potential success varies with the degree of relationship of the respective persons, preceding consultation is strongly recommended.

DNA testing is available for:

- determination of suspected paternity
- determination of suspected maternity
- determination of grand parentage
- paternity testing without the mother
- determination of suspected family relationships
- prenatal testing (amniotic fluid or chorionic villus sample required)
- testing of biopsy tissue material
- determination of identical or non-identical twins
- DNA-profile and blood groups

DNA testing is performed by using polymerase chain reaction (PCR)) method. DNA fragments with repetitive sequence motifs, short tandem repeats (STR), are enzymatically amplified and subsequently measured for their lengths. Depending on the case to be solved up to 30 STR loci may be analyzed.

Sampling: Materials necessary for proper collection and shipping of samples are provided by the laboratory. The following specimens are suited for analysis:

- 1 mL blood anticoagulated by EDTA
- 2-4 buccal swabs (each person to be examined)
- tissue material from autopsy or biopsy; dried blood spots; hairs with roots (at least 5-10)
- amniotic fluid: 10-20 mL of native, untreated fluid or cultured amniocytes
- chorionic villus sample: 100 mg of sample or 20 mL of cultured cells

Specimen should be collected by a physician or medical staff familiar with blood collection. Collection has to be documented on a special form to ensure identity of samples to be examined.

Pertussis see Bordetella pertussis

Phenprocoumon, Serum

Synonyms: Marcumar®

Background: As an oral anticoagulant phenprocoumon is a vitamin K antagonist. Parent compounds are 4-hydroxycoumarin and indan-1,3-dione, other derived compounds are warfarin, 4-hydroxycoumarin, dicumarol, acenocoumarol or anisindione.

Coagulation factors II, VII, IX, X and the anticoagulant proteins C and S are synthesized in the liver and inactive unless 9 to 12 amino terminal glutamic acid residues are carboxylated. The carboxyglutamate residues bind Ca^{2+} which is necessary for the catalytic complex. The reaction requires carbon dioxide, oxygen and reduced vitamin K. To generate reduced vitamin K, an exposide reductase reduces the vitamin K epoxide. The enzyme is inhibited by oral anticoagulants.

Phenprocoumon has a longer half life (5 days), a longer duration of action (7-14 days) and a slower onset as compared to warfarin.

Sampling: 2 mL serum

Reference Interval: Therapeutic Values 1.5–3.5 µg/mL
Toxic values: > 5 µg/mL

Phenytoin, Serum or Plasma

Related Information: Carbamazepine, Serum
Ethosuximide, Serum or Plasma
Phenobarbital, Serum or Plasma
Primidone, Serum or Plasma
Valproic Acid, Serum or Plasma

Synonyms: Antisacer®; Cerebyx®; Dilantin®; Dintoina®; Diphenylan Sodium®; DPH; Diphenylhydantoin ; Ditan®; Epanutin®; Epinat®; Fenitoina; Fenytoin®

Background: Introduced in 1938, phenytoin is a diphenyl-substituted hydantoin with low sedative properties. The soluble form is the phosphoester fosphenytoin which is rapidly converted into phenytoin in the plasma. Phenytoin acts on the conductance of the membranes for ions, in therapeutic concentrations particularly sodium channels, on membrane potentials, on the concentration of norepinephrine, acetylcholine and gamma aminobutyric acid. In high concentrations the release of serotonin and norepinephrine is inhibited, dopamine uptake is enhanced, and monoamine oxidase activity is inhibited. Calcium permeability is inhibited, so calcium dependent release of hormones and neurotransmitters may be affected.

The absorption of the drug is dependent on the formulation; phenytoin sodium is nearly completely absorbed from the gut, plasma peak time ranges from 3h to 12h post ingestion. Fosphenytoin is well absorbed after im injection. Phenytoin accumulates in brain, liver, muscle, and fat tissue.

Phenytoin is almost totally metabolized to inactive metabolites and excreted with the urine. If the metabolization capability of the liver is saturated, drug level increases rapidly to toxic levels, therefore only small increase of the daily dose of 30 mg each time is recommended. Steady state is reached after 5-7 days for low dosage, for high levels it takes 4-6 weeks. Since phenytoin is highly plasma bound, other plasma bound drugs can displace phenytoin. Metabolized by polymorphic cytochrome P450 2C9 and 2C19.

Limitations: Fosphenytoin is measured not as reliable as phenytoin.

Bioavailability 87%-93%; urinary excretion 6%-10%; plasma binding 70%-99% decreased in renal disease, hepatitis, neonates, hypalbuminemia, cirrhosis, nephritic syndrome, pregnancy, burn patients; volume of distribution 0.6-0.7 L/kg increased in neonates, renal disease; half life time 6-24h (children 10h) increased in premature newborns and decreased in renal disease; peak time 3-12h; peak concentration 5-30 µg/mL after a 300 mg dose orally in steady state.

Sampling: 2 mL serum

Reference Interval:	Therapeutic values	10-20 µg/mL
	Toxic values	> 25 µg/mL
	Lethal	> 100 µg/mL
	may precipitate seizures at	> 40 µg/mL

Phosphatase acid see Acid Phosphatase total, Plasma

Phosphatase alkaline see Alkaline Phosphatase, Serum

Phosphatase alkaline, Isoenzyme

see Alkaline Phosphatase, Liver- Intestine- Bone Isoenzymes, Serum
see Alkaline Phosphatase, Placental Isoenzyme, Serum

Phosphate Inorganic, Serum

Related Information: Amino Acid, Screening, Plasma or Urine
Calcium (Ca), Total, Serum
Calcium (Ca), Urine
Ethanol, Blood, Serum or Urine
Parathyroid Hormone, Intact, Serum
Vitamin D, Serum

Background: 99% of the body phosphate is stored in bone and striated muscle and only 1% in plasma. Clinically, hypophosphatemia is characterized by chronic myopathy, osteopenia, osteomalacia, and rhabdomyolysis. Phosphate also alters cardiac function with arrhythmias and cardiomyopathy. Low phosphorus levels also alter oxygen release from hemoglobin and may lead to hemolysis.
Useful in the evaluation of hyperphosphatemia associated with exercise, hypovolemia, acromegaly, hypoparathyroidism, skeletal metastasis, hypervitaminosis D, sarcoidosis, milk alkali syndrome, pulmonary embolism, renal failure (more than 80% function impairment) and liver failure, diabetes mellitus. In thrombocytosis, serum concentrations are elevated, but plasma concentrations are normal.
Decreased phosphate levels occur in hypoparathyroid state, antacid-, steroid-, diuretic-, medication, vitamin D deficiency, sepsis, renal disorders, dialysis, emesis, and diarrhea.
Limitation: Up to 40% of the adult population may have serum levels below or at the lower limit of the reference interval. Multiple sampling is recommended.
Sampling: 1 mL serum or plasma, assay can not be run with oxalate or citrate plasma. There is a diurnal nadir at noon, a peak at midnight and a plateau in the afternoon. Variation is about 0.2 mg/dL. Avoid hemolysis, keep sample refrigerated.

Reference Interval:	Infants	1.45-2.42 mmol/L
	Children	4.29-1.94 mmol/L
	Adults	0.81-1.45 mmol/L
	Hypophosphatemia	< 0.5 mmol/L

Phosphate Inorganic, Urine

Related Information: Calcitonin, Serum or Plasma
Calcium (Ca), Total, Serum
Calcium (Ca), Urine
Parathyroid Hormone, Intact, Serum
Somatotropin, Serum

Background: High urinary phosphate level occurs in primary hyperparathyroidism, vitamin D deficiency, renal tubular acidosis, state of elevated calcitonin, atrial natriuretic hormone or vasopressin.

Decreased urinary excretion occurs in malnutrition, hypoparathyroidism and vitamin D intoxication, metabolic alkalosis and elevated levels of glucosteroids or growth hormone.

Some drugs such as aluminium salts, diltiazem, aspirin, bicarbonate, corticosteroids, and diuretics may alter the excretion of phosphate.

Sampling: Ship to the laboratory a 5 mL aliquot of a 24 h urine collection. Note total quantity.

Reference Interval: Adults on unrestricted diet:
15-48 mmol/24h
Children age 0-6 years:
There is a decrease of the phosphate to creatinine ratio from 18 (first year of life) to 1 at the age of > 6 years (mol/mol).

Phospholipid-Antibodies, Serum

Related Information: Cardiolipin Antibody
Lupus Anticoagulants / Lupus Inhibitors, Serum or Citrateplasma
Applies to Phosphatidylcholine-, phosphatidylethanolamine-, phosphatidylglycerine-, phosphatidylinositol- and phosphatidylserine antibody

Background: Lupus anticoagulant, anticardiolipin antibodies (ACA) and phosphatidylcholine-phosphatidylethanolamine-, phosphatidylglycerine-, phosphatidylinositol-, phosphatidylserine antibodies are part of the heterogenous class of antilipid antibodies (APA).

Useful parameter in the assessment of SLE, the anti phospholipid syndrome (APS), in the diagnosis of recurrent thrombotic events, and in the diagnosis of recurrent thrombocytopenias of unknown origin.

Primary APS is defined as recurrent thrombosis or recurrent miscarriage without other risk factors,

secondary APS as thrombotic events in known SLE or collagenosis.
APA is part of the diagnostic criteria of SLE according to the American College of Rheumatology.
Limitation: May be transient positive during infections or medication.
Sampling: 2 mL serum
Reference Interval: Negative: < 12 E/mL

Plasmin Inhibitor see Alpha$_2$ - Antiplasmin, functional

Plasminogen, Plasma

Background: Plasminogen is converted into plasmin by tissue plasminogen activator (tPA) or by an urokinase type activator (uPA). Plasminogen lysis fibrin clots, fibrinogen and inactivates factor Va and VIIIa. Decreased plasminogen conditions are liver diseases, thrombolytic therapy, disseminated intravascular coagulation (DIC), and the rare hereditary plasminogen deficiency syndrome, predisposing patients to venous thrombosis. Incidence of the latter disorder is 0.3% -0.7% in the general population and up to 2% in patients with venous thrombosis and 1.4% in patients with arterial thrombosis. The serve form may present with ligneous conjunctivitis.
Limitations: Plasminogen levels can increase during pregnancy; newborn levels are lower at 60% and increase to 100% by the age of 6 month.
Sampling: 2 mL citrate plasma. Separate plasma as soon as possible, freeze plasma immediately and ship frozen.
Reference Interval: 85%-110%

Plasminogen Activator Inhibitor 1

Related Information: Plasminogen, Plasma
Synonyms: PAI-1
Background: PAI-1 is present in the liver, endothelial and platelets. PAI-1 inhibits tissue plasminogen activator (tPA) and urokinase type plasminogen activator (uPA).
Increased PAI-1 levels are associated with increased incidence of myocardial infarction, however the association is not significant in all studies and is not an independent factor. High plasma glucose levels or high insulin levels are associated with synthesis of PAI-1.
Limitation: As an acute phase reactant elevated levels occur after a thrombotic event. It also increases during pregnancy.
Sampling: 1 mL of citrate plasma. PAI-1 has a circadian rhythm with a morning peak and low in the afternoon. Plasma must be separated immediately, since platelets contain PAI-1. Store up to 2h on ice or freeze immediately. Ship frozen.
Test system used: Functional assay
Reference Interval: < 10 U/mL

Platelet Antibodies Free or Bound

Related Information: Platelet Count

Test includes: Antiplatelet antibodies attached to platelets and antiplatelet antibodies not bound to platelets.

Background: Platelet antibodies develop either as autoimmune antibodies in idiopathic thrombocytopenic purpura, (ITP), or are inducible by drugs (DIT) such as heparin (heparin-induced thrombocytopenia HIT), or are due to alloimmune reactions such as neonatal alloimmune thrombocytopenia (NAIT), posttransfusion purpura (PTP), post-transfusion refractoriness.

- IPT is characterized by an isolated thrombocytopenia induced by autoantibodies against the platelet glycoprotein IIb/IIIa or Ib/IX. Platelets are either normal in seize or enlarged. In children, IPT is an acute disorder with good prognosis, in adult the chronic form is predominant.
- NAIT is a condition during pregnancy due to maternal antibody reaction against father derived platelet antigen (the PI^{A1} antigen of the glycoprotein IIb/IIIa group) of the fetus. Newborn platelet counts are < 100 000 / µL, becoming normal within 2 weeks after birth. Incidence is approx. 1:1000.
- PTP is a condition where antibody responses induced by transfused platelets which express PI^{A1}antigen not only destroy the transfused but also the patients own platelets. Onset is usually one to two weeks after transfusion with sudden and severe thrombocytopenia (< 10 000 / µL), resolving within 2 weeks.
- DIT which may be severe (< 10000 / µL), but resolve within 1-2 weeks after discontinuing, is either caused by antibodies (immune cause), by bone marrow suppression or by platelet destruction. Immune reactions are found after quinidine, quinine, sulfonamides, sulfonylureas, salicylates and other drugs but in most of them with poor pharmaceutical proof to cause DIT. Bone marrow suppression is caused by ethanol, thiazide, procarbazine cytostatic drugs and platelets may be destroyed by ristocetin, bleomycin, and protamine.
- Post transfusion platelet refractoriness occurs after multiple transfusions which induce antibody production against HLA-A or HLA-B and less frequent other antigens.

Sampling: 5 mL EDTA whole blood and in addition 1 mL serum

Reference Interval: Antibodies not detectable

Platelet Count

Related Information: Activated Partial Thromboplastin Time
Blood Count, Complete
Lupus Anticoagulants / Lupus Inhibitors, Serum or Citrateplasma
Platelet Antibodies (free, bound)
Reticulocyte Count

Background: Thrombocytes are cells without nucleolus, 2-3 µm in diameter. Platelet production is under the control of thrombopoietin. Circulation time in the blood of platelets is 7-10 days; macrophages of the RES remove the cells from the circulation. Platelets are pooled to

30%-35% in the spleen, 65%-70% are circulating with circadian rhythm peaking during midday. Activated platelets are changing form and immunity by antigen expression on the surface by granula transport from the core to the surface membrane.
Platelet count is a useful parameter in the diagnosis of bleeding, in monitoring during cytostatic or radiation therapy, in the assessment of malignancies of the bone marrow, and in the diagnosis of autoimmune diseases.

Thrombocytosis:

Mild	500-700 /nL
Moderate	700-900 /nL
Severe	> 900 /nL

Causes for thrombocytosis:

- Primary: Disease of the bone marrow such as defects in stem cells associated with polycythemia vera, chronic myelogenous leukemia, idiopathic myelofibrosis, essential thrombocythemia (inci dence 2-3 per million, peak in the age group of 40-60 years and in late puberty).
- Secondary: Either due to release of thrombocytes from the spleen during stress (increase up to 50%, rapid decline within 1h), post partum, after surgery (initially decreasing, then increasing up to 2.5 fold after 1 week, decreasing to normal within 2 weeks), exercise, rebound following thrombocytopenia, bone marrow activation after bleeding episodes, iron deficiency, infections (particularly in children counts >700 / nL), inflammation or carcinomatosis.

Primary thrombocytosis is usually associated with higher platelet counts and both arterial and venous thrombosis, secondary thrombocytosis with venous complications only and in co-association with other risk factors.

Thrombocytopenia:

Moderate	100–50 /nl
Serve	< 50 /nl

Clinically thrombocytopenia presents with petechia, purpura, bleeding of mucous membranes, epistaxis, gastrointestinal, urogenital bleeding,
Causes are either decreased production or increased destruction of platelets:

- Decreased production (account for 5%-10% of cases of thrombocytopenia)
  Hereditary forms:
  Wiskott Aldrich Syndrome, Chediak-Higashi Syndrome, Alport-Syndrome, Fechtner Sy drome, Trousseau Syndrome, May Hegglin Syndrome, v. Willebrand TypIIB, Bernard Soulie Syndrome, mediterran macrothrombocytopenia,
  Acquired forms:
  Aplastic anemias, malignancies of the bone marrow, leukemias, chemotherapy, radiation.
- Increased destruction:
  Immune mediated:
  IgG binding to the glycoproteins of the membrane of the human platelet antigen system tri

gering an enhanced clearance of the complex. The form is in part drug induced (1 in 1 million individuals prescribed a drug develop thrombocytopenia).
Non immune mediated:
disseminated intravascular coagulation (DIC), sepsis or after multiple blood transfusions (usally serve thrombocytopenia).
Mild thrombocytopenia occurs in patients with splenomegaly due to platelet pooling (up to 90% in the spleen).

A heparin induced, non-immunologic form begins within 1-5 days after heparin therapy (incidence 25%). A heparin induced immunologic form begins 5-20 days after heparin therapy and is associated with thromboembolism (incidence 1%)
Carcinoma associated thrombocytopenia's are due to invasive bone marrow metastasis, splenomegaly, carcinoma related DIC or chemotherapy.
During pregnancy 15% of pregnant women display a platelet count of less than 150 /nL, 8% of the women even less than 130 /nL.
Sampling: 3 ml EDTA blood
Reference Interval: 150-450 / nL (150 000-450 000 /µL)
Platelet counts in healthy term infants and preterm infants less than 1500g is comparable to that in adults. The counts rises during the first months. Counts between 500/uL and 750/uL have been observed in infants under 2 years apparently healthy.
Intra day variation: 7%-10%

high risk for bleeding	< 10 /nL
high risk for thromboses	> 1000 /nL

Pneumococcal Antibody, Serology

Background: Pneumococcal polysaccharide vaccines contain more than 20 types of capsular polysaccharides, accounting for 80-90% of all bacteremic pneumococcal diseases. 80-95% of the individuals receiving vaccination respond by demonstrable antibodies. Vaccination is recommended for adults at high risk of complications from respiratory infections particularly those with cardiovascular and chronic pulmonary diseases, for adults and children older than 2 years at high risk of pneumococcal disease such as splenic dysfunction or asplenia, Hodgkin's disease, multiple myeloma, chronic liver disease renal failure, CSF leaks, immunocompromised state including HIV, and for healthy elderly (>65 years). Revaccination to consider after 3-5 years. Safety in pregnant woman has not been evaluated sufficiently. The efficiency of vaccines for children under 2 years is under investigation.
Sampling: 1 mL serum
Reference Interval: Immunity present > 15 mg/L

Pneumocystis carinii, DNA Detection

Background: In immunocompromised patients (transplantation, hematologic malignancies, AIDS, corticosteroid therapy), Pneumocystis carinii (PC) causes pneumonia and may affect to a lesser degree lymph nodes, liver, spleen bone marrow. In HIV infected patients, PC pneumonia may be the first sign of HIV infection.

Sampling: Sputum or bronchoalveolar lavage (BAL)

Reference Interval: Report of diagnostic finding
Direct detection by PCR: DNA not detectable

Poliomyelitis Virus Type I, II, III, Serology

Background: Poliomyelitis virus is now, due to vaccination programs, rarely seen, but still present and has to be considered in patients with acute aseptic meningitis if the patient has not been immunized.

Sampling: 1 mL serum

Reference Interval: Protective immunity

Negative	< 9 IU/mL	(no immunity present)
Borderline	9–12 IU/mL	(immunity questionable)
Positive	> 12 IU/mL	(immunity present)

Porphobilinogen, Urine

Related Information: Delta(5)-Aminolevulic Acid, Urine
Porphyrins, Quantitative, Urine or Stool

Background: Porphobilinogen is a heme precursor. The excretion increases in acute porphyrias, making it a good screening test for acute intermittent porphyria, hereditary coproporphyria and for variegata porphyria. During the latent phase of the diseases often within the reference interval.

Sampling: 10 mL aliquot of a 24h urine, keep cool and protect from light, note total quantity. Specific results are obtained when collected during acute attack of abdominal pain, pain of the extremities, tachycardia, hypertension, nausea, vomiting, neurologic abnormalities, dark urine.

Reference Interval: < 0.5 mg/g creatinine
< 1.6 mg /24 h

Porphyrins Quantitative, Urine or Stool

Related Information: Delta-Aminolevulinic Acid, Urine
Iron (Fe), Serum or Urine
Transferrin and Total Iron Binding Capacity, Serum
Porphobilinogen, Urine

Test Includes: Uroporphyrins (octacarboxylporphyrins), heptacarboxylporphyrins, hexa-carboxylporphyrins, pentacarboxylporphyrins, coproporphyrins (tetracarboxylporphyrins)

Background: Porphyrins are heme precursors which accumulate in case of an enzyme defect in the heme synteresis pathway. The accumulation pattern indicates the defective enzyme.

In secondary porphyrias, the most common form is toxic inhibition of porphobilinogen synthetase leading to an increased excretion of porphobilinogen (PBG) and delta-aminolevulinic acid (ALA). Clinically, porphyria presents with abdominal pain in absence of fever and leukocytosis, peripheral neuropathy, in some cases seizures, psychosis, and abnormalities of the CNS.

The test is used in combination with porphobilinogen to diagnose porphyria as a first choice approach. If both tests are negative, erythropoietic protoporphyria (accumulating the water insoluble protoporphyrin without urinary excretion) has to be considered. In case of delta –aminolevulinic acid dehydrogenase deficient porphyria, only ALA accumulates and urinary excretion increases.

