# Carbohydrate antigen 19-9 (CA 19-9) (serum, plasma)

## 1 Name and description of analyte

1.1 Name of analyte
Carbohydrate antigen 19-9 (CA 19-9)

1.2 Alternative names
Cancer antigen 19-9, cancer antigen-GI (CA-GI), sialylated Lewis-a antigen

1.3 NLMC code

1.4. Description of analyte
CA 19-9 is a glycolipid antigen defined by the mouse monoclonal antibody 1116-NS-19-9. In plasma it exists as a high molecular weight mucin glycoprotein which contains the sialyated Lewis-a epitope lacto-N-fucopentose II. 5-10% of the population will have the blood type Lewis (a-b-) and lack the fucosyltransferase required for the expression of the CA 19-9 antigen.
CA 19-9 is present on the epithelium of the foetal stomach, intestine, liver and pancreas, and traces can be detected in adult gastrointestinal tract and lung tissue. Greater amounts are found in saliva, bile, ovarian cyst fluid, seminal fluid, amniotic fluid, gastric and duodenal secretions, and urine.

1.5 Function of analyte
Unknown

## 2 Sample requirements and precautions

2.1 Medium in which measured
CA 19-9 is usually measured in serum or plasma.

2.2 Precautions re sampling, handling etc.
No special precautions

## 3 Summary of clinical uses and limitations of measurements

3.1 Uses
1. Assisting diagnosis of pancreatic and other gastrointestinal (GI) cancers, when used alongside other diagnostic procedures such as imaging and cellular pathology.
2. Assessing prognosis of pancreatic and other GI cancers, alongside other factors.
3. Detecting recurrence of pancreatic and other GI cancers.
4. Monitoring response to treatment of pancreatic and other GI cancers.

3.2 Limitations
Lewis-negative individuals do not express CA 19-9.
Serum [CA 19-9] can be raised in a variety of benign conditions including obstructive jaundice of any cause. Values within the reference range do not exclude malignancy.

CA 19-9 should *not* be used as a *screening test* for malignancy, either alone or in combination with other tumour markers.

## 4 Analytical considerations

4.1 Analytical methods
CA 19-9 is measured by immunoassay.
Formerly, immunoradiometric assays were used; however, these have been replaced in the main by automated immunometric assays employing, for example, chemiluminescent detection.

4.2 Reference method
None

4.3 Reference materials
None

4.4 Interfering substances
No major interferences. Interference can occur rarely due to endogenous anti-reagent or anti-analyte antibodies.

4.5 Sources of error
There is some variation in results produced by different methods, and the analytical platform used should be reported alongside the result. When monitoring individual patients, the same method should be used.
Non-linearity may be observed when diluting samples, with increased recovery at greater dilutions. This is due to the tendency of the CA 19-9 antigen to form aggregates.

## 5 Reference intervals and variance

5.1.1 Reference interval (adults)
The upper limit of normal (97.5$^{th}$ centile) is usually stated as 35–37 kU/L (assay dependent)
5.1.2 Reference intervals (others)
The range in children is not well defined, but may be a wider than in adults.
5.1.3 Extent of variation
5.1.3.1 Interindividual CV: 102%
5.1.3.2 Intraindividual CV: 16%
5.1.3.3 Index of individuality: 0.16
5.1.3.4 CV of method: 5–10%
5.1.3.5 Critical difference: 52%
5.1.4 Sources of variation
Lewis-negative individuals do not express CA 19-9. Amongst those who are Lewis-positive, CA 19-9 concentrations vary depending on the secretor genotype. Concentrations are significantly higher in women than in men.

## 6 Clinical uses of measurement and interpretation of results

6.1 Uses and interpretation
1. Assisting diagnosis of pancreatic and other GI cancers

CA 19-9 may be used alongside radiological techniques or invasive procedures such as endoscopic retrograde cholangiopancreatography, laparoscopy, or endoscopic ultrasound fine needle aspiration, to assist in the diagnosis of pancreatic and hepatobiliary cancers. The presence of an elevated serum
[CA 19-9] is not on its own diagnostic of malignancy.

2. Assessing prognosis of pancreatic and other GI cancers .
Pre-operative pancreatic cancer patients with [CA 19-9] greater than 1000 kU/L have a poorer outcome than those with lower levels. A post-operative [CA 19-9] <200 kU/L, and a post-operative decrease in [CA 19-9] by >200 kU/L, are both indicators of a good outcome.
CA 19-9 may also be useful in assessing the prognosis of hepatobiliary and colorectal cancers.
3. Detecting recurrence of pancreatic and other GI cancers
Serial measurement of CA 19-9 can detect recurrent or metastatic pancreatic cancer several months before it is clinical or radiologically evident. CA 19-9 may also be used to monitor for recurrence of other malignancies although it is uncertain whether this is of any clinical benefit.
4. Monitoring response to treatment of pancreatic and other GI cancers
CA 19-9 may be used alongside imaging to monitor response to treatment, in particular palliative chemotherapy. A correlation has been demonstrated between magnitude of decrease in CA 19-9 and both overall survival and time to treatment failure. However, an optimum frequency of testing and the magnitude of change in CA 19-9 that is clinically significant have not yet been fully established.

6.2 Confounding factors

- Lewis-negative individuals do not express CA 19-9. Among those who are Lewis-positive, serum [CA 19-9] varies depending on the secretor genotype.
- There is some variation in results produced by different methods, and the analytical platform used should be reported alongside the result. When monitoring an individual patient the same method should be used.
- Some assays show a degree of non linearity as sample dilution can change the tertiary configuration of the molecule and cause an increase in the number of epitopes available for antibody binding. This can result in