In the autosomal recessive congenital erythropoietic porphyria, early infancy onset with severe hemolysis and photosensitivity, uroporphyrinogen III cosynthase activity is reduced. Onset in early childhood presenting with elevated urinary levels of uroporphyrin and coproporphyrin (red urine), elevated fecal levels of uroporphyrin, coproporphyrin and zinc protoporphyrin. Plasma levels of uroporphyrin and coproporphyrin I levels are elevated. (see Uroporphyrinogen III Synthetase). In the erythrocytes uroporphyrin, coproporphyrin and zinc-protoporphyrin are increased.

The rare, early infancy onset, autosomal recessive hepatoerythropoietic porphyria (uroporphyrinogen decarboxylase deficiency) is characterized by elevated urinary uroporphyrin and heptacarboxylporphyrin III levels, elevated plasma uroporphyrin and an increase in erythrocytic zinc-protoporphyrin.

In acute intermittent porphyria (onset in adulthood), the second most common porphyria and with autosomal dominant inheritance, the porphobilinogen deaminase enzyme is defect. It presents with ALA, PBG, uroporphyrin, and coproporphyrin elevation in the urine as well as increased plasma porphyrins during the acute episode.

The acute attack of hereditary coproporphyria, a rare autosomal dominant form with, coproporphyrinogen oxidase defect, seen in adulthood presentes with increased urinary coproporphyrin, ALA and PBG as well as elevated fecal and plasma coproporphyrin III levels.

Porphyria variegate (autosomal dominant, protoporphyrinogen oxidase defect) presents in adulthood with urinary coproporphyrin higher than uroporphyrin during the acute phase and increased urinary ALA and PGB levels. Fecal protoporphyrin is higher than coproporphyrin.

Porphyria cutanea tarda, the most common form of porphyria, known as type I, (acquired) and type II and III (autosomal dominant), defined as an enzyme defect of uroporphyrinogen decarboxylase and presenting with increased urinary excretion of uroporphyrin and heptacarboxylporphyrin but normal PBG excretion. Fecal isocoproporphyrin and heptacarboxylporphyrin III are elevated. Plasma uroporphyrin is elevated.

Lead poisoning presents with urinary ALA higher than PBG (PBG often within normal range), elevated urinary coproporphyrin and increased free erythrocyte protoporphyrin.

Sampling: Urine: 10 mL aliquot of a 24h urine collected in a clean, dark container to protect from light. Keep at 4°C during the collection period and for transport.
Note total quantity.
Stool: approx. 5 g stool
Erythrocytes: 1 mL EDTA blood

Reference Interval:

Urine (µg/24h)	
Uroporphyrins (octacarboxyl)	3-25
Heptacarboxylporphyrins	< 7
Hexacarboxylporphyrins	< 6
Pentacarboxylporphyrins	< 7
Coproporphyrins (tetracarboxyl)	
Male	25-150
Female	8-110
Feces	< 34 µg/g of stool

Potassium, Serum or Plasma

Related Information: Aldosterone, Serum or Plasma
Amino Acid, Screening, Plasma or Urine
Calcium, Serum
Chloride, Serum, Plasma, Blood
Digoxin, Serum
Magnesium, Serum
Potassium, Urine
Renin, Plasma
Sodium, Serum or Plasma

Synonyms: Kalium

Background: Useful in elderly patients, in intravenous alimented patients, therapeutic diuretic medication, renal diseases, evaluation of hypertension. Evaluation of muscular weakness, confusion, gastrointestinal disorders, laxative abuses, fistula and tube drainages, cardiac arrhythmias, mineralocorticoid dysbalance,

Hypokalemia:

Occurs in 90% of hypertensive patients with primary aldosteronism. Also found in patients with secondary hyperaldosteronism and in patients with Cushing syndrome,

Loss of potassium into the gastrointestinal tract occurs by vomiting, diarrhea, laxatives, tumors, jejunoileal bypass, enteric fistulas, malabsorption,

Occurs in burns, alkalosis, Bartter syndrome, Gitelman syndrome, alcoholism, anabolic status, folic acid deficiency.

Drugs which may cause hypokalemia: caffeine, verapamil overdose, chloroquine overdose, diuretics, mineralocorticoids, high dose penicillin, nafcillin, ampicillin, carbenicillin, aminoglyco-

sides, cisplatin, foscarnet, amphotericin B, beta adrenergic agonists, theophylline overdose, insulin overdose.

Hyperkalemia:

May be associated with trauma, potassium containing medication, high dose trimetoprim –sulfamethoxazole, ACE inhibitors, Addison disease, ketoacidosis in diabetes mellitus, in status of increased serum osmolality, in renal diseases, malignant hyperthermia, in renal tubular acidosis. Suppression of aldosterone release by heparin may lead to hyperkalemia.

Limitations: False hyperkalemia is caused by hemolysis, which may be undetectable, after collection. False high values may occur in the serum of patients with thrombocythemia, since platelets release Potassium during coagulation. WBC also release potassium when clotting, particularly in patients with chronic myelogenous leukemia. Low sodium intake may mask the hypokalemia in aldosteronism.

Serum/plasma potassium is ph dependent. Increase of ph of 0.1 decreases potassium by 0.6 mmol/L. Therapeutic increase in ketoacidosis will decrease plasma/serum potassium. During insulin administration, plasma/serum potassium decrease due to move of potassium into cells.

Sampling: Avoid small needles. Hand clenching and stasis increase potassium values ! Avoid any hemolysis. Separate serum or plasma within 1h.

Reference Interval: Plasma 3.5–5.5 mmol/L

Serum values may be 0.1 mmol/L higher.

Even slight hemolysis increase values substantially since red cell potassium concentration is approx 100 mmol/L.

Critical values: Newborns < 2.5 mmol/L and > 7.0 mmol/L

Adults < 2.5 mmol/L and > 6.5 mmol/L

Prednisolone, Serum

Related Information: Aldosterone, Serum or Plasma

Aldosterone, Urine

Adrenocorticotropic Hormone, ACTH, Plasma

Cortisol, Serum or Plasma

Cortisol, Free, Urine

Sodium, Serum

Potassium, Serum

Synonyms: Delta-cortef®; Econopred®; Pediapred®; Hydelta-t.b.a.®

Background: Corticosteroids have numerous and widespread effects, including alteration of carbohydrate, protein and lipid metabolism, maintenance in fluid and electrolyte balance, preservation of the appropriate function in cardiovascular, immune, kidney, muscle, and the endocrine system, and in stress coping.

Mainly affected components of the immune defense are:

- Macrophages and monocytes: arachidonic acid, prostaglandins and leukotrienes are inhibited by induction of lipocortin, an inhibitor of phospholipase A2. Inhibition of release or production of Interleukin-1, IL-6, TNF-alpha.
- Endothelial cells: IL and arachidonic acid: same effects as in macrophages. Effects on endothelial leukocyte adhesion molecule-1 and intracellular adhesion molecule-1.
- Basophils: Histamine and leukotriene IgE dependent release is inhibited.
- Fibroblasts: Suppression of growth factor induced DNA synthesis.
- Lymphocytes: Inhibition of IL-1, IL-2, IL-3, IL-6, TNF-alpha, GM-CSF, Interferon-gamma.

Corticosteroids are grouped according their antiinflammatory and sodium retaining potency:

	Antiinflammatory potency	Sodium retaining potency	Half life time (hours)	Equivalent dose oral, I.V.(mg)
Cortisol	1	1	8-12	20
Cortisone	0.8	0.8	8-12	25
Fludrocortisone	10	125	12-36	
Prednisone	4	0.8	12-36	5
Prednisolone	4	0.8	12-36	5
6 alpha-methylprednisolone	5	0.5	12-36	4
Triamcinolone	5	0	12-36	4
Betamethasone	25	0	36-72	0.75
Dexamethasone	25	0	36-72	0.75

Sampling: 2 mL serum
Reference Interval: 5-30 ng/mL

Pregnancy-Associated Protein A, Serum

Related Information: $Alpha_1$-Fetoprotein (AFP), Serum
Chorionic Gonadotropin (HCG, β-HCG), Serum
Estriol
Down Syndrome Risk Calculation

Synonyms: PAPP-A

Background: Useful to asses the risk of trisomy 21 (Down syndrome) in the first trimester screening with PAPP-A and either hCG or free beta HCG in maternal serum is feasible, since trisomy 21 is associated with high concentrations of beta HCG or HCG, low concentrations of PAPP-A and high values of fetal nuchal translucency by ultrasound.
MEDLAB offers a Down Syndrome Risk Calculation.

Primidone, Serum

Related Information: Carbamazepine, Serum
Folic Acid, Red Blood Cells
Folic Acid, Serum
Phenobarbital, Serum
Phenytoin (Diphenylhydantoin, DPH), Serum
Valproic Acid, Serum or Plasma

Synonyms: Desoxyphenobarbital, Hexamidinum; Majsolin®, Mylepsin®, Mysoline®,Primaclone, Prysolin®

Test includes: Metabolites: Most active: Phenobarbital. Phenylethylmalonamide (PEMA)

Background: Therapeutic levels are reached after 48h. Phenobarbital to primidone ratio is approx. 2.5 and higher in patients on additional anticonvulsants, lower during chronic non-compliance.

Primidone decreases activity of oral anticoagulants.

Primidone and phenobarbital are renal excreted and transformed.

Half life: adults 4-12h, children 4-6h. Protein binding: 20%

Sampling: 2 mL serum or plasma. For monitoring, consistent sampling time recommended.

Reference Interval: Primidone:

Children < 5 years	7-10 µg/mL
Adults	5-12 µg/mL
Phenobarbital, serum:	15-40 µg/mL

Critical values: >12 µg/mL primidone causes CNS depression, vertigo, visual disturbance, areflexia, somnolence, lethargy. Clinical symptoms correlate best with primidone levels. Biphasic overdose: First peak after a few hours and second after 48h after ingestion.

Toxic: >15 µg/mL

Procalcitonin (PCT), Plasma

Related Information: C- Reactive Protein, Serum
Interleukin 6 (IL-6)

Background: PCT is a 13 kD protein of 116 amino acids identical to the sequence at position 60-91 of the human prohormone of calcitonin. PCT is known in two froms both measured in the assay, but PCT-1 as the predominant form in serum.

PCT production is upregulated by endotoxins, TNF-alpha, and Interleukin-6 to a significant increase after 6-8h, peaking after 12-50h and declining with a half life time of 25-35h. Renal impairment increases half life up to 40%; hemofiltration may method dependent decrease PCT.

As compared to C-reactive protein, PCT increase earlier, the decline respond faster to therapy and the specificity is higher for bacterial infections.

The parameter is indicated in

- Infectious diseases to differentiate non-bacterial causes in which PCT does not increase such as viral infections, autoimmune diseases, allergies, local limited bacterial infections, chronic inflammatory diseases, toxic ARDS against bacterial infections including sepsis, bacterial meningitis, pancreatitis, septic ARDS, and malaria. In septic patients the marker indicates progression and indicates the degree of systemic inflammatory involvement.
- in monitoring postoperative patients undergoing extensive surgery, patients with severe injuries, shock, and rhabdomyolysis, which are conditions increasing PCT.

Sampling: 2 mL serum

Reference Interval:

Normal	0.005-0.05 ug/L (higher in newborns)
clinical cut off	< 0.5 ug/L
inflammatory diseases rheumatoid arthritis, Crohn's disease, Colitis ulcerosa, scleroderma, sarcoidosis, systemic lupus erythematodes)	< 0.5 ug/L
Viral infections (including meningitis)	< 0.5-1 ug/L
Local bacterial infections	< 0.5-2 ug/L
Pneumonias caused by mycoplasma or chlamydia	< 0.5-2 ug/L
Non bacterial infections	< 0.5 ug/L, rarely 1-2 ug/L
ARDS non septic	< 2 ug/L
Bacterial infections, severe sepsis, septic shock	> 2-10 ug/L or higher

Procollagen Type I Propeptide

Related information: Alkaline Phosphatase, Serum
Osteocalcin, Serum or Plasma

Synonyms: Procollagen Extension Peptides, PINP

Background: Type I collagen makes up more than 90% of bone matrix, which is released from osteoblasts as extended amino and carboxyl terminal procollagen and transformed in the liver. The specificity for bone formation is limited due to collagen Type I formation in the skin and by fibroblasts. In combination with other markers valuable for monitoring bone turnover and therapy.

Sampling: 2 mL Serum, unstable at 37°C, refrigerate at 4°C.

Reference Interval: Male: 30-202 µg/L
Female: 50-170 µg/L

Procollagen Type III Propeptide

Background: Osteoblasts secrete procollagen molecules which will be cleaved at both ends. The products are cleared by the liver.

Increase parallels non skeletal collagen turnover.

May be elevated in schistosomiasis, subdural hematoma hemorrhage, chronic and acute liver disease, myelofibrosis, skin fibrosis after burn trauma, and polycythemia vera.

Sampling: 2 mL serum

Reference Interval: 0.3-0.8 E/mL

Progesterone, Serum

Related information: Chorionic Gonadotropin (HCG, §-HCG), Serum
Estradiol, Serum
17-alpha-Hydroxyprogesterone (17-OHP)

Background: Progesterone is synthesized in the corpus luteum and after 8 weeks of pregnancy by the placenta. Levels rise during the luteal phase. During pregnancy, increase at the end of the first trimester. Low values in case of miscarriage or ectopic gestation. Beta hCG and progesterone are both lowered in abnormal pregnancy.

For evaluation of infertility, determine luteinizing hormone and progesterone on day 21, progesterone >10 ng/ml in two tests 3-4 days apart indicates adequate luteinization.

High concentrations of 17 hydroxyprogesterone may increase progesterone measurement.

Sampling: 2 mL serum, stable at room temperature for 24h, at 4°C for 7 days, frozen for 3 month. Please indicate trimester of pregnancy or day of menstrual cycle.

Reference Interval:

male	adult		0.01-0.5 ng/mL
female	prepubertal		0.1-0.6 ng/mL
	follicular		< 1 ng/mL
	luteal		3-25 ng/mL
	pregnancy	first trimester	9.0 - 47 ng/mL
		second trimester	16.8-146 ng/mL
		third trimester	55.0-255 ng/mL
	postmenopausal		< 1 ng/mL (3.2 nmol/L)

(converting: ug/L x 3.18=nmol/L)

O-P

Prograf® see Tacrolimus (FK 506), Whole Blood

Progressive Systemic Sclerosis Antibody see Scl-70 Antibody

Prolactin, Serum

Related Information: Dehydroepiandrosterone Sulphate (DHEA-S), Serum
Estradiol, Serum
Follicle Stimulating Hormone (FSH), Serum

Background: Prolactin is an anterior pituitary hormone for initiation and maintenance of lactation. Prolactin is secreted in pulses superimposed on a circadian rhythm. Prolactin secretion is increased by physiologic stimuli such as sleep, exercise, hyperglycemia and as side effect of many drugs.

Tumors: Amenorrhea, irregular menses and galactorrhea may indicate prolactinomas. The interpretation of prolactin values in screening for prolactin secreting tumors must consider that non secretory tumors compressing the pituitary stalk may cause increased prolactin secretion. Prolactin values must be interpreted with imaging to confirm a prolactin secretion >1000ng/mL by a pituitary adenoma >1cm. Values between 250 and 1000ng/mL require careful evaluation.

A second pitfall is due to various forms of circulating prolactin. One form, macro-prolactin, a complex of autoantibody IgG- prolactin, is biologically inactive but immunological in the test reactive. Estimations are up to 25% of diagnosed hyperprolactinism may be caused by macro-prolactin.

Male infertility: A therapeutic option in subfertile men with elevated prolactin levels is bromocriptine. Gynecomastia is not associated with prolactin levels.

Sampling: 2 mL serum

Reference interval:

0-1 month		0-90 ng/mL
2-11 month		0-30 ng/mL
children		2.6-21 ng/mL
Male		3-30 ng/mL
Female		3-30 ng/mL
pregnancy	1. trimester	< 50 ng/mL
	2. trimester	< 100 ng/mL

Prostate Specific Antigen, Free, Serum

Related Information: Prostate Specific Antigen, Serum

Synonyms: fPSA; Free PSA

Background: Since in adenocarcinoma of the prostate a higher amount (> 90%) of PSA will be complexed, free and complexed PSA values may be useful if PSA values are between 4-10 ng/mL.

Free PSA / Total PSA is typically > 25% in healthy men but < 25% in men with prostatic adenocarcinoma. A cut off of 25% detect 98% of carcinomas at age 50-59 years, dropping to 90% at 70-75 years in patients presenting a total PSA between 4-10 ng/mL.

Sampling: 1 mL serum, stable for 48h refrigerated. Patient's preparation: Avoid prostatic digital examination or biopsy at least 48 h, better 3-4 weeks prior to test. PSA has little diurnal variation.

Reference Interval: < 0.5 ng/mL

Prostate Specific Antigen (PSA), Serum

Related Information: Acid Phosphatase, Total, Plasma
Prostate Specific Antigen, Free, Serum

Background: PSA is a serine protease, produced nearly exclusively by epithelial cells of prostatic tissue, and function as a liquefaction of seminal coagulum.

Although PSA is a useful marker in diagnosis and monitoring adenocarcinomas after surgery and metastasis of the carcinoma, it may be increased in 25%-46% of the patients with benign prostatic hyperplasia, depending on the cut off. Proportion of patients with beginn prostatic hypertrophy are < 4 ng/mL in 91%, 4-10 ng/mL in 8% and > 10 ng/mL in 1%.

Overall, about one third of patients with levels > 4 ng/mL prostatic carcinoma will be confirmed by biopsy, in two thirds diagnosis will be rejected. 20%-40% of patients with carcinoma have PSA levels > 4 ng/mL, but PSA may be below the cut off in advanced carcinoma stages. By range, proportion of patients with prostate carcinoma are < 4 ng/mL in 15%, 4-10 ng/mL in 20%, >10 ng/mL in 65%.

Interference: Finasteride used in treatment of benign hyperplasia of the prostate causes an up to 50% increase of PSA levels.

Sampling: 1 mL serum, stable for 48 h refrigerated. Patients preparation: Avoid prostatic digital examination or biopsy at least 48 h, better 3-4 weeks prior of taking the sample.

Reference Interval: Male < 4 ng/mL. Higher cut off would decrease sensitivity but would decrease biopsy rates because of higher specificity.

By age:	Age (years)	upper limit PSA (ng/mL)
	40-50	2.5
	50-59	3.5
	60-69	5
	70-79	6.5
	80-89	7.5

Prostatic Acid Phosphatase, Serum

Related information: Acid Phosphatase, Total, Plasma
Prostate Specific Antigen, Free, Serum
Prostate Specific Antigen, Serum

Synonyms: Tartrate inhibitable phosphatase, PAP

Background: In males, approx. half of the normal total acid phosphatase is of prostatic origin and can be inhibited by tartrate. Metastasis into bone by prostatic adenocarcinoma increases PAP. Sensitivity to detect adenocarcinoma of the prostatic gland in the elderly is in early stages low at 20%, in late stage up to 90%. Sensitivity for detection of metastasis of prostatic adenocarcinoma is approx. 60%.

Sampling: 1 mL serum, within 3 h approx. 20% loss of activity at room temperature occur. Patients preparation: Avoid prostatic digital examination or biopsy at least 48 h prior of sample drawing. High serum bilirubin (> 3 mg/dL) interferes with determination of serum tartrate resistant phosphatase.

Reference Interval: < 4 U/L (total acid phosphatase has also to be measured)

Protein, Liquor see Cerebrospinal Fluid (CSF, Liquor)

Protein C

Related information: Activated Protein C Resistance
Antithrombin III
Protein S

Background: Protein C with protein S as a cofactor regulates anticoagulation activity. Protein C is a vitamin K dependant zymogen of a serine protease, MW 62000 and function as an anticoagulant together with protein S by degrading activated factor V and VIII. Activation of protein C takes place by interaction with a thrombin-thrombomodulin complex on the surface of endothelial cells. Protein C also promotes fibrinolysis. Type I protein C deficiency is quantitative, Type II results from qualitatively abnormal protein C. As first step of diagnosis a functional assay to detect Type I and Type II disorders is recommended, an antigen assay is needed if the functional assay value is decreased.

Hereditary protein C deficiency is present in 0.14% to 0.5% of the general population and accounts up to 9% of patients with thrombosis and younger than 70 years. Heterozygote protein C deficient patients have a sevenfold increased risk of for venous thrombosis at activity values of 35% to 65%. Homozygous deficiencies are rare with 1:500 000, presenting as newborns with purpura fulminans and disseminated intravascular coagulation (DIC).

Acquired conditions for protein C decrease are decreased hepatic synthesis in liver diseases or L-asparaginase therapy as well as vitamin K deficiency or warfarin therapy. DIC or consumption from thrombosis or surgery may decrease protein C values. Nephrotic syndrome may change protein C levels. Increases are reported with oral contraceptives and pregnancy.

Rare cases of autoantibodies to protein C have been reported.

Warfarin (Coumadin R) decreases protein C levels, patient should be off therapy for 10 days for protein C test.

Half life time is short with 6-8h; decrease is an early indicator for liver dysfunction in coagulopathies.

Sampling: 1 mL citrate plasma. Transport to laboratory soon, or separate plasma and store on ice for up to 4 h, or freeze plasma.

Reference Interval: Activity (qualitative): Adult: 70%-140%
Children: at birth 17%-53%,
rising to 50% by the age of 6 month
and reach adult values by the age of 16
Immunogenic (quantitative): 1.7-3.1 mg/L

Protein Electrophoresis, Serum

Related information: Albumin, Serum
Alpha$_1$ Antitrypsin, Serum or Phenotyping
Immunoglobulin A (IgA), Serum, Saliva, CSF
Immunoglobulin G (IgG), Serum, Urine, CSF
Immunoglobulin G Subclasses (IgG subclasses)
Immunoglobulin M (IgM)
Protein, Total, Serum

Test includes: Total protein value

Background: Different net charges of proteins are used in separation. Protein concentrations are altered as a result of diseases or stages.

Diagnostic use: multiple myeloma, Waldenstroem macroglobulinemia, amyloidosis, monoclonal gammopathy. Useful in disease staging in acute or chronic inflammation, autoimmune hepatitis, cirrhosis, humoral immunodeficiency, alpha$_1$ antitrypsin abnormalities, monoclonal, -oligoclonal, -polyclonal gammopathies.

Indications: Back pain, osteoporosis, osteolytic lesions, hypercalcemia, Bence Jones proteinuria, elevated serum creatinine, recurrent infections, peripheral neuropathy, congestive heart failure, nephrotic syndrome, hepatomegaly, splenomegaly, screening for alpha$_1$ antitrypsin deficiency, evaluation of chronic liver disease.

Interpretation:

Symptom	Protein	Disease
acute inflammation	normal to decreased albumin increased α_1 and or α_2 globulin increased γ globulin	acute phase reaction
chronic inflammation	normal to deceased albumin elevated α_1 and/or α_2 globulin increased γ globulin	autoimmune disorder, chronic inflammation, chronic liver disease, primary biliary cirrhosis, cancer
hypoalbuminemia	decreased albumin	cancer, malnutrition, protein loosing diseases
hypogammaglobulinemia	normal to decreased albumin decreased γ globulin	congenital immunodeficiencies
polyclonal gammopathy	elevated γ globulin	autoimmune disease, chronic infection, autoimmune hepatitis, cirrhosis
liver cirrhosis	decreased albumin elevated γ globulin	
protein loosing state	decreased albumin elevated α_2 globulin decreased γ globulin	nephrotic syndrome, gastroenteropathies, exudative skin disorders
monoclonal gammopathy	increased γ globulin	AIDS, Gaucher disease, myeloma, CCL, lymphoma, macrolobulinemia
antitrypsin deficiency	decreased α_1 globulin	
hyperbetaglobulinemia	normal to decreased albumin increased β globulin	hyperlipidemia, diabetes mellitus, iron deficiency anemia

Sampling: 1 mL serum, separate serum soon and refrigerate

Reference Intervals:		
Albumin	55.0 -68.9%	35.0-55.0 g/L
$alpha_1$ Globulin	2.0-4.5%	1.3-3.9 g/L
$alpha_2$ Globulin	5.9-11.1%	4.5-8.5 g/L
beta Globulin	8.0-13.9%	5.9-11.4 g/L
gamma Globulin	10.0-20.0%	8.0-16.0 g/L

Protein Quantitative, Urine

Related information: Albumin, Serum
Creatinine, Serum or Plasma
Creatinine, Urine
Creatinine Clearance
Glycosylated Hemoglobin A1c , Blood
Osmolality, Urine
Protein Electrophoresis, Serum
Protein Total, Serum

Background: Useful in the evaluation of proteinuria, renal diseases, complicated diabetes mellitus, nephrotic syndrome, metal poisoning, renal vein thrombosis, systemic lupus erythematosus, constrictive pericarditis, amyloidosis, hypertension, glomerulonephritis, Goodpasture syndrome, Henoch-Schoenlein purpura, thrombotic thrombocytopenic purpura, collagen diseases, cryoglobulinemia, preeclampsia, drug induced nephrotoxicity, allergic reactions, renal tubular lesions, monitoring of myelomas and macroglobulinemia Waldenstroem (Bence Jones), evaluation of hypoproteinemia, Wilson's disease and Fanconi syndrome.
Usually > 3.5 g/24h reflects a glomerular lesion in adults, in children >1 g/m^2/24h.
Tubular lesions: usually < 1g/24h
In patients with orthostatic proteinuria, combined with an overnight 12h up to 180 mg value and during the 12 h ambulatory up to 1000 mg, needs further work up.
Interference: Tolbutamide, penicillin, cephalosporins, sulfonamides may increase values.
Sampling: 24h urine (see section sample collection page)
Reference Interval: < 150 mg/24h
up to 250 mg/24h after intensive exercise.
Urinary protein tends to increase with age, exercise and standing posture.
Critical values: Nephrotic syndrome: children > 1g/m^2/24h
adults: > 3.5 g/24h

Protein S-100, Serum see S-100, Serum

Protein S Total

Related Information: Antithrombin III
Factor V Mutation (Leiden Mutation)
Protein C

Background: Protein S together with protein C and regulates anticoagulant activity by degrading activated factor V and VIII. 60% of total protein S is bound to C4b binding protein and inactive, 40% unbound and active. Quantitative deficiencies (Type I) and Qualitative (Type IIb and IIa) are distinguished.

Protein S levels are decreased by estrogen, pregnancy or warfarin. Warfarin influences protein S levels for up to 10 days after cessation of warfarin.

Factor VIII levels > 200% decrease protein S in functional PTT based assays, Factor VIII should be measured as well, Factor V Leiden may also lower values. Functional Test cannot be performed under hirudin or argatroban anticoagulation therapy.

Use: First perform functional assays to detect all subtypes of deficiency, if decreased, perform free antigen assay in addition, if decreased, perform total (free and bound) antigen assay.

Additional information:

A) Hereditary

Protein S deficiency is present in 0.7% of the population, but up to 8% in patients younger than 70 years with thrombosis, onset usually between 10 and 50 years in heterozygotes and levels at 20%-60%. Skin necrosis induced by coumarin possible.

Homozygotes rare and fatal present in newborns with DIC or Purpura fulminans.

Classification: All hereditary deficiencies have low functional protein S values.

- normal free protein S values: Type IIb only,
- low total protein S values: Type I only,

B) Acquired

- during liver diseases, levels of protein C may be normal, but protein S and antithrombin are usually decreased, since protein S is also synthesized in endothelial cells and megakaryocytes.
- asparaginase treatment
- vitamin K deficiency or warfarin treatment
- consumption status from thrombosis or DIC
- up to 2 month after pregnancy or estrogen therapy
- acute phase reactions (due to C4b elevation)
- nephrotic syndrome
- varicella infection (possibly via autoantibodies)
- HIV

Sampling: Citrate plasma, 1 mL, invert gently, fill vial completely, deliver to laboratory soon, or separate cells and store on ice up to 4h, or freeze plasma.

Reference Interval: Activity: 65%-140%, quantity: 13-21 mg/L
Lower for women
Birth to 6 months: activity 12%-60% of adult values

Protein Total, Serum

Related information: Albumin, Serum
Alpha$_1$ Antitrypsin, Serum
Alpha$_1$ Antitrypsin Phenotyping
Immunoglobulin A (IgA), Serum, Saliva, CSF
Immunoglobulin G (IgG), Serum, Urine, CSF
Immunoglobulin G Subclasses (IgG subclasses)
Immunoglobulin M (IgM)
Protein Electrophoresis, Serum
Protein, Quantitative, Urine

Background: Useful in evaluation of protein status, nutritional status, edema, protein altering diseases. Hemolysis can falsely elevate total protein.

Limitation: Increased by phenazopyradine, sulfasalazine, anabolic steroids, angiotensin, bumetanide, corticosteroids, digitalis, furosemide, oral contraceptives, hetastarch, laxatives, tacrolimus.

Interpretation:

Increased:

Dehydration, chronic liver diseases such as autoimmune hepatitis, cirrhosis, neoplasms such as myelomas, macroglobulinemia, tropical diseases such as kala-azar, granulomatous diseases such as sarcoidosis, collagen diseases such as lupus erythematosus, and other inflammatory diseases.

Decreased:

Pregnancy, cirrhosis, liver diseases especially in chronic alcoholism, prolonged immobilization, hear failure, nephrotic syndrome, glomerulonephritis, neoplasia, enteropathies, Crohn disease, Colitis ulcerosa, starvation, malabsorption, hyperthyroidism, burns, serve skin diseases, chronic stages of diseases.

Sampling: 1 mL serum or plasma, transport to laboratory soon or separate cells and refrigerate. Venous stasis during venipuncture can cause increased values.

Reference Intervals:

Adult:	66-87 g/L
Early childhood:	61-76 g/L

Note: Plasma contains fibrinogen, elevating the plasma protein concentration up to 4 g/L as compared to serum protein concentrations.

Ambulatory values may be slightly higher than those found in recumbency.

Proteinase-3 (PR3) see Antineutrophil Cytoplasmatic Antibody (ANCA)

Prothrombin Mutation see Factor II mutation

Prothrombin Time

Related Information: Activated Partial Thromboplastin Time
Fibrinogen, Functional
Protein C
Protein S, Total
Thrombin Time

Synonyms: PT; Thromboplastin Time; Quick's Value

Background: PT is defined as the time from activation of Factor VII to the formation of the fibrin clot, testing the function of the extrinsic pathway and the subsequent common pathway of coagulation. (The intrinsic pathway is measured by the activated partial thromboplastin time, PTT.)
Prolongation of PT occur:
Hereditary: Such as factor VII deficiency (normal PTT) or possibly combined with PTT prolongation in fibrinogen, factor II, V and X deficiencies.
Acquired: Vitamin K deficiencies, warfarin therapy, liver diseases (PTT slightly and later affected than PT) Disseminated intravascular coagulation (PT changes earlier and greater than PTT)
Heparin therapy (PT normal to minor changes, PTT affected)
Hirudin / argatroban (PT and PTT values change)
Lupus anticoagulants (PT or PTT may be prolonged)
Limitations: PT prolongs at single factor deficiencies more than 15% to 45%. PT is not affected in factor VIII, IX, XI, XII prekallikrein or high-molecular weight kininogen deficiencies, but PTT is affected. Factor XIII deficiency does affect neither PT nor PTT.

Sampling: 2 mL citrate plasma. Avoid strictly contamination with heparin! Separate plasma within 2 days.

Reference Interval:

Normal:	70%-130%
Therapeutic value:	12% -33% or INR Value 2.0-4.5

Protoporphyrin Free, Erythrocyte

Related Information: Delta-Aminolevulinic Acid, Urine
Ferritin, Serum or Plasma
Transferrin and Total Iron Binding Capacity, Serum
Porphobilinogen, Urine
Porphyrins, Quantitative, Urine or Stool

Synonyms: FEP; Free Erythrocyte Protoporphyrin; RBC Protoporphyrin

Background: FEP is a heme precursor. It is increased in erythropoietic porphyria, lead poisoning, iron deficiency. For the latter two zinc protoporphyrin is as better parameter.
Erythropoietic porphyria is an autosomal dominant disorder caused by ferrochelatase deficiency with an onset in childhood and is classified as a nonacute cutaneus porphyria. Usually, the fecal excretion of protoporphyrins as well as plasma and erythrocytic levels are increased

Sampling: To obtain best results, patients should be fasting, alcohol abstinent for 1 day
1 mL EDTA whole blood
Reference Interval: 1-10 µg/dL of erythrocytes

Pseudocholinesterase, Serum

Related Information: Pseudocholinesterase Inhibition Assay
Background: The true cholinesterase is a red cell, lung or brain enzyme, the pseudocholesterinesterase (PChE) is an enzyme in the serum.
The assay is used to screen patients preoperatively for inherent succinylcholine anesthetic sensitivity to prevent prolonged anesthetic apnea, as the laboratory part of the assessment of the cholinergic syndrome. Theses patients need as little as 0.04mg/kg of succinylcholine to result in neuromuscular blockade due to hereditary low PChE activity.
The assay is also used in the evaluation of organophosphorus exposure or intoxication, which leads to a decrease PChE activity.
Limitations: Estrogens, oral contraceptives and liver diseases may lower PChE activity. Low serum PChE does not rule out succinylcholine caused anesthetic incidents.
Sampling: 1 mL serum or heparin plasma. Avoid hemolysis.
Reference Interval: Within the first two month of life lower.

Thereafter:	Male:	5 320–12 920 U/L
	Female:	4 260–11 250 U/L

Pseudocholinesterase Inhibition Assay

Related Information: Pseudocholinesterase, Serum
Background: Dibucaine and fluoride inhibits the normal form of pseudocholinesterase, whereas abnormal forms are less inhibited. 4% of the populations have abnormal forms.
At least four alleles code for the sensitivity to succinylcholine and the inhibition produced by fluoride and dibucaine. E1a codes for inhibition resistance by dibucaine, E1f for fluoride resistance, E1s for a very low enzyme activity, E1u for the usual allele.
It may be possible to conclude from the dibucaine count to the genotype:

Alleles	Dibucaine percent inhibition
E1u E1u	84
E1u E1a	73
E1a E1a	32
E1s E1s	81
E1u E1f	0

Limitations: Not all variants of abnormal PChE can be detected by the dibucaine or the fluoride test.

Sampling: 1 mL serum or heparin plasma.

Reference Interval:	Assay with fluoride	percent inhibition
	Normal homozygous:	40–60%
	Atypical homozygous:	74–84%
	Atypical heterozygous:	50–66%
	Assay with dibucaine	percent inhibition
	Normal homozygous:	80–88%
	Atypical homozygous:	15–25%
	Atypical heterozygous:	60–68%

Pyridinolines

Synonyms: Deoxypyridinoline, Hydroxylysylpyrolidine, Lysylpyroidine, Pyridinium Collagen Cross-Links, Pyridinoline Crosslinks

Background: Markers for bone matrix resorption and degeneration. As a bone resorption marker, values fall within 2-12 weeks during remodeling, during bone formation the marker fall within 3-6 month.

Elevated in osteoporosis, Paget disease, metastatic bone resorption, primary and secondary hyperparathyroidism, hyperthyroidism.

Decrease of cross links in hypothyroidism.

Also useful in assessment of patient s risk of fracture, therapy monitoring.

Limitation: Variation day by day up to 20%, affected by renal clearance.

Sampling: Urine, 5 mL, but a 24 h urine collection is preferred due to diurnal variation. Protect from light. Refrigerate. Freeze for storage longer than 2 days.

Reference Interval: Assay measures de(s)oxypyridinoline: 3.0-7.4 nmol/mmol creatinine

Pyridoxal-5-Phosphate see Vitamin B 6, Plasma or Serum

Pyridoxine see Vitamin B 6, Plasma or Serum

Q Fever see Coxiella burnetii

Quick`s Value (Prothrombin Time) see Prothrombin Time

Rabies Antibody, Serology

Background: Usually transmitted by bite of bates or exposure such as open wounds or inhalation of aerosols of bat urine. Vaccination available for high risk individuals such as vegetarians. Immunoglobulins available.

Sampling: Animal: Punch biopsy from the neck with many hair follicles, snap freeze, ship at -70°C to reference lab. Ideally, animal brain, frozen -70° C. Follow instructions from reference lab. Domestic animals suspected of rabies should be kept for 10 days, survival makes rabies unlikely.

Human: Cerebrospinal fluid, serum, saliva, brain biopsy, nuchal skin.

Information: www.Cdc.gov/ncidod/dvrd/rabies

To asses immune status: 2 mL serum

Reference Interval: Rabies Antibody Immunity > 0.5 IE/mL

Renin Activity, Plasma

Relate information:
Aldosterone, Serum or Plasma
Aldosterone, Urine
Potassium, Serum or Plasma
Potassium, Urine
Sodium (Na), Serum
Sodium (Na), Urine

Background: Conversion of angiotensinogen to angiotensin I is catalyzed by renin. Angiotensin I is further cut by a "converting enzyme" to angiotensin II, which stimulates the secretion of aldosterone and is an active vasopressor. To test plasma renin activity is useful in the diagnosis of hyperaldosteronism known to be two major types:

1) primary hyperaldosteronism (Conn Syndrome) in which aldosterone is autonomously produced by an adrenal adenoma. Usually renin is low and does not increase in response to stimuli such as volume depletion, hyponatremia or upright posture.
2) secondary hyperaldosteronism as a response to cardiac failure, cirrhosis, renovascular hypertension, renin secreting tumors, forced diuresis, vomiting with usually high renin activity.

Sampling: There is a circadian variation with a morning maximum and late afternoon minimum. Sampling has to be standardized, best in the morning and upright position, both to be recorded to the laboratory.

A 5ml specimen should be drawn into a pre chilled EDTA or heparin tube and kept on ice to be transported immediately to the laboratory or plasma has to be separated in a 4°C pre-chilled centrifuge and to be frozen immediately. No freeze-thaw cycles.

To test for primary hyperaldosteronism: Sample first specimen at 8 am for renin activity after 30 min in an upright position before placing patient on low sodium diet for 3-6 days and sample second specimen under exact same conditions. To give a maximal stimulation, in addition a diuretic can be administered before the second sampling. There may be in some patients with

Conn syndrome an increase in renin activity. Interpretation only validated by concurrent serum aldosterone levels.

Reference Interval:	3-19 pg/ml	unstimulated
	5-40 pg/ml	stimulated

Respiratory Syncytial Virus, Serology

Synonyms: RSV

Background: As the most common viral agent causing respiratory infections in children, up to 50% of infants have experienced an infection with fever, wheezing cough, rhinorrhea.

Since young infants have maternal IgG antibodies, false positive results are possible, a fourfold increase of IgG antibodies can only detected in 50% of the children younger than 6 month.

Sampling: 1 mL of serum when patient develops signs of infection and 10 to 30 days later a second sample is required.

Reference Interval:	IgG antibody	negative	< 20 RE/mL
	IgA antibody	negative	< 0.7 COI
		borderline	0.7-1.0 COI
		positive	> 1.0 COI

Reticulocyte Count

Related Information: Erythropoietin (EPO), Serum
Blood Count, Complete

Background: Monitoring response to anemia therapy. Marker for success of marrow engraftment after transplantation. Marker of early response to immunosuppression during therapy of aplastic anemias.

In transfused patients, dilution my decrease reticulocyte counts. False high counts may occur due to intracellular parasites, large platelets, drug therapies, erythropoietic protoporphyria, cold agglutinins.

Sampling: 1 mL EDTA blood

Reference Interval:

Adults	0.5-1.5%
at birth	1.6-8.3% , mean 5.3% falling to adult level by the end of week two.
Absolute count:	10-80 x 10^9 /L
	Reticulocytes > 100 x 10^9 /L indicates increased erythropoiesis.

Corrected reticulocyte count for anemic patients:

Reticulocyte Index = reticulocytes (%) x patients Hct / normal Hct

Rheumatoid Factor, Serum or Body Fluid

Related information: Antinuclear antibodies
C-Reactive Protein, Serum
Cryoglobulin, Qualitative, Serum or Plasma
HLA-B27
Immunoglobulin M (IgM)

Synonyms: RF

Background: RF is in most of the cases an IgM class antibody, occasionally of IgG, IgA, or IgE classes, reacting with the Fc region of other immunoglobulins, often of the IgG class and form immune complexes mediating in high concentrations tissue injury.

Up to 85% of patients clinically diagnosed with rheumatoid arthritis (RA) have positive RF. However, 3% of the general population has low levels of RF, in the group of 65 years and older up to 20% have increased levels. As little as 5% of RF positive individuals will develop RA and the risk correlates with RF values. High values are also associated with prevalence of subcutaneous nodules, necrotizing vasculitis, and poorer long term prognosis. Positive RF in joint fluid may be an early indicator before serum RF increases.

Specificity for RA is low but increases with high values and repeated positive tests. High levels of RF are also present in most of patients with Sjoegren syndrome and essential mixed cryoglobulinemia. Low values are predominant in connective tissue diseases, in chronic and inflammatory disorders such as infective endocarditis, tuberculosis, liver diseases, sarcoidosis, idiopathic pulmonary fibrosis, and hematologic diseases. They may be associated with hypergammaglobulinemia.

Sensitivity of RF is also not high, 35% of patients with RF have negative RF test results. In children with juvenile RA, only 30% have elevated RF levels.

Usually, negative for RF are patients with Reiter's syndrome, ankylosing spondylitis, psoriasis.

For disease and therapeutic monitoring, RF is not the appropriate parameter, C Reactive Protein and Sedimentation rates are more useful.

Sampling: 1 mL serum

Reference Interval: < 14 IU/mL

Riboflavin see Vitamin B2, Serum

Ribonucleoprotein U1-snRNP Antibody

Related Information: Smith (SM) Antibody
SS-A/Ro and SS-B/La Antibodies

Background: The U1-snRNP antibody binds to U1-snRNP which is a ribonucleoprotein assembled of protein A, protein C and other proteins complexed with a small nuclear RNA fragment (see also Smith (SM) Antibody).

The U1-snRNP antibody is defining mixed connective tissue disease (MCTD), which is an overlap syndrome of systemic lupus erythematosus (SLE), scleroderma, polymyositis, arthritis, arthralgia, esophageal dysmotility, Raynaud phenomena, but rare renal involvement. Rheuma factor (RF) is positive in 50% of the patients.

High levels of U1-snRNP antibodies are highly suggestive for MCTD particularly if anti-DNA antibodies (Antibodies, dsDNA and Antibodies, ssDNA), Smith (SM) Antibody, and histone antibodies are absent. However low levels of U1-snRNP antibody are found in SLE, scleroderma and other diseases.

Sampling: 1 mL serum

Reference Interval: Negative: <10 U/mL

Rickettsiosis see Coxiella burnetii, Serology

RNP-U1 see Ribonucleoprotein U1-snRNP Antibody

Rota Virus, Serology

Related Information: Helminths, Feces, Microscopy
Enterohemorrhagic E.coli (EHEC), (E.coli O157)
Enteropathogenic E.coli (EPEC)
Rota Virus, Direct Detection
Shigella, Culture and Serology

Background: Human rotavirus is the most common cause of severe diarrhea in infants 6 month to 3 years of age, transmitted as a highly contagious agent via the fecal-oral route and occurs predominantly in winter. Group A is as common in developing as well as in industrialized countries, group B primarily in China, group C occurs more sporadically. Incubation period is 1-2 days with abrupt onset, accompanied by vomiting, fever, diarrhea, abdominal pain and lasts usually 5-8 days and is rarely fatal, although it may be complicated by serve dehydration. Other causes to consider are adeno-calici-astro-corona-norwalk- or norwalklike-viruses.

Sampling: 2 mL serum, sampling at onset of disease and 1-2 weeks later.

Reference Interval: Negative: Children titer < 1:10
Adult titer < 1:40

Rota Virus, Direct Detection

Related Information: Helminths, Feces, Microscopy
Enterohemorrhagic E.coli (EHEC), (E.coli O157)
Enteropathogenic E.coli (EPEC)
Rota Virus, Serology
Shigella, Culture and Serology

Background: Please see: Rota Virus, Serology

As a limitation of direct Rotar virus detection (EIA) false positive results in healthy neonates occur, however in symptomatic individuals the results are reliable.

Sampling: Approx. 2 g stool

Reference Interval: Report on antigen detection: negative

Rubella, Serology

Background: Due to a wide use of mumps-measles-rubella immunization in children in western countries, the incidence has fallen since 1994 and is targeted by the CDC to be eradicated. However, several outbreaks have been reported in populations not immunized. The infection is characterized by a macular exanthema, lymphadenopathy, pharyngitis, conjunctivitis, the incubation period is 2-3 weeks and subclinical infections are common.

Pregnancy: Pregnant women who become infected with rubella have a high risk to transmit the virus via the placenta to infect the fetus. Infection of the fetus may cause fetal death, premature delivery, severe congenital defects such as deafness and congenital heart disease. Excretion of rubella in intrauterine infected neonates lasts for month in nasopharyngeal secretions and urine after birth. Rubella vaccination is therefore strongly recommended in women in childbearing age and being not pregnant at time of receiving the vaccination.

Since IgM antibodies do not cross the placenta, IgM antibody in the child suggests rubella infection, whereas a single positive IgG antibody titre may be due to maternal transfer of IgG via the placenta.

Sampling: 1 mL of serum is needed for the acute, first serologic sample and for a second, convalescent sample after 2-3 weeks. Rise in titer more than three fold suggests rubella infection or vaccination.

Reference Interval:

HAH method:	negative:	titer < 1:8 immunity absent
	borderline:	titer 1:16 immunity questionable
	positive:	titer > 1:16 immunity present

Immunoglobulin classes:

Positive IgG indicates immunity, positive IgM indicates either infection or recent vaccination.

IgG antibody	negative:	< 10 IU/mL, immunity absent
IgM antibody	negative:	< 15 AU/mL
	borderline:	15-25 AU/m
	positive:	>25 AU/mL

S-100, Serum

Background: S-100 is a 21kD protein, belongs to calcium binding protein family indicating a role as an intracellulare calcium receptor. Functions are regulation of cell differentiation and proliferation and the protein is interacting with the p53 tumor suppressor. Two subunits (alpha and beta) are forming the isoforms S-100B (beta-beta), S-100A (alpha-beta), S-100A1 (alpha-alpha). High concentrations of S-100B occur in astrocytes of the CNS, low concentrations in the peripheral nervous system. S-100A1 occurs in cardiac muscle cells, in the kidney and in the skin. S-100A is synthesized by malignant melanoma.

S-100 is used in the diagnosis, as a prognostic parameter and therapy monitoring of the malignant melanoma. S-100 is highly specific. In melanomas, S-100 correlates to the tumor stage: Stage I only up to 10% of the patients display elevated levels, stage IV the diagnostic sensitivity is 30%-90%.

S-100 is also used in neurodegenerative diseases and neuro-destructive injuries (ischemia, infections, and traumas) and to assess the function of blood brain barrier. Injuries are followed by an increase within several hours, peaking at day 1-3 and decline with a half life time of 2-3h. There is a correlation between seize of the neuro destruction assessed by CT, clinical status and prognosis for rehabilitation.

Limitations: In carcinomas of the lung, gastrointestinal tract, urogenital tract or other sites or autoimmune diseases the max. concentration may reach 0.6 µg/L but is usually in the range of healthy individuals. As an exception S-100 may reach levels of 2 µg/L in severe bacterial infections. Elevated levels may occur in cirrhosis, renal failure, myocardial infarction.

Sampling: 1 mL serum

Reference Interval:

Male:	< 0.18 µg/L
Female:	< 0.15 µg/L

Salicylate, Serum or Plasma

Synonyms: Anacin®, ASA, Ascriptin®, Aspirin®, Bufferin®, Easprin®, Ecotrin®, Empirin®, Measurin®, Synalgos®, ZORprin®

Background: Salicylate is the active compound from aspirin as an analgesic, antipyretic and anti-inflammatory drug. Acute poisoning include clinical signs such as nausea, vomiting, hyperpnea, tinnitus, convulsions as well as hypocalcemia, respiratory alkalosis, dehydration, oliguria, metabolic acidosis, hepatotoxicity. Chronic poisoning may include fever, vomiting, tachypnea. Half life: 2-3h; protein binding 90%-95%; volume distribution 0.1-0.3 L/kg.

Sampling: 2 mL serum, time to peak concentration 1-2h, optimal sampling 4-6h after dosage.

Reference Interval:

100-150 µg/mL	antiplatelet, antipyretic, analgesic effects
150-300 µg/mL	antirheumatic, anti-inflammatory effects
250-400 µg/mL	therapy of rheumatic fever; Mildly toxic causing tinnitus, dizziness, nausea, sweating, headache, diarrhea, tachycardia;

Toxic: more than 400 µg/mL, may be lethal at 700 µg/mL. Half life 2-3h, prolonged up to 20h at toxic levels.

Salivary amylase, Serum see Amylase, Isoenzymes, Serum

Salmonella, Culture and Serology

Background: Salmonella are gram negative, lactose negative rods, possessing the O cell wall antigen, the flagellar H antigen and the capsular Vi antigen which are used for taxonomic purposes. Salmonella are transmitted by food and water contaminated by human or animal wastes. Besides S. typhi, all other species have human and animal (poultry, eggs, dogs, snakes, lizards, iguanas) reservoirs.

Salmonella species are the cause of enterocolitis, enteric fever and septicemia with metastatic infections such as osteomyelitis. There are three methods for naming salmonellae. The most common the Kaufman and White scheme assign different species names (usually named for the city in which they are first isolated) to each serotype, approx 1500 species are known so far.

For clinical purposes there are typhoidal species (S. typhi and S. paratyphi) and non typhoidal species (many strains of S. enteritidis).

Clinical courses: Enterocolitis is characterized by invasion of the epithelial cell layer and the infection is limited to the mesenteric lymph nodes with rare bacteremia. Dose of infection is high, 100 000 organisms are necessary, in contrast to Shigella sp, were 10 organisms are sufficient to start an enterocolitis.

Typhoid forms are characterized by few intestinal symptoms and spread by the blood circulation to the gall bladder, the liver and spleen. A chronic carrier state may develop.

Septicemia accounts for 5%-10% of Salmonella infections and may lead to osteomyelitis, pneumonia, meningitis, typically in children with sickle cell anemia.

Sampling: Culture: In enterocolitis, the organism is most easily isolated from a stool sample. At least 3 samples of approx. 2 g of fresh stool to send to the laboratory. In a carrier state, stool cultures are also appropriate.

In enteric fevers, a blood culture is most likely to reveal the organism during the first 2 weeks of disease.

Serology: If there is no recovery of salmonella species in blood or stool, serology may establish the diagnosis. At least two specimens are necessary, 2-3 weeks apart.

Reference Interval:

Culture:	Report on diagnostic finding		
Serology:	Differentiation of antibody classes against S. typhimurium and S. enteritidis:		
	IgA, IgG, IgM antibody	negative	< 1.0 COI
		borderline	1.0-1.2 COI
		positive	> 1.2 COI

Scl-70 Antibody

Related Information: Antinuclear Antibody
Jo-1 Antibody
SS-A/Ro and SS-B/La Antibodies
Ribonucleoprotein U1-snRNP Antibody
Smith (SM) Antibody

Synonyms: Progressive Systemic Sclerosis Antibody,
Topoisomerase I Antibody, Scleroderma Antibody

Background: Topoisomerase I is a 100kD nuclear enzyme responsible for twisting and untwisting the DNA helix during replication. Scl-70 antibody is directed against a 70 kDa proteolytic fragment of the Topoisomerase.

Systemic sclerosis is a chronic disorder characterized by diffuse fibrosis of the skin and internal organs occurring in the third to fifth decades with a 2-3 times higher incidence in women. Two forms are known: A limited form in 80% of the patients, and diffuse form in 20% of the patients. The limited form is characterized by calcinosis cutis, Raynaud's phenomenon, esophageal motility disorder, hardening of the skin of the face and hands. The diffuse form is characterized by skin changes also at the proximal extremities and trunk, tendon friction, rubs, cardiac diseases such as pericarditis, heart block, myocardial fibrosis, diverticulosis of the gut, renal involvement.

30%-60% of the patients with diffuse scleroderma have antibodies to Scl-70 of the IgG class, infrequently of the IgA and IgM class. Scl-70 antibody positive patients with scleroderma are more likely to have visceral involvement such as pulmonary fibrosis as well as shin diseases. 60-95% of the patients with scleroderma are ANA positive, 25%-35% are Rheuma factor positive

Sampling: 1 mL serum

Reference Interval: Negative

Scleroderma Antibody see Scl-70 Antibody

Selenium (Se), Serum or Plasma

Related Information: Selenium (Se), Urine

Background: As a constituent of glutathione peroxidase and iodothyronine deiodinase it is an important essential trace element of human nutrition. Se is incorporated into other proteins as selenomethionine. There are ongoing discussions on the role in anticancer (colorectal, lung, prostate) and cardiovascular diseases.

In long term parenteral nutrition Se levels should be monitored, useful in diagnosis of cardiovascular disease of unknown cause.

Deficiencies, which may be endemic in regions where soil Se is low, thus present in the food chain, can come into clinical attention by whitening in the nail beds, erythrocyte macrocytosis, cardiomyopathy, painful week muscles, skin or hair depigmentation and elevation of transami-

nases and creatinine kinases.

Se is lowered in HIV infection, severe illnesses, kwashiorkor, inflammation of the bowl, renal failure, low protein diet, phenylketonuria, maple syrup urine disease, low birth weight. Levels are increased under glucocorticoid therapy. Toxic sate is characterized by nausea, diarrhea, mental changes, peripheral neuropathies, hair loss.

Sampling: 2 mL serum or plasma. Containers must be trace metal free. Use powder free gloves.

Reference Interval: Serum 60-130 µg/L. For whole blood 40% higher.
Serum reflects resent intake, red cells reflects long term intake.
Critical values: > 500 µg/L

Selenium (Se), Urine

Related Information: Selenium (Se), Serum or Plasma

Background: Reflects resent intake, if patient is in Se balance.

Limitations: Do not use spot values, urine Se is higher after a meal, fasting urine may give better results, for assessing Se state of the patient, 24 h urine is necessary. Usually, Se loss in the urine is an overflow loss, although Se is excreted by the skin and stool. In chronic hepatic diseases, selenoproteins are produced in insufficient quantities and Se serum concentrations are reduced.

Sampling: Collect 24h urine in an acid washed plastic urine container. Since hair shampoos contain Se, avoid contamination by hairs. Ship a 10 mL aliquot to laboratory.

Reference Interval: 5-30 µg/24h
Toxic: probably > 500 µg/L

Serotonin, Blood

Related Information: 5-Hydroxyindoleacetic Acid (5-HIAA), Quantitative, Urine

Synonyms: 5-HT; 5-Hydroxytryptamine, Urine

Background: Chromaffin cells of the intestinal tract and in central or peripheral neurons synthesize serotonin from tryptophan. May be used in the diagnosis of carcinoid syndrome, but urinary 5-Hydroxindoleacetic acid is more sensitive.

Sampling: 3 mL of ETDA blood, freeze plasma within 4h, stable 7 days at -20°C, ship frozen

Reference Interval: 50–240 µg/L

Sex Hormone Binding Globulin (SHBG), Serum

Background: The major fraction (98%) circulating in the blood of testosterone is bound to SHGB. SHBG is decreased in obese individuals, during steroid therapy and in nephrotic syndrome. Hyperthyreosis, hepatitis, cirrhosis, estrogen and antiepileptic therapy increase serum SHBG. Useful in the determination of free testosterone under conditions mentioned above to achieve a precise estimation of testosterone.

Sampling: 1 mL serum

Reference Interval:		
	Male	10–73 nmol/L
	Female	16–120 nmol/L
	Gravidity	200–700 nmol/L

SGPT see Alanine Aminotransferase (ALT), Serum

Shigella, Culture and Serology

Background: Shigella species organisms are a non fermenting gram negative, non glucose fermenting nonmotile and non H_2S producing rods. Four groups of O polysaccharide antigen are known: A,B,D, and D. Shigella species have no other but human reservoirs and no chronic carrier state. Transmission by the fecal oral route. Outbreaks are food born and second waterborne by low dose of infection (100 organisms). Children account for 50% of infections.

Clinically after an incubation period of 1-4 days fever, abdominal cramps and bloody diarrhea in mild to severe forms depending on the age (in children and elderly patients more severe) occurs. Shigella dysenteriae causes a more severe disease than Shigella sonnei does. Inflammation and local ulceration of the ileum and colon occurs, but the organism does not enter the blood stream. Shiga-toxin is not necessary to invade the gut wall, only non-invasive strains are non-pathogenic.

Treatment: Mild forms are self limiting after 2-4 days, severe forms ciprofloxacin may be indicated.

Sampling: Culture: Fresh stool; Serology: 1 mL serum. Early and reconvalescent serum 2 weeks apart recommended.

Reference Interval: Serology: Widal's reaction: < 1:50
Test includes: Sh. sonnei, Sh. flexneri, Sh. dysenteriae

Sm Protein (Smith) see Smith (SM) Antibody

Smith (Sm) Antibody

Related Information: Antibodies, dsDNA and Antibodies, ssDNA
Antinuclear Antibody

Background: Smith antibodies recognize at least 6 different proteins, which are complexed (snRNP's) with small (less than 300 nucleotides) nuclear RNA fragments (snRNA). The snRNP's are U1-, U2,-U4-, U6- ; the most important proteins within theses complexes are B' (a 29kDa protein) , B (a 28kDa protein), and D (a 16kDa protein).

The Smith antigen belongs to the group of extractable nuclear antigens (ENA), which includes also SS-A/Ro, and SS-B/La antigens and nuclear ribonucleoprotein (RNP) antigens.

Useful in confirming the diagnosis of systemic lupus erythematosus since SM antibodies are highly specific for systemic lupus erythematosus (SLE). Smith antibodies are rarely drug induced LE.
Sm antibodies are present in 10%-20% of Caucasian patients with SLE, in 30%-40% of Asian and African patients and up to 60% in young black females with SLE.

Sampling: 1 mL serum

Reference Interval: Negative: < 10 U/mL

Smooth Muscle Antibodies (SMA)

Related Information:
Alanine Aminotransferase (ALT), Serum
Alkaline Phosphatase, Serum
Antimitochondrial Antibodies
Antinuclear Antibody
Aspartate Aminotransferase (AST), Serum
Bilirubin, Fractionated, Serum
Hepatitis A Antibodies, IgG and IgM (IgG anti-HAV, IgM anti-HAV)
Hepatitis B Virus DNA Detection (HBV-DNA)
Hepatitis B (HBV), Serology and Antigen Detection
Hepatitis C Antibody (Anti-HCV) or Genotyping
Hepatitis C Virus RNA Quantification (HCV-RNA)
Hepatitis D Serology
Hepatitis E Antibody (Anti-HEV
Liver Kidney Microsomal Antibodies (LKM Antibodies)
Soluble Liver Antigen (SLA)-Antibody (Anti-SLA)

Background: SMA are IgG or IgM class antibodies, directed against microfilamental F-actin, which is present in all smooth muscles.
Useful parameter to differentiate between autoimmune hepatitis types and other forms of hepatitis such as chronic viral hepatitis (Hepatitis B, D, C), drug induced chronic hepatitis (methyldopa, nitrofurantoin, propylthiouracil), Wilson's disease, alpha$_1$ antitrypsin deficiency.
SMA are found in 50-80% of patients with autoimmune hepatitis type 1 and type 3.
Type 1 is also associated with ANA, high IgG immunoglobulin levels, and occurrence of other extrahepatic autoimmune syndromes but nearly always lacking Liver Kidney Microsomal Antibodies of the type 1 (LKM-1). In 10% of the type-1 patients Soluble Liver Antigen (SLA)-Antibodies (Anti-SLA) are detectable.
Limitation: Positive test results may occur in patients with primary biliary cirrhosis, rarely in viral hepatitis, infectious mononucleosis, tumors, alcoholic cirrhosis and in up to 5% in healthy individuals.

Sampling: 1 mL serum

Reference Interval: Titers:
< 1:20 negative
≥ 1:20 positive
> 1:160 chronic aggressive disease

Sodium (Na), Serum

Related Information: Antidiuretic Hormone, Plasma
Chloride (Cl), Serum or Urine or CSF
Lithium (Li), Serum
Osmolality, Serum or Urine
Potassium, Serum or Plasma or Urine
Renin Activity, Plasma
Sodium (Na), Urine
Urea-Nitrogen and Urea, Serum or Plasma
Urea Nitrogen, Urine
Uric Acid, Serum or Urine

Background: Sodium is the most important cation in the extracellular space, whereas potassium in the intracellular space, together with the anions it contributes 95% of the extracellular osmotically activity. The distribution of water between the extracellular and intracellular space varies only by 1-2%.
Calculation of serum osmolality:
mosmol/kg H_2O = 1.86 x sodium + glucose + urea (if in mmol/L) or
mosmol/kg = 1.86 x sodium + 0.056 x glucose + 0.17 x urea + 9 (if sodium in mmol/L and glucose in mg/dL and urea in mg/dL)

1. Hyponatremia (< 136 mmol/L, severe <120 mmol/L)
   Hyponatremia occurs, if net H_2O uptake exceeds H_2O excretion.
   Causes:
   1.1. hypotonic hyponatremia with decreased volume of extracellular fluid
      1.1.1 Renal sodium losses:
      Diuretics
      Salt wasting syndrome
      Osmotic diuresis (by mannitol, glucose)
      Glucocorticoid deficiency
      Ketonuria
      Renal tubular acidosis
      1.1.2 Extrarenal losses:
      Diarrhea and vomiting
      Pancreatitis, peritonitis, bowl obstruction, burns, trauma by sequestration in third space.

   1.2 Hypotonic hyponatremia with increased volume of extracellular fluid
      Congestive heart failure
      Cirrhosis
      Nephritic syndrome
      Renal impairment
      Pregnancy

1.3 Hypotonic hyponatremia with normal volume of extracellular fluid
Syndrome of inappropriate antidiuretic hormone in malignancies, pulmonary diseases (infectious, respiratory failure, ventilation) and in central nervous system disorders (psychosis, inflammation, stroke, hemorrhage, trauma, demyelinating diseases) and drugs (carbamazepine, chlorpropamide, clofibrate, nicotine, opiates, oxytocin, phenothiazine, tricyclics), hypothyreosis, postoperative state.

2. Hypernatremia
Diabetes insipidus (neurogenic, post traumatic, tumors, tuberculosis, sarcoidosis, aneurysms, meningitis, Guillain Barré syndrome, nephrogenic in renal diseases, hypercalcemia, hypokalemia, drugs).
Idiopathic hypernatremia
Osmotic diuresis due to hyperglycemia, mannitol, diarrhea, sweating.

Sampling: 1 mL serum

Reference Interval:

		mmol/L
adult		135-145
infants	0-7 days	133-146
	7-31days	134-144
	1-6month	134-142
	6 month -1 year	133-142
	older than 1 year	134-143

Sodium (Na), Urine

Related Information:
Aldosterone, Serum or Plasma or Urine
Chloride (Cl), Serum or Urine or CSF
Lithium (Li), Serum
Osmolality, Serum or Urine
Potassium, Serum or Plasma or Urine
Renin Activity, Plasma
Sodium (Na), Serum
Urea-Nitrogen and Urea, Serum or Plasma
Urea Nitrogen, Urine
Uric Acid, Serum or Urine

Background: Useful parameter in the assessment of volume disorders, acute renal failure, oliguria and in the diagnosis of hyponatremia.

Urinary Sodium (mmol/L)	serum sodium	state	cause
> 30	hyponatremia	hypovolemic	diuretics, mineralocorticoid deficiency, salt wasting nephritis
> 30	hyponatremia	hypervolemic	acute or renal failure
> 30	hypernatremia	hypovolemic	osmotic diuresis
> 30	hypernatremia	hypervolemic	primary/secondary aldosteronism, Cushing s syndrome, sodium bicarbonate or sodium administration
> 20	hyponatremia	euvolemic	hypothyroidism, glucocorticoid deficiency syndrome of inappropriate antidiuretic hormone drugs, water intoxication
< 30	hyponatremia	hypovolemic	vomiting, diarrhea, burn wounds
< 30	hypernatremia	hypovolemic	excessive sweating, diarrhea
< 10	hyponatremia	hypervolemic	liver cirrhosis, nephritic syndrome, cardiac failure

Urinary sodium varies in central and nephrogenic diabetes insipidus and hypodipsia
Urinary sodium > 40 mmol/L may indicate acute tubular necrosis

Sampling: Ship to laboratory a 5 mL aliquot of a 24h urine, note total quantity.

Reference Interval: Excretion varies with dietary intake. Diurnal variation with a low excretion during the night.

male	average 160 mmol/24h	range 135-210 mmol/24h
female	average 135 mmol/24h	range 115-170 mmol/24h

Soluble Liver Antigen (SLA)-Antibody (Anti-SLA)

S-T

Related Information:
Antimitochondrial Antibodies
Antinuclear Antibody
Anti Liver/Kidney Microsomal Antibodies, Anti LMK-1 antibodies
Bilirubin, Fractionated, Serum
Parietal Cell Antibody
Smooth Muscle Antibodies
Thyroglobulin Antibody
Thyroperoxidase Autoantibody

Background: Autoimmune hepatitis is classified within 3 categories:

Type 1: or lupoid hepatitis: Smooth muscle cell antibodies (SMA) or antinuclear antibodies (ANA), as well as in 10% antibodies to SLA (hepatocyte cytokeratins 8 and 18) are present.

Female preponderance, juvenile age or 45-70 years old, normal IgA levels, pro gression to cirrhosis possible.

Type 2: patients have anti liver/kidney microsomal antibodies (anti LKM-1 antibodies).

Type 2a patients are 2-15 years old and have no SMA.

Type 2b patients are older than 40 years. Type 2b is associated with hepatitis C virus.

Type 3: patients produce anti SLA , anti SMA and antimitochondrial antibodies (AMA), but not with anti LMK-1 antibodies. Type 3 show a female preponderance, aged 30-50 years, normal IGA levels, often also with extrahepatic manifestation.

Sampling: 1 mL serum, keep cool!

Reference Interval: Negative: < 20 E/mL

Soluble Transferrin Receptor, Serum or Plasma

Related Information: Ferritin, Serum or Plasma
Hemochromatosis DNA
Iron (Fe), Serum or Urine
Transferrin and Total Iron Binding Capacity, Serum

Synonyms: Transferrin Receptor, soluble; sTfR

Background: sTfR is a truncated, smaller (proteolytic cleaved by 100 amino acids) form from the cellular transferrin receptor, originating from normoblasts. The transferrin receptor was first isolated from serum in 1990 after discovery in 1986. Increasing iron deficiency up regulates cellular transferrin receptors and sTfR. The marker can be used to differentiate between iron deficiency anemias, with sTfR increase, from anemia in chronic diseases, with normal sTfR values. In patients with inflammatory diseases such as rheumatoid arthritis, sTfR is unaffected by acute phase responses and therefore superior to ferritin or transferrin determination.

High turnover erythropoiesis also increases sTfR. The test is considered a sensitive early indicator of iron deficiency.

Also it is useful in monitoring erythropoietic response to erythropoietin together with serum ferritin and reticulocyte hemoglobin content.

The ratio of serum transferrin receptor to serum ferritin gives an estimation of body iron in mg per kg of body weight.

Less specific but in combination with other parameters used in: autoimmune hemolytic anemia, sickle cell anemia, hereditary spherocytosis, beta thalassemia, alpha-thalassemia, polycythemia vera, vitamin B-12 deficiency, folic acid deficiency.

Sampling: 1 mL serum. Blood specimen is stable for 1h, serum must be separated, transported to the lab or frozen. Specimen cannot be processed if severe hemolysis, icterus or lipemia occur.

Reference Interval: 1.9-5.0 mg/L

Somatomedin C (IGF-1), Serum or Plasma

Related Information: Insulin-Like Growth Factor Binding Protein 3 (IGF-BP3), Serum
Somatotropin, Serum

Synonyms: Insulin-Like Growth Factor-1; IGF-I; Sm-C; Sulfation Factor

Background: Used in diagnosis of diagnosis of acromegaly and monitoring of growth hormone treatment. Low values are in hypopituitarism, malnutrition, delayed puberty, diabetes mellitus, cirrhosis, Elevated values may occur in precocious puberty, pregnancy, obesity, diabetes mellitus, pituitary gigantism, acromegaly, diabetic retinopathy.

In combination with elevated growth hormone levels low IGF-1 levels are seen in Laron dwarfism.

Sampling: 2 mL serum or plasma, overnight fasting is preferable. Separate serum or plasma soon.

Reference Interval:

Children:	1–4 years	49–327 ng/ml
	5–6 years	50–297 ng/ml
	7–9 years	57–388 ng/ml
	10–12 years	88–693 ng/ml
	13–16 years	183–996 ng/ml
Adults:	male	49–342 ng/ml
	female	63–279 ng/ml

Somatomedins see Insulin-Like Growth Factor Binding Protein 3 (IGF-BP3), Serum

Somatotropin, Serum

Related Information: Insulin-Like Growth Factor Binding Protein 3 (IGF-BP3), Serum
Somatomedin C, Serum or Plasma (IGF-1)

Synonyms: Growth Hormone; GH; hGH

Background: The anterior pituitary gland secretes in multiple short spikes GH with a half life of 20 min, under the influence of GH releasing hormone, GH releasing peptide-6 and GH inhibitory hormone (somatostatin) from the pancreas. The maximum occurs during initial phase of deep sleep, smaller amounts are excreted after exercise or eating.

GH affects lipolysis, protein synthesis, cardiac function, red cell mass by direct or indirect action via insulin like growth factor.

Diseases: Pituitary adenomas cause acromegaly, deficiency may cause short statue. In adults, deficiency of GH may cause body fat increase, decrease of muscle mass and strength and bone density, abnormal lipoprotein and carbohydrate turnover.

Since GH secretion is unpredictable random samples may be within the reference range even in patients with acromegaly or other pituitary gland disorders. It is strongly recommended to use one of the dynamic tests for GH insufficiency.

Suppression test is done by 100 g oral glucose after fasting overnight and samples are drawn at baseline, 30 min, 60 min, 120 min: GH is expected to be > 2 ng/ml at 60 min and 120 min.

If a GH deficiency is expected, either use the gold standard the Insulin Tolerance Test or use instead two of the stimulation tests with arginine, glucagons, L-dopa, clonidine, diazepam or pentagastrin. If combining growth hormone releasing hormone, 1 µg/kg body weight with growth hormone releasing peptide-6, 1 microgram/kg body weight, administered IV., the normal GH values are expected to be > 20 ng/ml, values < 10 ng/ml are considered to indicate deficiency.

Sampling: 1 mL serum, stable for 4 h, stable 12 month frozen

Reference Interval:			
	Cord blood		8-41 ng/ml
	Newborn		5-53 ng/ml
	Infant 1-12 month		2-10 ng/ml
	Adult	male	0-4 ng/ml
		female	0-18 ng/ml
	> 60 years	male	1-9 ng/ml
		female	1-16 ng/ml

Squamous Cell Carcinoma Antigen (SCCA)

Background: Lacking sensitivity and specificity, SCCA is not useful in screening procedures but in monitoring therapy and follow ups in patients with squamous cell carcinomas of the cervix, lung, and esophagus, anal and head-neck.

- Carcinoma of the cervix: Incidence of elevated levels in the primary squamous cell carcinoma 65 - 80%, for the type of adeno-squamous cell carcinoma lower (50%), and for the adenocarcinoma 0 - 20%. The specificity varies between 93 - 97%. The incidence of elevated levels increases with the tumor stage: from 0-20% in the early stage to 60 - 100% in stage IV. There is a good correlation between clinical outcome and SCCA serum concentration.

Prognostic value: SCCA > 30 µg/L indicate a short survival and rapid relapse. A predictive threshold for metastasis of the lymph node and prognosis may be estimated by the combination of SCCA (1.5 µg/mL) and CA125 (35 mU/L).

- Squamous cell carcinomas of the lung: Overall sensitivity of SCCA is 30%, 40 - 80% of the patients display elevated levels. There is a correlation for the sensitivity and the stage of the carcinoma, increasing from 30 - 50% in stage I to 70 - 100% in stage IV. CYFRA 21-1 was found to be the most sensitive marker in lung carcinomas (46% with a specificity of 95%) superior to CEA, SCCA and NSE.
- Head and neck carcinomas: Diagnostic sensitivity 30%-80%.
- Carcinoma of the esophagus: Sensitivity 30 - 40%, stage dependent and up to 50% stage IV.

Limitations: Elevated levels (> 2-3 µg/L) occur in benign diseases such as liver cirrhosis (10%), pancreatitis (30 - 60%), renal impairment (up to 80%, correlation with creatinine), chronic lung diseases (up to 40%), in diseases of the female reproduction system (up to 40%), in diseases of the larynx and ears (20 - 46%), in patients with psoriasis (up to 80%).

Sampling: 1 mL serum

Reference Interval: Monoclonal test type: 1.4-1.9 µg/L
No increase during pregnancy

SS-A/Ro and SS-B/La Antibodies

Related information: Cardiolipin Antibody
Antibodies, dsDNA and Antibodies, ssDNA
Antinuclear Antibody
Jo-1 Antibodies
Scl-70 Antibody

Background: Sjoegren syndrome is an autoimmune disorder characterized by dryness of the eyes, mouth and other areas covered by mucous membranes associated frequently with rheumatoid arthritis and other autoimmune diseases such as SLE, primary biliary cirrhosis, scleroderma, polymyositis, Hashimoto thyroiditis, and pulmonary fibrosis. The disorder predominates in women with a 9:1 ratio and occurs in most cases between the age of 40-60 years. Sjoegren's syndrome is linked to HLA-DR-2 and DR-3 antigens.

Laboratory results include mild anemia, leucopenia, eosinophilia, polyclonal hypergamma-globulinemia, rheumatoid factor positivity in 75-95% of the patients, and antinuclear antibodies in 95%, Ku antibodies may be present in 20% of the population.

Antibodies directed to SS-A/Ro are present in 70 - 100% of primary and in 40 - 70% of secondary Sjoegren's syndrome patients. Antibodies to SS-A/Ro are strongly associated with neonatal lupus in babies born to mothers with SLE, characterized by congenital heart block (by SS-A antibodies binding to the conducting tissue) and photosensitive dermatitis for the first 6 month of life caused by maternal IgG crossed the placenta.

Antibodies to SS-B/La are present in 60 - 90% in primary and 30 - 60% of secondary Sjoegren's syndrome.

Anti-Sm, Anti SCL-70, Anti Jo-1 are absent in Sjoegren's syndrome

Sampling: 1 mL serum

Reference Interval:			
	SS-A/Ro	negative:	< 5 U/mL
	SS-B/La	negative:	< 5 U/mL

ss-DNA-Antibody see Antibodies, ssDNA

S-T

Stool, Microbiology

Overview: Please see Germ differentiation of:
Salmonella
Shigella
Yersinia enterocolitica
Campylobacter jejuni / coli,
Dyspeptic E. coli, E. coli 157 (EHEC),
Clostridium difficile
Candida species

Trichosporon spp
Geotrichum candidum
Clostridium difficile toxin A and B
Detection of: Rota-, adeno- and astrovirus, norwalk-like-Virus
Parasite
Helminth eggs

Sampling: approx. 2 g stool in sterile tube

Streptococcus pneumoniae, Serology see Pneumococcal Antibody, Serology

Synovial Fluid Analysis

Related Information: Chlamydia
Borrelia, Serology
Neisseria gonorrhoeae
Rheumatoid Factor, Serum or Body Fluid
Uric Acid, Serum or Urine

Synonyms: Knee fluid

Background: Useful in the diagnosis of rheumatic disease and diseases causing joint symptoms, increase in joint fluid, destructions in the joint space such as gout, infection, pseudogout. Most helpful in infections of the joint, less valuable in previously established diagnosis of rheumatic disease.

In gout, patients are mostly male (male to female ratio 7:1), middle aged, or postmenopausal women, with typical first metatarsophalangeal joints, midfoot ankles knees and wrist, erosions of displaced joints, inflammation with monosodium urate crystals, and possibly underlying diabetes, obesity, hypertension, hyperlipidemia.

In calcium pyrophosphate dehydrate crystal deposition disease, male to female ratio is 1.5:1, mostly elder patients, with no hyperuricemia, typically localized at the knees, wrists, metacarpophalangeal joints, elbows, shoulders. X-ray presenting as chondrocalcinosis and inflammation. Possibly underlying diseases are hyperparathyroidism, hemachromatosis, hyper-magnesemia, hyperphosphatasia, and hypothyroidism.

Decreased glucose indicates inflammation, but only if compared to serum glucose. High LDH but normal serum LDH indicates rheumatoid arthritis, infectious arthritis or gout; it is normal in degenerative joint diseases.

In gonococcal infection of the joint, synovial fluid white cell count averages 50 000 cells/µL and positive gram strains in 25% of the cases. Nongonococcal infectious arthritis may be caused by Staphylococcus aureus in immunocompromised or due to trauma. Less frequent, Streptococci sp and gram negative Bacilli are isolated.

Lyme disease has to be considered if eosinophile count in the synovial fluid exceeds 2%.

60% of Whipple disease patients present with arthritis. DNA for Tropheryma whippelii is tested positive in the synovial fluid as well as neutrophil counts are elevated.

Sampling: If Neisseria gonorrhoeae infection is suspected, Thayer Martin media agar is best inoculated with joint fluid at the bedside.

For microscopy and analysis: 1 mL synovial fluid (or less) in sterile tube and 1ml (or less) in EDTA tube for cell count.

Reference Interval:		
	Cell numbers:	up to 200/µl (mean 75/µl)
	Total protein:	11–22 g/L
	Uric acid:	3–7 mg/dL
	Glucose:	60–95 mg/dL
	Lactate:	9–16 mg/dL
	LDH:	< 200 U/L

Tacrolimus (FK 506), Whole Blood

Related Information: Cyclosporine A (monoclonal)

Synonyms: FK-506; Prograf®

Background: FK-506 is a macrolide lactone immunosuppressant used in renal, liver, heart, lung, bone marrow transplants and in the treatment of atopic dermatitis. Tacrolimus is more active than cyclosporine, but also nephrotoxic, so co administration is not recommended and kidney function has to be closely monitored.

At least 9 metabolites are known mainly produced by the cytochrome P-450 system.

Bioavailability 5-70%; urinary excretion < 1%; plasma binding 70-99% mainly to albumin and alpha-1-acid glycoprotein; volume of distribution 0.7-1.4 L/kg increased in cirrhosis; half life time 8-17h increased in cirrhosis; peak time 1.1-1.9h, peak concentration 21-41 ng/ml after a single 7 mg dose. Steady state reached within 2-3 days.

Sampling: 1 ml whole EDTA blood. Whole blood recommended since tacrolimus binds to erythrocytes and lipoproteins. Plasma levels are up to 20% lower.

Reference Interval:		
	Therapeutic:	Range 3-20 ng/mL through
	for liver transplants	4-10 ng/mL
	for renal transplants	6-12 ng/mL
	for pancreas transplants	10-18 ng/mL
	for bone marrow	10-20 ng/mL

Teicoplanin, Serum

Synonyms: Targocid®

Background: Close to vancomycin, it is a glycopeptide antibiotic composed of 6 glycopeptides. It is effective against Streptococcus species. including Pneumococcus sp., Staphylococcus sp, all aerobe gram positive bacteria including methicillin resistant S. aureus (MRSA),

Enterococcus sp., Listeria sp.. Some studies have shown a higher activity against Clostridium difficile as compared to vancomycin.
Resistance: Few strains of S. aureus, moderate numbers of Enterococcus sp. are resistant. Cross resistance with vancomycin is incomplete.
It is not effective against gram negative bacteria.
Teicoplanin is indicated in serious infections with Staphylococcus sp. and Enterococcus sp.
Half life time is 3.6h, prolonged to 7-30h after repeated dosages. Protein binding 90%; no crossing of the blood brain barrier; 50% excretion by the kidney within 4 days.
Sampling: 2 mL serum
Reference Interval: Therapeutic Interval: 5-60 mg/L
(Average serum levels after I.V. dose of 0.4 g are 32 mg/L at 1h, 5 mg/L at 24h after first dose)

Tempra® see Acetaminophen, Serum

Testosterone, Serum

Related Information: Adrenocorticotropic Hormone, ACTH, Plasma
Androstenedione, Serum
Cortisol, Serum or Plasma
Cortisol, Free, Urine
Dehydroepiandrosterone Sulphate (DHEA-S), Serum
Follicle Stimulating Hormone (FSH), Serum
Luteinizing Hormone (LH)

Background: Testosterone (T) is secreted by the testicular Leydig cells, is active and has a more active metabolite, dihydrotestosterone (DHT). DHT is produced by a 5-alpha reductase of the skin, prostate, internal genitals. T Is also converted into the estrogenic hormone estradiol (E2) by an aromatase of the fat tissue of the breast. The secretion of T is regulated by a negative loop by the pituitary luteinizing hormone (LH), which is released by the hypothalamic gonadotropin releasing hormone. Peak levels of T occur in the early morning and minimum levels are in the early evening. T is bound in the serum by sex hormone binding globulin (SHBG) to 60% and to 30% by albumin, only 1%-4% is free. To asses the free T is useful in obese patients who may have low SHBG.
Determination of T is useful in polycystic ovary syndrome which is characterized by androgen excess such as anovulation, hirsutism, acne and is in most cases accompanied by elevated T levels.
Useful in male hypogonadism patients with primary testicular insufficiency: Low T values in combination with high LH and FSH levels.
Limitations: Cimetidine may elevate T values. In athletes taking exogenous T, endogenous T may be suppressed.
Morning values are 20% higher than evening levels. Short physical activity may elevate, long term exhausting activities may decrease values, also serve diseases particularly of the liver,

kidney and cardiopulmonary system decrease T.

Sampling: 1 mL serum or heparin plasma for free testosterone, 1 mL serum for total testosterone.

Reference Interval: Total Testosterone, Serum: (ng/mL)

Years of age	Male	Female
1-9	< 0.4	< 0.4
10-11	< 2.0	< 0.7
12-13	< 8.0	< 1.2
14	< 12.0	< 1.2
15-16	1.0-12.0	< 1.2
17-18	3.0-12.0	0.2-1.2
19-40	3.0-9.5	0.2-0.8
> 40	2.4-9.5	0.2-0.8

Free Testosterone, Serum:

Male	9.0–27.0 pg/mL
Female	0.3–3.2 pg/mL

Tetanus Antitoxin Antibody IgG

Background: Clostridium tetani, a gram positive, spore forming with high environmental resistance, obligate anaerobe is proliferating at the site of a deep injury. Tetanospasmin, a neurotoxin causes the spastic paralysis. The reservoir is the gastrointestinal tract of animals.
Although seldom in the industrialized countries, mortality is still 50%. Immunity after vaccination wanes by age, booster immunizations are strongly encouraged.

Sampling: 1 mL serum

Reference Interval:

< 0.1 IU/mL	no immunity
0.1-0.5 IU/mL	immunity may be not protective
0.5-1 IU/mL	booster recommended in 3 years
1-5 IU/mL	booster recommended in 5 years
> 5 IU/mL	booster recommended in 8 years

Theophylline, Serum

Related Information:
Amiodarone, Serum
Caffeine, Serum
Carbamazepine, Serum
Carbamazepine-10,11-Epoxide, Serum
Phenobarbital, Serum
Phenytoin (Diphenylhydantoin, DPH), Serum
Verapamil, Serum or Plasma

Synonyms: Aminophylline; Elixophyllin®; Ethylenediamine; Phyllocontin®; Slo-Phyllin®; Sustaire®; Theo-Dur®; Theolair™; Truphylline®.

Background: Used in COPD and asthma. Displays anti-inflammatory and immunomodulatory characteristics. Good tolerance if within the therapeutic range.

Half life in healthy and non smoking adults: 6-10h, in healthy children 2-9h, in patients with cirrhosis up to 30h, with congestive heart diseases up to 24h, in premature infants 15-58h.

Half life is shorter in smokers; usually smokers need 1.5-2 times as much as non smokers and are variable with co-administration of phenobarbital. Possible decrease in theophylline concentrations is caused by rifampin, carbamazepine, phenytoin, aminoglutethimide.

Volume of distribution 0.4-0.6 L/kg; protein binding 52-60%

Sampling: 1 mL serum

In general: Sampling time 2h after dosage or 6h for sustained preparations.

Peak concentrations: Oral 1h, uncoated tablets 2h, chewable tablets 1-2h, enteric coated tablets 4-5h, extended release tablets up to 7h

Reference Interval: Therapeutic: 10-20 µg/mL,
60% of maximal broncho-dilatator effects at 10 µg/mL.
10-15 µg/mL are effective in COPD patients.
Toxic effects such as diarrhea, nausea, abdominal pain, headache, dizziness, agitation, tremor may occur at 15-25 µg/mL; tachycardia at 25-35 µg/mL and at > 35 µg/mL ventricular tachycardia, premature ventricular contractions, seizures.

Thiamin see Vitamin B

Thrombin Time

Related Information: Activated Partial Thromboplastin Time
D-Dimers
Fibrinogen, Functional
Applies to Fibrinopeptide A and B

Background: The test is measuring the clotting time in the last step of the coagulation cascade (fibrinogen to fibrin). Useful in the diagnosis of hereditary or acquired dysfibrinogenemia.

- Hereditary dysfibrinogenemia, caused by various mutations, leading to mild bleeding or venous or less frequent arterial thrombosis. Prevalence in patients with venous thrombosis is 0.8%. In addition to changed thrombin time, PT or PTT may be prolonged.

- Acquired forms include liver diseases, hepatoma, acute phase reactions with high levels of fibrinogen. Thrombin time can be prolonged in disseminated intravascular coagulation (DIC) and thrombolytic therapy. Prolongation, together with ReptilaseR time, has been observed in amyloidosis, due to inhibition of conversion fibrinogen to fibrin.

The thrombin time has been used in monitoring heparin therapy if PTT was not reliable, but has been replaced by antifactor Xa assays, since thrombin time is too sensitive.

The assay is performed by adding to the patient's plasma thrombin and clotting time is measured. Thrombin cleaves fibrinogen, releasing fibrinopeptide A and B from fibrinogen and converting fibrinogen into fibrin-clot.

Sampling: 2 mL citrate plasma, tube must be approximately completely filled, invert gently to mix well. Separate plasma soon. Plasma is stable on ice up to 4h. Test is highly sensitive to traces of heparin, hirudin or argatroban anticoagulants.

Reference Interval: 14-20 seconds

Thromboplastin Time, Partial (PTT) see Activated Partial Thromboplastin Time

Thromboplastin Time (Quick`s Value) see Prothrombin Time

Thyroglobulin, Serum

Background: Secreted by the thyroid follicular epithelial cells, thyroglobulin stores the thyroid hormones T_4 and T_3. Used for monitoring patients with differentiated thyroid carcinomas after resection.

Sampling: 1 mL serum, do not draw sample soon after needle biopsy, thyroid surgery or radioiodine therapy.

Reference Interval:

Euthyroid patients and normal TSH:	1.4-59 ng/mL
Total thyrotomy or suppressed TSH:	< 0.5 ng/mL

Thyroglobulin Antibody

Related Information: Thyroperoxidase Autoantibody
Thyrotropin Receptor Antibody

Synonym: Anti Thyroid Globulin Antibody

Sampling: 1 mL serum

Reference Interval: Negative < 60 U/mL

Thyroid Stimulating Hormone, Serum

Related Information: Thyroglobulin Antibody
Thyroid Stimulating Hormone, Serum
Thyroxine, Free, Serum
Thyroxine, Total, Serum
Triiodothyronine, Free and Total, Serum

Synonyms: TSH; sTSH; Thyrotropin

Background: TSH, synthesized by the anterior pituitary gland, stimulates secretion of T_3 and T_4 and is regulated by a feedback loop, involving TRH from the hypothalamus. The prevalence of hypothyroidism is up to 14% in older individuals, and since subclinical hypothyroidism (increased TSH and normal FT_4) has been shown to be a risk factor for atherosclerosis and myocardial infarction, TSH in combination with T_4 or FT_4 has to be considered as a screening test in this population.

- Primary Hypothyroidism: An increased TSH level is an early indicator for later decrease in T_4.
- Secondary Hypothyroidism: Due to the insufficiency of the pituitary gland to react to T_4 level TSH remain low but in part within the normal range. Therefore it is necessary to obtain TSH and T_4 values simultaneously.
- Resistance to thyroid hormone: a familial disease characterized by insensitivity to thyroid hormones, elevated T_4 and T_3 levels and normal to elevated TSH, demanding a clinical evaluation of patients on familiar risk to avoid the diagnose of hyperthyroidism.

To monitor thyroxine therapy, a 8-10 week interval has to be considered to achieve a stable steady state of normal TSH levels.

Sampling: 1 mL serum, separate serum within 5h and refrigerate for max. 5 days.
TSH release is pulsatile and a diurnal rhythm exists with peak levels around 11 PM. Drugs and diseases often alter TSH, to obtain proper diagnosis, patients should be in a clinically stable state.

Reference Interval: Validated for Southern Germany:

Adults	21-54 years	0.2-2.8 mIU/L
	55-87 years	0.2-3.0 mIU/L
Newborns/Children	Premature neonates	0.3-13 mIU/L
	Birth	0.5-20 mIU/L
	2-20 weeks	0.8-5.0 mIU/L
	21 weeks to 20 years	0.3-4.5 mIU/L

For the US reference ranges have been reported as:

Adults	21-54 years	0.4-4.2 mIU/L
	55-87 years	0.5-8.9 mIU/L
Newborns/Children	Premature neonates	0.7-27.0 mIU/L
	Birth	1.0-39.0 mIU/L
	2-20 weeks	1.7-9.1 mIU/L
	21 weeks to 20 years	0.7-6.4 mIU/L

For the Middle East one report systematically investigated TSH:

Adults 18-54 years (average 27 years)

Male	0.52-4.89 mIU/L
Female	0.48-6.30 mIU/L

Critical value: Less than 0.1 mIU/L indicates wither primary hypothyroidism or exogenous thyrotoxicosis. Patient may be on risk for atrial fibrillation.

Thyroperoxidase Autoantibody

Related Information: Thyroglobulin Antibody
Thyroid Stimulating Hormone, Serum
Thyroxine, Free, Serum
Thyroxine, Total, Serum

Synonyms: Antithyroid Peroxidase Antibody; Microsomal Antibody; Thyroid; Thyroid Antimicrosomal Antibody;

Background: Thyroperoxidase is a major antigen in cell mediated cytotoxic thyroid disease. Elevated antibodies titers against thyroperoxidase support the diagnosis of autoimmune thyroiditis in patients with hypothyroidism. However, 10% of the adult population has moderate elevated titers without signs of disease.

Sampling: 1 mL serum, stable 3 days at 4°C.

Reference Interval:

Negative	< 20 IU/mL
Positive in adults	> 20 IU/mL
In autoimmune thyroiditis	> 50 IU/mL

Thyrotropin Receptor Antibody, Serum

Related Information: Thyroglobulin Antibody
Thyroid Stimulating Hormone, Serum
Thyroperoxidase Autoantibody
Thyroxine, Free, Serum
Thyroxine, Total, Serum

Synonyms: LATS; Long-Acting Thyroid Stimulator; Thyroid Stimulating Autoantibody; Thyroid Stimulating Immunoglobulins; TRAb; Ts Antibodies; TSH- Receptor Antibodies; TSIG

Background: Contributes to the pathogenesis in Grave's disease. Sensitivity for Grave's disease 80-95%, useful in patients without hyperthyroidism and clinical signs of infiltrative ophthalmopathy or dermopathy and in patients with toxic nodular goiter.

Limitations: Low serum immunoglobulin levels or serum protein my give false negative results.

Sampling: 1 mL serum

Reference Interval: Negative < 2 U/L

Thyroxine Binding Globulin

Related Information: Thyroxine Free, Serum
Thyroxine Total, Serum
Triiodothyronine Free and Total, Serum

Synonyms: T_4 Binding Globulin; TGB

Background: There are at least 3 proteins binding T_3 and T_4 : albumin, transthyretin, thyroxine binding globulin (see Thyroxine, Total, Serum). Differences in total T_3 and T_4 (abnormal) and free T_3 or T_4 (normal) values suggests altered TBG state, particularly in euthyroid individuals. An increase of TBG may be due to estrogens or a wide variety of drugs. Decrease may be caused by chronic diseases or familial deficiency (1:5000).
Useful in diagnosis of hereditary deficiency of TBG.

Sampling: 1 mL serum

Reference Interval:

0-1 week	3-8 mg/dL
1-12 months	3-6 mg/dL
2-10 years	2-5 mg/dL
> 15 years	1.2-2.5 mg/dL

Thyroxine Free, Serum

Related Information: Thyroid Stimulating Hormone, Serum
Thyrotroponin Receptor Antibody, Serum
Thyroxine Binding Globulin, Serum
Thyroxine Total, Serum
Triiodothyronine Free and Total, Serum

Synonyms: Free T_4; free Thyroxine; FT_4 free; Unbound T_4

Background: Free T_4 is the active form and the precursor of T_3. Although measurement of T_4 is used in the diagnosis of hyperthyroidism, the levels depend on the amount of thyroxine binding globulin, thus not reflecting the alteration of the clinical state. Mild alterations of the concentration of thyroxine biding proteins does not alter T_4 measurement to a greater extent. A familial form of hyperthyroxinemia is caused by a variant of albumin which binds T_4 abnormally.
Limitations: Rheumatoid factor, anti-thyroxine autoantibodies, low molecular weight heparin therapy, pregnancy, phenytoin may alter free T_4 levels. FT_4 may be increased in amiodarone treatment.

Sampling: 1 mL serum

Reference Interval: Validated for Southern Germany:
0.8-1.8 ng/dL (10.3-23.3 pmol/L)

For the US reference ranges have been reported as:

Adults:	0.8-2.7 ng/dL (10.3-35 pmol/L)
Newborns:	2.6-6.3 ng/dL (33.5-81.3 pmol/L)

For the Middle East one report systematically investigated TSH:
Adults: 18-54 years (average 27 years)

Male	0.76-1.43 ng/dL (9.92-18.62 pmol/L)
Female	0.69-1.32 ng/dL (9.00-17.15 pmol/L)

Thyroxine Total, Serum

Related Information: Thyroid Stimulating Hormone, Serum
Thyroxine Binding Globulin and Thyroxine Free, Serum
Triiodothyronine Free and Total, Serum

Synonyms: T_4; Tetraiodothyronine; Thyroxine

Background: 70% of T_4 is bound to thyroxine binding globulin TBG, 20% to transthyredin and 10% to albumin, most of the T_3 is bond to TBG. 0.03% of T_4 and 0.3% of T_3 remains unbound to protein. About 35% of T_4 is monodeiodinated to T_3 and 15-20% is changed to tetraiodothyroacetic acid and excreted in the urine or bile.

Binding to TGB is increased in neonatal state, pregnancy, estrogens, contraceptives, clofibrate, hepatitis, acute intermittent porphyria, and lymphoma. A decrease in TGB binding is observed in nephritic syndrome, androgens administration, prednisone, hepatitis, stress, salicylates, phenylhydantoin.

Sampling: 1 mL serum

Reference Interval:

1-3 days	11.8-22.6 ug/dL
1-2 weeks	9.8-16.6 ug/dL
1-4 months	7.2-14.4 ug/dL
4-12 months	7.8-16.2 ug/dL
1-5 years	7.3-15.0 ug/dL
5-10 years	6.4-13.3 ug/dL
10-15 years	5.6-11.7 ug/dL
> 15 years	5.0-11.0 ug/dL
Pregnancy	5.5-16.0 ug/dL

Tissue Polypeptide Antigen (TPA), Serum

Related Information: Carcinoembryonic Antigen (CEA), Serum
CA 19-9 (Gastrointestinal), Serum

Synonyms: Tissue Polypeptide Specific Antigen; TPS; TPA

Background: TPA is composed of low molecular weight epithelium associated cytokeratines predominant in cells undergoing mitosis but in minor concentrations during the interphase. TPA concentration is a marker of disease progression and remission, occurring in inflammatory diseases and many tumors.

Useful in combination with CEA to monitor breast, colorectal, ovarian, bladder, lung tumors. It may be helpful in the distinction between cholangiocarcinomas, which are positive, and hepato-

cellular carcinomas, which are negative.
Limitations: Increased values during pregnancy
Sampling: 2 mL serum
Reference Interval: Negative < 80 U/L

Total Iron Binding Capacity see Transferrin and Total Iron Binding Capacity, Serum

Toxocara canis, Serology

Background: Toxocara canis is the major cause of visceral larva migrans. The hosts are canids, including the domestic dog and feral fox. The dogs are usually less than 6 month old when the larvae undergo all four larval stages and are caught up and adult parasites develop in the small intestine. In older dogs larval maturation is haltered at the second larval stage (L2). Nearly all dogs are infected due to a reactivation of the L2 stage in pregnant bitches, crossing the placenta and are excreted with the milk.
The eggs produced in the dog's intestine by the adult female nematode are passed by the feces into the soil. If humans ingest contaminated soil, the egg hatches into larvae in the small intestine. The larvae migrates into liver, brain, eyes and are halted at the second larval stage , thus humans and other animals are paratenic hosts. Infection however can follow ingestion of fertilized embryonate eggs or uncooked tissue of another paratenic host.
Serologic studies show that 2-8% of the population has evidence of previous infection, in children prevalence is up to 35% in tropical areas, peaking between 3-10 years of age. Main route of transmission is fecal oral.
Treatment: albendazole or mebendazole
Sampling: 2 mL serum
Reference Interval: Antibody negative

Toxoplasmosis, Serology

Background: Toxoplasma gondii is an obligate intracellular protozoan parasite. The hosts are domestic cats and other felines. Humans, other mammals and birds are intermediate hosts, where the T. gondii occurs in two forms: rapidly multiplying (intracellular) tachyzoites and dormant bradyzoites which persist for years in the form of tissue cysts (most common in brain and muscle). The host can be infected by the oral route with oocysts, tachyzoites and bradyzoites.
Cats become infected by eating birds or other sources of raw infected meat. Other animals and humans become infected either from oocysts in soil or contaminated food or tissue cysts in undercooked meat. During pregnancy, tachyzoites invade the placenta and the fetus.
Epidemiology: Beef, pork and lamb meat is infected in 5-92%. Oocyte shedding in cats is estimated to be 1%. Prevalence increase with age, in child bearing age it is estimated in

Europe, Northern Africa and Australia to be 37-58%, in America and Sub-Saharan Africa 51-77%, Southeast Asia India and China it is 4-39%.

In 90% of cases no clinical symptoms are apparent during acute phase. Symptoms are enlarged lymph nodes mainly at head and neck.

Maternal immunity due to toxoplasmosis passed before conception protects the fetus from infection. The risk of congenital infection depends on the time of acquisition of an acute maternal infection. 15%-25% in the first trimester, 30%-54% in the second and 60-65% in the third. The severity of congenital disease is conversely related to the gestational age. Signs of infection at delivery are present in 21%-28% if infection occurred in the second trimester and up to 11% in the third trimester. 10% are born with severe disease such as strabismus, chorioretinitis, encephalitis, microencephaly, hydrocephalus, convulsions. Nonspecific signs are anemia, jaundice, thrombocytopenia, diarrhea, and pneumonitis. For confirmation of fetal infection, amniotic fluid should be assayed by PCR for T. gondii as well as culture assays.

Therapy: In gestational toxoplasmosis drug therapy may be considered with spiramycin if the fetus is not infected since spiramycin concentrates in the placenta but does not cross the placenta. In case of a confirmed (for example by toxoplasnosis-DNA test in amniotic fluid, test not reliable before week 18) infection of the fetus sulfadiazine plus pyrimethamine plus folic acid may be an option after week 16 of pregnancy until delivery. Pyrimethamine should not be used in the first 12-16 weeks of pregnancy because the concern of teratogenicity. All infected newborns should stay on therapy.

Symptomatic T. gondii infection in immunocompetent, non-pregnant individuals without visceral involvement does not need treatment. In immunocompromised hosts, sulfadiazine plus pyrimethamine and folic acid is recommended.

Classification: Toxoplasma gondii belongs to the phylum Apicomplexa (together with Plasmodium spp., Cryptosporidium spp., and Theileria spp.) which is an early-branching eukaryotic lineage containing a number of important human and animal pathogens. Their complex life cycles and unique cytoskeletal features distinguish them from other eukaryotes. Apicomplexans rely on actin-based motility for cell invasion. Closely related genera are Neospora and Hammondia.

Sampling: 2 mL serum

Reference Interval:

Differentiation of immunoglobulin class:		
IgA antibody	negative:	< 20 AU/mL
IgG antibody	negative:	< 6 IU/mL
	borderline:	6–8 IU/mL
	positive:	> 8 IU/mL
IgM antibody	negative:	< 6 AU/mL
	borderline:	6–8 AU/mL
	positive:	> 8 AU/mL
Enhanced marker for acute infection:		
	IgG avidity test low:	< 0.15 (acute infection)
	borderline:	0.15–0.25
	avidity test high:	> 0.25 (past infection)

Transferrin and Total Iron Binding Capacity, Serum

Related Information: Copper (Cu), Serum or Urine
Erythropoietin (EPO), Serum
Ferritin, Serum or Plasma
Hemochromatosis DNA
Iron (Fe), Serum or Urine
Occult Blood in Stool (Hemoccult)
Soluble Transferrin Receptor, Serum or Plasma
Applies to Transferrin Saturation (%)

Background: Please see also Iron (Fe), Serum

After absorption, iron is bound to transferrin, a single chain protein of 80 kDa, synthesized in the liver. Binding to transferrin is ph dependent, at pH 7.4, very strong, no binding at pH 4.5. Cells acquire iron from transferrin by the transferrin receptor (TfR) a transmembrane glycoprotein which is predominant in all cells and particularly in placenta, liver and erythroid precursor cells. Serum iron concentrations reflects the Fe^{3+} bound by transferrin. Approx 30% of transferrin is occupied by Fe^{3+}, a large capacity to bind Iron is left. Transferrin saturation is the ratio of plasma iron to total iron binding capacity (TIBC).

Interpretation of transferrin and iron is difficult since serum iron is decreased by infection, inflammation, malignancy, ascorbate deficiency and it may be increased by liver diseases, iron ingestion and decreased erythropoiesis. There is a great circadian fluctuation (30% higher iron values in the morning) and a more than 30% day to day variation in serum iron.

Therefore, measurement of transferrin and iron is of limited use for

- Iron deficiency caused by inadequate absorption (celiac disease, inflammatory bowl disease, dietary, red cell defects).
- Increased losses: Tumors, gastritis, ulcer, parasitic disease, genitourinary diseases.

Useful parameter in:

- Iron overload state: If the transferrin binding capacity is exceeded, iron is deposited in parenchymal cells or reticuloendothelial system (transfusion overload). To establish the diagnosis of hemochromatosis: Transferrin saturation > 55% and ferritin > 400 µg/L together with the clinical signs. In the classical HLA related hemochromatosis, saturation increases before ferritin goes up and in 90% of the patients homozygosity for the C282Y mutation is responsible for this type of iron storage disease.

Overview on iron status indicators changes:

Status	Ferritin	Transferrin	Serum Iron	Iron Saturation
Iron deficiency	down	up	down	down or normal
Anemia in chronic diseases	up or normal	down or normal	down	down or normal
Sideroblastic anemia	up	down or normal	up or normal	up
Hemolytic anemia	up	down or normal	up	up
Hemochromatosis	up	normal or down	up	up
Acute liver impairment	up	variable	up	up
Protein deficiency		down or normal	down or normal	down or normal

Limitations: TIBC and transferrin are elevated in patients on oral contraceptives, saturation is normal. Transferrin saturation is low in acute or chronic infection, iron may be low as well but does not indicate iron deficiency. Some patients have anemia but normal transferrin concentrations. In very high iron level and iron poisoning, TIBC may give false high results.

Sampling: 2 mL serum, due to circadian rhythm, fasting morning sample is preferred.

Reference Interval: Transferrin:

Adults		200-400 mg/dL
Children	2-5 years	280-350 mg/dL
	6-10 years	260-360 mg/dL
	11-18 years	260-360 mg/dL

TIBC is an approximation to transferrin and can be calculated as
TIBC (µg/dl) = transferrin (mg/dL) x 1.25

Percent saturation (Tfs%): Please see Iron, Serum to calculate:
Transfe. Saturation, Tfs (%) = Iron, Serum (µg/dL) x 70.9 : transferrin (mg/dL)

Newborn		29.4-46.0%
Premature		11.4-42.2%
1-5 year(s)		7.0-44.0%
6-9 years		17.0-42.0%
10-14 years	female	11.0-36.0%
	male	2.0-40.0%
14-19 years		6.0-33.0%
Adult		16.0-45.0%

Transferrin Saturation see Transferrin and Total Iron Binding Capacity, Serum

Treponema pallidum (TPAH) Serology

Related Information: Borrelia, Serology

Synonyms: Lues Serology; Syphilis Serology; Treponemal Antibodies

Background: Members of three genera of spirochetes are known to causes human diseases: Treponema (syphilis and nonvenereal treponematoses) ; Borrelia (B. burgdorferi: Tick born Lyme disease, B. recurrentis: Louse born relapsing fever); Leptospira (leptospirosis).

Mode of transmission: Intimate contact of skin or mucous membranes containing spirochetes and during pregnancy across the placenta typically after the third month of pregnancy (congenital syphilis) to the fetus.

During the first stage of infection the spirochetes multiply at the site of inoculation to form a local, nontender ulcer (chancre) in 2-10 weeks. The ulceration heals spontaneously but the organism is widely spread into various tissues forming lesions of the secondary syphilis characterized by

maculopapular rash, moist papules on skin or mucous membrane which are highly infectious. Approx 30% of primary and secondary stages will clear without treatment, one third will stay latent with positive serology and in some patients with reappearing second stage infectious episodes. One third of patients will develop the tertiary stage with only rarely seen treponema containing lesions.
Immunity is incomplete, antibodies can not prevent disease progression and multiple infections can be acquired but patients with late stage syphilis are less likely to acquire a new infection.
Treatment: Penicillin or erythromycin.
Laboratory diagnosis:
Direct detection: Only the non-pathogenic Treponema spp. which are part of the normal human flora of mucous membranes can, in opposite to T. pallidum, be cultured. Spirochetes can be demonstrated in the lesions of primary and secondary syphilis by darkfield microscopy or by direct fluorescent antibody DFA test.
Nonspecific serologic tests: Nontreponemal antigens (cardiolipins) react with antibodies in the serum of patients with syphilis. The VDRL (Venereal Disease Research Laboratory) and RPR (Rapid Plasma Reagin) are positive in most cases of primary and always in secondary syphilis. The titers decreases and become negative during efficient treatment. False positive may occur in leprosy, hepatitis, infectious mononucleosis, autoimmune diseases.
False negative titres occur as a result of the prozone phenomena occurring when the antibody is in excess in the patient's serum.
Specific serologic tests: Specific T. pallidum antigens react with patient's antibodies in immunofluorescence based test such as FTA-ABS or hemagglutinin based tests such as TPAH or MHA-TP. Theses tests become positive in the primary stage of syphilis and remain positive for life. The titer does not correlate with treatment or reinfection.

Sampling: 1 mL serum

Reference Interval:

TPHA nonreactive	< 1:80
TPHA reactive	> 1:80

Validation of the result: antibody differentiation by immunoblotting

Triglycerides, Serum or Plasma

Related Information:
Apolipoprotein A-1 and B-100, Serum
Cholesterol, Total, Serum or Plasma
Glycosylated Hemoglobin A1c , Blood
High Density Lipoprotein Cholesterol, Serum or Plasma
Low Density Lipoprotein Cholesterol

Background: Triglycerides (TG) are composed of a glycerol backbone esterified with three fatty acids. Transportation in the blood in form of chylomicrons or as very low density lipoproteins. Tissue storage fat consists of 95% TG.
Useful in coronary risk assessment: TG is needed to calculate the LDLC value using the Friedewald formula:

LDLC (mg/dL) = Cholesterol, Total (mg/dL) - HDLC (mg/dL) – [triglycerides (mg/dL) / 5]
But TG must be below 400 mg/dL and chylomicrons must not be present and not to use in familiar dysbetalipoproteinemia.
Elevated TG may be due to hypothyroidism, nephritic syndrome, diabetes mellitus, ethanol intoxication, pancreatitis, glycogen storage diseases, estrogen therapy, oral contraceptives, thiazides, beta adrenergic blocking agents. Pregnancy may be associated with increased TG.
Sampling: 1 mL of fasting serum or plasma, fasting should last for 10-12h and patient should be on a stable diet for 3 weeks.

Reference Interval: According to Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. JAMA, 2001, 285(19) pp 2486-97

Normal TG	< 150 mg/dL
Borderline TG	150-199 mg/dL
High TG	200-499 mg/dL
Very high TG	>500 mg/dL

Triiodothyronine Free and Total, Serum

Related Information: Thyroglobulin, Serum
Thyroid Stimulating Hormone, Serum
Thyrotropin Receptor Antibody, Serum
Thyroxine Free and Total, Serum

Background: Mainly (70-80%) produced by conversion of T_4 to T_3 as the more metabolic potent (3 fold as compared to T_4) form and with less affinity to TBG, approx 30-40% of T_4 is converted to T_3. 0.3% is free in peripheral blood as compared to 0.02% of T_4. Only the free fraction of T_4 and T_3 parallel the cellular uptake and determines the status of the thyroid function in an individual. Increasing total T_3 and unchanged protein bound fraction may occur during pregnancy or estrogen therapy, Total T_3 may be reduced in androgen therapy, prednisone, dexamethasone, glucocorticoids well as in iodine deficiency and anorexia nervosa.
Use: Diagnosis of hyperthyroidism as T_4 and T_3 are increased. Diagnosis in the rare form of thyrotoxicosis of isolated T_3 increase. To investigate patients with supraventricular tachycardia, fatigue, weight loss, proximal myopathy. Monitoring T_4 therapy.
Limitations: Patients with chronic diseases and altered nutrition may have decreased T_3 levels. Oral contraceptives, pregnancy. Subclinical hyperthyroidism may display normal T_3, also T_3 is normal in mild hypothyroidism. Changes in TGB can affect total T_3 but to a lesser extent free T_3.
Half life: T_3 1 day; T_4 7 days. Production per day T_3: 33 µg; T_4: 80 µg
Sampling: 1 mL serum

Reference interval: Triiodothyronine, Free

Validated for Southern Germany (MEDLAB)

Adults	2.19-3.49 pg/mL	(3.4-5.4 pmol/L)
Children	3.10-4.14 pg/mL	(4.8-6.4 pmol/L)

Validated for Germany

Adults	2.0-4.4 pg/mL	(3.1-6.8 pmol/L)

For the Middle East one report systematically investigated TSH:

Adults 18-54 years (average 27 years)

Male	2.82–4.43 pg/mL	(4.36-6.85 pmol/L)
Female	2.19–3.76 pg/ mL	(3.39-5.82 pmol/L)

Triiodothyronine, Total

Age	ng/dL
1-3 days	100-740
1-11 months	105-245
1-5 years	94-241
6-10 years	94-241
11-15 years	82-213
16-20 years	80-210
20-50 years	70-204
50-90 years	40-181

Troponin T, Serum

Related Information: Creatine Kinase (CK, NAC-activated)
Creatinine Kinase Isoenzymes, Serum
Myoglobin, Blood, Serum or Plasma

Background: Cardiac troponin T is a highly specific and sensitive test in myocardial infarction. Other markers are MB fraction of creatinine kinase (CKMB), cardiac troponin I, whereas CKMB and myoglobin is less sensitive than the troponins. The troponins remain elevated for 5-7 days. Limitations: May be elevated in renal failure and muscle injuries.

Sampling: 2 mL serum. First sample should be drawn at admission, a second sample at 6-9h and a third sample at 12-24h.

Reference Interval: < 0.2 ng/mL, change is important for diagnosis of myocardial infarction.

Trypanosoma cruzi (Chagas Disease), Serology

Background: The cycle in the reduviid bug begins with the ingestion of trypomastigotes present in the blood of the reservoir host including domestic animals and wild species as armadillo, raccoon and rats, further differentiation in the insects gut into epimastigotes and trypomastigotes which are shed into the insects feces and enter the blood of the the reservoir host when the bug bites. Non-flagellated amastigotes form within the host cells, preferentially in reticoendothelial, myocardial and glia cells. Amastigotes differentiate to trypomastigotes to enter the flood and are taken by the reduviid bug.

Chagas disease occurs in Central and South America in rural areas due to the bugs spread in the walls of the rural houses.

Clinically, edema near the bite site occurs with fever, lymphadenopathy and hepatosplenomegaly, resolving within 2 month. Progression to the chronic phase is characterized by the cardiac muscle involvement with myocarditis, arrhythmias and loss of tone due to infected glia cells which leads to megacolon or megaesophagus.

Laboratory diagnosis is made by demonstrating trypomastigotes in the thick or thin film of patient's blood. However trypomastigotes are rare in the acute phase and absent in the chronic phase. Bone marrow aspirates or muscle biopsy specimens may reveal amastigotes.

Serology is helpful in acute and chronic forms.

Sampling: 1 mL serum

Reference Interval: Antibodies not detectable

Tumor Necrosis Factor (Cachectin), Serum

Background: A useful marker in sepsis, trauma, heart diseases and in unspecific monitoring of chronic inflammatory diseases. In heart failure, TNF alpha may be considered as an indicator for poor prognosis.

In the CSF, it is used to monitor the activity of multiple sclerosis and to distinguish between bacterial and other forms of meningitis.

Plasma half life time of the active trimer < 5 min. The levels of the active TNF-trimer will be elevated for 4-6 h, the levels of the total TNF for 24 h.

Limitations: Therapy regimes in transplant patients using antibodies may cause false positive results.

Sampling: 2 mL serum. Separate cells within 2 h. Freeze immediately at -20°C if test will be performed within one week; otherwise freeze at -70°C, ship frozen.

Reference Interval:		
	Total TNF alpha	5–15 pg/mL
	Active Trimer	< 5 pg/mL

Tylenol® see Acetaminophen, Serum

Urate see Uric Acid, Urine or Serum

Urea Nitrogen to Creatinine Ratio

Related Information: Creatinine, Serum or Plasma
Osmolality, Serum
Urea Nitrogen, Serum or Plasma

Synonyms: BUN to Creatinine Ratio

Test includes: Serum creatinine and serum urea nitrogen.

Background: Useful to distinguish between pre- and postrenal diseases, gastrointestinal bleeding, and renal diseases.

High BUN/creatinine ratio: Decreased renal perfusion, hypovolemia, hypotension, catabolic state (creatinine normal), upper gastrointestinal bleeding with very high ratios above 36, high protein diet, urinary tract obstruction. Steroids and tetracyclines may increase the ratio.

Decreased ratio: Low protein intake, malnutrition, ketosis, liver diseases, rhabdomyolysis, low levels of antidiuretic hormone, late pregnancy. Drugs increasing creatinine, but not urea nitrogen: cimetidine, trimethoprim, anti-anabolic effects of tetracyclines.

Sampling: 2 mL serum

Reference Interval: 10–20, infants higher (10-30)

Urea-Nitrogen and Urea, Serum or Plasma

Related Information: Creatinine, Serum or Plasma
Cystatin C, Urine, Urine
Osmolality, Serum
Sodium (Na), Serum
Urea Nitrogen to Creatinine Ratio

Synonyms: Blood Urea Nitrogen; BUN

Background: Urea is the end product of protein metabolism and is renal excreted by glomerular filtration. BUN is a useful parameter in assessing renal function, particularly in combination with serum creatinine.

Elevated in: Acute or chronic renal diseases, severe congestive heart diseases, shock, dehydration. Bleeding into the GI may increase urea nitrogen without larger elevation of creatinine levels.

Decreased in: Late in pregnancy, low protein diet, severe liver diseases.

Limitations: BUN is specific for glomerular function and less sensitive for early stages of renal diseases and may be earlier abnormal than creatinine. In patients undergoing dialysis, the urea reduction in percent during dialysis is a parameter although less sensitive than serum albumin for successful treatment.

Sampling: 1 mL serum or plasma, heparinized sample is not accepted.

Reference Interval:

			urea (mg/dL)
Children	Newborn		6-53
	1-3 year(s)		11-36
	4-13 years		15-36
	14-19 years		18-45
Adults	Female	< 50 years	15-40
		> 50 years	21-43
	Male	< 50 years	19-44
		> 50 years	18-55

(Urea-Nitrogen = urea / 2.14)

Critical value: Possible panic range: Urea above 210 mg/dL is defined as uremia (BUN >100)

Ureaplasma Urealyticum see Mycoplasma hominis

Uric Acid, Serum

Related Information: Ammonia, Plasma
Creatinine, Serum or Plasma
Molybdenum (Mo), Serum or Urine
Sodium, Serum
Synovial Fluid Analysis
Uric Acid, Urine

Synonyms: Urate

Background: The end product of purine metabolism is uric acid. As one marker for gout serum levels do not establish or rule out the diagnosis, more specific are demonstrated uric acid crystals in an aspirate of joint fluid. Clinically, typically gout is located monoarticular in a lower extremity joint. However, in an acute episode of gout uric acid must not necessarily be elevated. Elevated levels occur in renal diseases, prerenal azotemia, preeclampsia. Acute uric acid nephropathy, nephrolithiasis and chronic urate nephropathy are renal diseases caused by uric acid. Other Impairments of renal function are lead poisoning, acidosis, and hemolytic anemia. Drugs which cause higher levels of uric acid are cancer chemotherapeutics such as cyclosporine by cell destruction, diuretics, anti-infectiva in Tbc such as ethambutol, niacin pyrazinamide and salicylate.
Decreased levels occur during xanthinuria, liver disease, hyponatremia, low protein intake.

Sampling: 1 mL serum or plasma (EDTA, citrate or sodium fluoride tubes are not accepted). Stable for 3 days at room temperature, at 4°C for one week.

Reference Interval:

Male	4.4-7.0 mg/dL
Female	2.4-5.7 mg/dL
Children	2.0-6.0 mg/dL

Uric Acid, Urine

Related Information: Calcium (Ca), Urine
Creatinine, Urine
Synovial Fluid Analysis
Uric Acid, Serum

Synonyms: Urate, Urine

Background: Urate is reabsorbed by the proximal and distal tubules and excreted by the distal portion of the proximal tubules, within a total elimination of urate by the kidney of 75%. 25% are secreted by the intestinal tract.

Use: Patients with hyperuricosuria and hyperuricemia are on risk for renal uric acid and calcium oxalate calculus formation.

A secretion > 1000 mg/24h should prompt a screening for hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesh-Nyhan syndrome). Another indicator used is the uric acid to creatinine ratio: Normal: 0.21-0.59, enzyme defect: 0.62-2, complete absence of enzyme function: 2-5.

Used in differential diagnosis of acute renal failure: A ratio > 1 favors acute renal failure due to acute uric acid nephropathy, a ratio < 1 favors failure due to other causes.

Sampling: 24 hour urine collection in a container prefilled with 10 mL of a sodium hydroxide solution for preventing a precipitation in acid urine. Do not refrigerate! Send an aliquot of 5 mL to the laboratory.

Reference Interval: 250 – 750 mg / 24h

Correlation between urine uric acid and nephrolithiasis:

< 300 mg/24h	11%
300-699 mg/24h	42%
700-899 mg/24h	34%
900-1099 mg/24h	41%
> 1000 mg/24h	50%

Urin Analysis Chemical, Screening

Related Information: Albumin, Urine
Cystine, Urine
Osmolality, Urine
Oxalate, Urine
Primidone, Serum
Protein, Quantitative, Urine
Urine Analysis, Microscopic
Vitamin C, Serum or Plasma

Test includes: Opacity, color, appearance, specific gravity, ph, protein, glucose, occult blood, ketones, bilirubin, urobilinogen, leucocytes

Background: The tests are for screening purposes. If a parameter is positive, a confirming chemical method will be used.

Sampling: For screening purposes, 10 mL of first voided morning urine may be preferred, since later specimens are more diluted and small increases in protein red cells or leucocytes are less likely to be detected. 10 mL of urine should be transported to the laboratory as soon as possible, otherwise refrigerate.

Reference Interval:

Test	Reference Interval
Specific gravity	1.003-1.029
Ph	4.5-7.8
Protein	negative
Glucose	negative
Ketones	negative
Bilirubin	negative
Occult blood	negative
Leucocyte esterase	negative
Nitrite	negative
Urobilinogen	0.1-1 EU/dL
RBC s	0-3/µl
WBC s	0-10/µl

Urine Analysis, Microscopic

Synonyms: Microscopic Urine Examination, Microscopic Urine Analysis

Test includes: Casts, Crystals, Erythrocytes, Leucocytes, and Spermatozoa

Background: The microscopy on urine is one of the oldest diagnostic procedures in medicine providing useful information on renal, bladder, biochemical disorders and on intoxication.

Interpretation:

Crystalluria: Urine should be fresh and not refrigerated.

Calcium oxalate crystals: Are uniform, small double pyramides in a base to base order, similar to crosses on a square, but sometimes ovoid forms are present which can be confused with red cells and yeast cells. To distinguish under polarized light oxalate crystals are birefringent, cells are not anisotropic and cell lysis with acetic acid (2 - 3%). Abundant calcium oxalate or hippurate crystals may suggest ethylene glycol ingestion.

Uric acid crystals: Are brown to reddish brown, rectangular, rhomboidal.

Ammonium urates: Are irregular blobs and crescents in alkaline urine and may be confused with red cells.

Calcium phosphate: Crystallizes as flower like narrow rectangular needles.

Cystine crystals: Large hexagonal irregular plates, and are limited to patients with cystinuria.

Triple phosphate crystals (calcium-magnesium-ammonium-phosphate): Form coffin-lid shaped angularly domed rectangles, particularly in alkaline urine. They may suggest urea splitting bacte-

rial infection particularly in the presence of leukocyturia.
Protease inhibitor medication: Is associated in up to 50% of the patients with crystalluria with radial clusters in starburst form.
Casts:
White cell casts: Are renal originating leucocytes, particularly in pyelonephritis.
Red cell casts: Are of renal origin, suggest glomerulonephritis as do dysmorphic red cells.
Hyaline casts: Are observed after intensive exercise and in various kidney diseases.
Epithelial casts: Occur in acute tubular injuries, tubular necrosis, in eclampsia, heavy metal poisoning, and ethylene glycol intoxication.
Granular casts: Suggests intensive exercise, glomerular and tubulointerstitial disorders.
Waxy casts: Are characteristic in severe chronic renal diseases.
Fatty casts: Are seen in nephrotic syndrome, glomerular diseases, such as minimal change disease, membranous glomerulopathy, and membranoproliferative glomerulonephritis.
Broad casts: Are shed by damaged tubules or collecting ducts.
Others:
Hematuria: Dark brown urine indicates a renal cause, red urine suggest an extrarenal source.
Spermatozoa: Seen after retrograde ejaculation.

Sampling: 10 mL urine. Avoid contamination, use sterile tube and midstream urine. Casts are more likely to be observed in morning urine sample, as well as due to higher concentration erythrocytes and leucocytes. To obtain best results urine should be fresh and warm. If the specimen can not be transported to the laboratory immediately, refrigerate to 4-8°C.

Reference Interval: (per high power field)

Casts	0-4
Erythrocytes	0-2
Leucocytes	0-4
Bacteria	negative

Uroporphyrins see Porphyrins, Urine, Stool, Quantitative

Valproic Acid, Serum or Plasma

Related Information: Carbamazepine, Serum
Phenobarbital, Serum
Phenytoin (Diphenylhydantoin, DPH), Serum
Primidone, Serum

Synonyms: Depacon®; Depakene®; Depakote®XR; Depamide®; Dipropylacetic® Acid; Divalproex Sodium; Epilim®; Ergenyl®; Leptilan®; 2-Propylpentanoic Acid; 2-Propylvaleric Acid; Valkote®; Valproate Semisodium; Valproate Sodium

Background: Used in various seizure types and in some bipolar disorders and in migraine headaches. The mechanism the therapeutic effect is by enhancing the inhibiting effect of gamma aminobutyric acid in the brain. The drug is metabolized in the liver. By blocking the P450 enzyme system, valproic acid inhibits the metabolization of other drugs. A substantial to fatal hepatotoxicity, particularly in young children, has been described.
In pregnancy, valproic acid is contraindicated since a higher incidence of neural tube,-cardiac and skeletal defects have been reported.
Bioavailability 100%; urinary excretion 1-5%; plasma binding 90-95% decreased in renal disease, cirrhosis, pregnancy, elderly, neonates, burn patient; volume of distribution 0.2 L/kg; half life time 11-17h increased in cirrhosis and neonates and decreased in children; peak time 1-4h; peak concentration 26-42 ug/mL after a 250 mg oral dose steady state.
Sampling: 2 mL serum. Steady state reached after 3 days
Reference Interval: 50-100 µg/mL
Toxic: >150 µg/mL
In patients with hypoalbuminemia clinical toxicity has been observed within normal serum levels, measurement of the free drug in theses patients may be necessary.

Vancomycin, Serum

Synonyms: Lyphocin®; Vancocin®; Vancoled®
Background: Vancomycin is a glycopeptide active against gram-positive bacteria, interfering with cell wall synthesis and facilitating therefore uptake of aminoglycosides. As a third line antibiotic, vancomycin should be used only if no other options have remained. Renal and ototoxic effects. Elimination by glomerular filtration. Bile concentration up to 50% of plasma values; CSF 1-30% of plasma concentration.
Urinary excretion 70-90%; plasma binding 20-40%; volume of distribution 0.4L/kg decreased in obesity; half life time 4-7.5h increased in renal disease and in the elderly and decreased in obesity.
Sampling: 2 mL serum. Peak after 30-60 min after I.V. application.
Reference Interval: Therapeutic values:
Minimum: 5-10 µg/mL
Maximum: 20-40 µg/mL
Toxic values: > 80 µg/mL ototoxicity may occur at > 37 µg/mL

Vanillylmandelic Acid, Urine

Related Information: Catecholamines, Fractionation, Plasma or Urine
Creatinine, Urine
Homovanillic Acid (HVA), Urine
Metanephrines, Urine

Synonyms: 3-Methoxy-4-Hydroxymandelic Acid, VMA

Applies to: Creatinine, measured concomitantly in children

Background: VMA is a metabolite of catecholamines, epinephrine, and norepinephrine. In the diagnosis pheochromocytoma it is less sensitive than metanephrine and equal to norepinephrine, but more sensitive than epinephrine and dopamine.

Sampling: 10 mL of an 24h urine collected in a container prefilled with 10 mL of a 20% hydrochloric acid (do not use boric acid). Note total quantity.

Reference Interval:

1st year	< 27 µg/mg creatinine
1-2 years	< 18 µg/mg creatinine
2-4 years	< 13 µg/mg creatinine
5-9 years	< 8.5 µg/mg creatinine
10-14 years	< 7 µg/mg creatinine
Adults	< 8 mg / 24 hours

Varicella-Zoster Virus, Serology

Background: Varicella–zoster virus is an enveloped alpha herpesvirus with a linear, double stranded DNA. The primary disease is Varicella (chickenpox), Zoster (shingles) is the recurrent form. Both forms are infectious.

Varicella: In developed countries peak incidence is at the age of 5-9 years in winter and spring epidemics. Maternally derived antibodies protects infants up to 6-9 month of life. 90% of the adults are immune by seropositivity. In contrast, in the tropics seropositivity is only 50-80% in adults. The risk of infection in day care centers is 50%, incubation period 10-25 days. The fatality rate rises with age, at 55 years it reaches 1 per 600 cases.

Herpes zoster as an infection of sensory nerve ganglions it complicates waning immunity affecting elderly or immunocompromised individuals and may be triggered by stress such as diseases, trauma, HIV, malignancy, chemotherapy.

Varicella zoster virus first infects the respiratory mucosa, invading the lymphatics leading to asymptomatic viremia 7 days after infection. The virus replicates further in most tissues and appears in peripheral blood cells. The virus produces the typical Type A intranuclear inclusions, syncytium and gigant cells and in the skin the Tzanck cells. The clinical disease begins about 15 days after infection, including viremia, and skin, lung, gut, reticuloendothelial system infection, and possibly being complicated by pneumonitis, myocarditis, cardiomyopathy, hepatitis, Guillain-Barre syndrome, ventriculitis, granulomatous arteritis, meningoencephalitis. Congenital chickenpox can result in neonatal systemic disease and malformations. Immunity persist after primary infection, and unlike herpes simplex virus, the virus is not detectable during latency. Immune status: IgG positive value indicates immunity, but does not assure, even in high titers, protection from shingles.

Serologic diagnosis: IgM antibodies to VZV are not detectable until 6 days after the exanthema appears and peak around 2 weeks. IgG antibodies start to be detectable at day 9 after onset of the rash in primary varicella and slightly later after reactivation of zoster. Acute and convalescent

sera drawn 2 weeks apart are recommended.

Prophylaxis: Live attenuated vaccine is available, 98% of the children and 94% of adults develop protective antibodies. After 5-10 years, breakthrough after exposure is 10-20%, however as a mild course.

For postexposure prophylaxis, human antiglobulin is available to administer within 96 h.

For treatment of varicella, acyclovir is licensed. For herpes zoster valaciclovir, a prodrug of acyclovir has enhanced bioavailability and famciclovir are in use. Antiviral treatment is without impact in children but reduces severity in adults.

Pregnancy: The congenital varicella syndrome includes microphthalmia, hypoplastic limbs and autonomic nervous system damage with gastroesophageal reflux and CNS abnormalities occurs in maternal varicella infection acquired in most cases before week 20 of gestation, occasional case reports at week 26-28. After week 20, manifestations include skin scars and childhood shingles. Subclinical maternal varicella infection may cause neurologic symptoms without other signs of congenital varicella syndrome. Varizella Zoster virus hyperimmune globulin (VZVIG) is effective in prophylaxis for babies born to mothers who have chickenpox 5 days prior and 4 days after delivery. The use of VZVIG is also suggested to nonimmune pregnant women exposed during the first 20 weeks of pregnancy to chickenpox because of a higher risk to develop serve pulmonary complications.

Sampling: 1 mL serum

Reference Interval: Differentiation of immunoglobulin class

IgA antibody	negative	< 1.0 COI
IgG antibody	negative	< 250 mIE/mL
IgM antibody	negative	< 1.0 COI
	borderline	1.0–1.2 COI
	positive	>1.2 COI

Vasopressin see Antidiuretic Hormone, Plasma

Very Low Density Lipoproteins, Serum

Related Information: Cholesterol, Total, Serum or Plasma
High Density Lipoprotein Cholesterol, Serum or Plasma
Low Density Lipoprotein Cholesterol
Triglycerides, Serum or Plasma

Synonyms: VLDL

Background: VLDL are smaller than chylomicrons but less rich in triglycerides and have a lower lipid to protein ratio. In the presence of excessive amounts, plasma appears turbid. VLDL display a wide variety in seize and are composed in the liver: Cholesterol 4%-8%, cholesteryl esters 16-22%, phospholipids 15-20%, triglycerides 45-65% and 6-10% are proteins such

as apoB-100, apoC and apoE.

Sampling: 2 mL serum. For best results the patient should be on stable diet for 3 weeks. Sample drawing after fasting for 10h is necessary if triglycerides are requested. Total cholesterol is 10 - 15% lower in a recumbent position, as well as 5% lower in a sitting position.

Reference Interval: < 40 mg/dL

Vitamin A, Serum or Plasma

Related Information: Vitamin E, Serum
Zink (Zn), Serum or Urine or Seminal Fluid

Background: Vitamin A, subdivided in two natural forms retinol, vit A-1 and 3-dehydro-retinol (vit. A-2) is a fat soluble, essential vitamin utilized by epithelial cells and in the visual cycle. Beta carotene is one of the 50 forms of provitamin A.

The test is used in diagnosis of hypovitaminosis, in most of the cases caused by insufficient intake or diet or fat malabsorption.

Hypervitaminosis A may develop in patients with reduced disposal in myxedema, diabetes mellitus, renal diseases.

Teratogenicity has been reported.

Sampling: 2 mL of fasting EDTA or heparin plasma or serum, protect from light, keep refrigerated.

Reference Interval: Possible deficiency state < 10 µg/dL
Possible toxic > 140 µg/dL

Vitamin B 1 (Thiamin), Serum

Background: Known for centuries, beriberi polyneuritis diseases is a thiamin deficient state.

Thiamine consists of a pyrimidine linked by a methylene bridge to a thiazole nucleus, functioning as a coenzyme in the pyrophosphate form. Thiamine pyrophosphate function in carbohydrate metabolism as a coenzyme in decarboxylation of keto acids (pyruvate, ketoglutarate) and in the hexose monophosphate shunt, thus patients on parenteral nutrition with dextrose thiamine has to be supplied sufficiently.

Toxicity is rare and only sporadically reported after long term parenteral administration.

Deficiency: Beriberi, occurring in Asia due to rice diet, in alcoholics, and clinically presents as a neurological disorder (peripheral neuritis with hyperesthesia, local anesthesia, muscle strength loss, poor memory) or with cardiovascular symptoms (abnormal ECG, cardiac failure).

The inherent subacute necrotizing encephalomyelopathy in children may be linked to thiamin dysfunction, since plasma pyruvate and lactate are elevated.

A form of megaloblastic anemia with deafness and diabetes mellitus has been described and is thiamine responsive. Pregnancy increases slightly thiamine requirement.

Sampling: 3 mL EDTA blood

Reference Interval: 20–100 ng/mL

Vitamin B 2 (Riboflavin), Serum

Background: The water soluble riboflavin acts as a coenzyme after transformation into biological active riboflavin phosphate, also named flavin mononucleotide (FNM) and flavin adenine dinucleotide (FAD).

The conversion by flavokinase to FMN is sensitive to thyroid hormone and is inhibited by chlorpromazine and by tricyclic antidepressants, quinacrine interferes as well. Riboflavin is not stored in the body.

Deficiency: First signs are sore throat and angular stomatitis, later glossitis, cheilosis, seborrheic dermatitis, followed by anemia (normochromic and normocytic with reticulocytopenia) and neuropathy.

Rich in Riboflavin are milk, cheese, organ meets, eggs, green leaf vegetables, whole grain.

Sampling: 3 mL EDTA blood

Reference Interval: 50–150 ng/mL

Vitamin B_3 see Niacin, Serum

Vitamin B 6, Plasma or Serum

Related Information: Homocyst(e)ine, Total, Plasma

Synonyms: Pyridoxal-5-Phosphate; Pyridoxine

Background: Important as a coenzyme in heme synthesis, deficiency may lead to a hypo-chromic form of sideroblastic anemia (ring sideroblasts) or to megaloblastic anemia.

Other forms of hypovitaminosis, clinically characterized by dermatitis, cheilitis, glossitis and by laboratory characteristics cystathioninuria, homocystinuria, hyperhomocysteinemia may be due to reduced intake and during therapy with levodopa, disulfiram, contraceptives, theophylline, phenelzine, isoniazid, cycloserine, pyrazinoic acid.

Sampling: 2 mL EDTA plasma or serum, protect from light. Transport to laboratory soon, moderate stable, 50% loss within a week at –20°C.

Reference Interval: 4-25 ng/mL

Vitamin B 12, Plasma or Serum

Related Information: Gastrin, Serum
Homocyst(e)ine, Total, Plasma
Methylmalonic Acid, Serum, Plasma or Urine

Synonyms: Cobalamin; Cyanocobalamin

Background: Cobalamin is an essential vitamin, synthesized by microorganisms, available in dietary animal products and needed for DNA synthesis, methylation reactions and in the citric acid cycle. B-12 applies to all forms of cobalamin, predominant form in the serum is methylco-

balamin and for the cytosol deoxyadenosyl cobalamin.

The daily requirement is estimated to 1-4 µg/day. The liver storage can provide B-12 for 4-5 years (daily loss approx. 0.1%). Sensitive early indicators for deficiency are an elevation of methylmalonic acid in serum or urine or a significant increase of mean corpuscular volume (MCV). Cobalamins are absorbed through microvilli in the terminal ileum after the release of cobalamins at low ph from proteins by peptic digestion in the stomach, therefore hypochlorhydria cause reduced absorption.

Useful parameter in the evaluation of patients presenting with weakness, anemia (macrocytic, megaloblastic anemia, MCV > 98 fl) or neurologic abnormalities (tumbness, loss of vibratory sensitivity). Used in the diagnosis of malabsorption, macrocytosis, hypersegmented neutrophils, leukopenia.

Decreased absorption may be causes by interference with methotrexate, pyrimethamine, diuretics, pentamidine, trimethoprim, phenytoin, barbiturates, contraceptives, anti-Tb medication, biguanides.

Decreased serum concentrations are associated with inflammatory bowel diseases, bacterial overgrowth, Diphyllobothrium tapeworm, jejunoileal bypass surgery.

Increased conditions: chronic granulocytic leukemia, chronic renal failure, diabetes mellitus, hepatitis.

Sampling: 2 mL serum

Reference Interval: 250–900 pg/mL
Due to the large storage pool by the liver, cut off values are not clearly established.

Vitamin C, Serum or Plasma

Related Information: Oxalate, Urine

Synonyms: Ascorbate; Ascorbic Acid

Background: Half life approx. 2 weeks, if intake is stopped, for one month vit. C will be compensated, after 2-3 month scurvy develops.

Recommended daily intake is 100 mg/day up to a maximum of 1 g/day. High intake may promote oxalate kidney stones. Vitamin C is dialyzed, patients need replacement.

Sampling: 2 mL fasting serum or plasma. Separate serum or plasma very soon (stable 30 minutes at room temperature), freeze to ship at -20°C stable for 4 days. Avoid thawing-freezing cycles.

Reference Interval:

Plasma	0.6-2.0 mg/dL
Leukocytes	20-50 µg/10^3 WBC

Vitamin D, Serum

Related Information: Calcium, Serum or Urine
Magnesium, Serum or Urine
Osteocalcin, Serum or Plasma
Parathyroid Hormone, Intact, Serum
Phosphate Inorganic, Serum

Synonyms: Cholecalciferol

Applies to: 25–hydroxycholecalciferol (inactive precursor, plasma half life time 2-3 weeks), 1,25–dihydroxycholecalciferol, also named calcitriol (biologically active form, plasma half life time is 4-6h).

Background: Increased in patients with hypercalcemia due to extrarenal production of 1,25–dihydroxycholecalciferol (sarcoidosis, lymphoma, cat-scratch disease). Also in patients with primary hyperparathyroidism, vit. D intoxication, lack in response by issue to 1,25 OH vit. D.
Decreased 1,25 OH cholecalciferol in hypoparathyroidism, hypercalemia in malignancy, renal failure, hyperphosphatemia, hypomagnesemia, vit D dependant rickets.

Sampling: 1 mL serum or plasma for 25- hydroxycholecalciferol; 3 mL serum or plasma for 1,25–dihydroxycholecalciferol;

Reference Interval: Varies with sunlight exposure and diet

25–hydroxycholecalciferol	Winter	15-50 ng/mL
	Summer	15-80 ng/mL
1,25–dihydroxycholecalciferol		15-60 pg/mL
	Pregnancy	34-96 pg/mL

Vitamin E, Serum

Related Information: Cholesterol, Total, Serum or Plasma
Vitamin A, Serum or Plasma

Synonyms: Alpha Tocopherol, Tocopherol

Background: As a fat soluble, widely distributed vitamin in diet, deficiency is less likely to occur. Deficiency may occur in premature infants, biliary atresia, cystic fibrosis, hemolytic anemia, neurologic disorders, long term dialysis and in acanthocytosis.

Sampling: 1 mL serum, protect from light

Reference Interval: 3–20 µg/mL

Vitamin K-1, Serum

Related Information: Factor II Mutation (Prothrombin Mutation)
Factor V Mutation (Leiden Mutation)
Protein C
Protein S, Total

Background: Vitamin K is a fat soluble vitamin, essential for the synthesis of clotting factors by the liver as a co factor in carboxylation of glutamic acid residues to form gamma-carboxy-glutamic acid.

Since bile salts are necessary for absorption, an obstruction of the bile ducts may cause vitamin K deficiency. Besides dietary intake, the vitamin is also synthesized by intestinal bacteria; antibiotic treatment may cause a deficiency. Vitamin K deficiency is characterized by decrease of factor II, VII, IX, X, Protein C and Protein S. Prolongation of PT occurs.

Coumarin blocks vitamin K dependent carboxylation, therefore, according to the half life time of the clotting factors, factor VII, and Protein C in the serum decreases first, thereafter factor X, II and IX .

Cephalosporins interfere directly with vitamin K regeneration.

Sampling: 2 mL serum

Reference Interval: 50–900 ng/L

Xylose Absorption Test, Serum

Related Information: Endomysial Antibodies
Gliadin IgG/IgA Antibodies

Synonyms: d-Xylose Absorption Test, Serum,

Background: d-xylose is absorbed in the duodenum and jejunum and excreted by the kidney. The test screens for carbohydrate malabsorption and differentiates from pancreatic insufficiency, since pancreatic enzymes are not necessary for xylose absorption. Diseases such as celiac disease, tropical sprue, M. Crohn, surgical bowl resection impair xylose resorption.

Sampling: Patient should be fasting at least for 4 h and remain in a supine position during the test. Patient should be withdrawn from interfering medications (aspirin, indomethacin, neomycin, glipizide, atropine). Draw first sample (1 mL serum) before administer 25 g xylose orally in water, 10% w/v in adults. In children use 0.5g / kg body weight. Draw second (1 mL serum) sample after 60 minutes.

Reference Interval:

Adult,1 h, 25 g of d-xylose	> 25.mg/dL
Adult,1 h, 25 g of xylose, renal insufficiency	> 20 mg/dL
Adult,1 h, 5 g dose of d-xylose	20-40 mg/dL
Children < 12 years, 1 h , 5g dose	> 20 mg/dL

Yersinia enterocolitica and Yersinia pseudotuberculosis, Culture and Serology

Background: Yersinia enterocolitica and Yersinia pseudotuberculosis are gram negative oval rods. Transmission occur by contamination of food (milk, water, meat) with excreta from the reservoir animals such as pigs, goats, sheep, dogs, cats. Y. enterocolitica causes enterocolitis that is clinically indistinguishable from that caused by Salmonella or Shigella. It is characterized by abdominal pain, gastroenteritis and possibly bloody diarrhea. Both Yersinia sp. can cause an acute appendicitis resembling mesenteric adenitis. Yersinia infection may be associated with reactive arthritis and Reiter's syndrome, but Salmonella spp., Shigella spp. and Campylobacter spp. may also trigger these autoimmune diseases.

Limitations: Low antibody titers of IgG class may persist for years.

Sampling: Culture: 2 g of fresh stool; Serology: 1 mL serum, acute and convalescent serum recommended (at least 1 week apart)

Reference Interval:

Culture:	Report of diagnostic finding	
Serology:	Differentiation of immunoglobulin class	
Y. enterocolitica and Y. pseudotuberculosis		
IgA antibody	negative:	< 0.5 COI
	borderline:	0.5–1.0 COI
	positive:	> 1.0 COI
IgG antibody	negative:	< 0.5 COI
	borderline:	0.5–1.0 COI
	positive:	> 1.0 COI
Validation by immunoblot		

Zinc (Zn), Serum or Urine or Seminal Fluid

Related Information: Albumin, Serum
Copper (Cu), Serum or Urine

Background: Zn is an essential trace element with effects on weight, immune function, growth and development. It is a functional compound of more than 300 enzymes. Zinc is mainly eliminated by the feces, minor quantities by the urine. Serum zinc represents approx 1% of total body zinc stores.

Serum zinc is poorly correlated with the status of the zinc stores. In mild zinc deficiency status, serum zinc may be normal. High urine but low serum levels are found in cirrhosis, neoplastic diseases, increased catabolism and in states of urinary loss of zinc such as viral hepatitis, hemolytic anemias, sickle cell diseases, alcoholism, renal diseases. Serum levels are lowered in fever, sepsis, inflammation, corticosteroid therapy, oral contraceptives, pregnancy, and myocardial infarction. Since albumin is the major binding protein for zinc, hypoalbuminemia presents with low serum zinc levels. Copper and zinc are competitive in intestinal resorption, dietary zinc supplement may decrease cooper levels. Also folic acid and iron may compete with zinc absorption.

Drugs decreasing zinc levels are phenytoin, prednisone, valproic acid.

Zinc deficiencies may occur in breast fed infants whose mother's milk is low of zinc, premature infants with low hepatic stores, in growing children, in prepubertal boys with delayed sexual maturity, in malabsorption disorders and diarrhea, in diabetes, nephrotic syndrome, cirrhosis, in AIDS patients, burn patients, in patients receiving high intravenous supplement of amino acids, in pregnant women due to the high uptake by the fetus.

Acrodermatitis enteropathica is characterized by zinc malabsorption which develops in babies presenting with facial and diaper rash when weaned, progressing to growth retardation, diarrhea, impaired T cell function, infections, delayed testicular development. Usually serum and urine zinc concentrations are low, but serum zinc may be normal in some cases.

Sampling: Serum: 1 mL serum. Blood to collect in a metal free container, avoid powdered gloves, avoid probe to contact rubber. Avoid hemolysis or stasis, since red cells contain zinc concentrated 10 times as compared to serum. Serum should be separated immediately after sampling since zinc concentration in whole blood samples increases 5-8% per h.

Urine: For precise evaluation, due to a circadian rhythm, a 24h urine specimen is recommended. Collect in a metal free container and keep cool. Avoid contact with rubber, if specimen can only be obtained by a catheter, a silicon catheter should be used. Ship 10ml to the lab, note total quantity.

Reference Interval:			
	Serum:	Adults	600-1200 µg/L
		Children	750-1000 µg/L
	Urine:		140-800 µg/24h
		Patients supplemented with zinc	> 2000 µg/24h
	Seminal fluid:		90–250 µg/mL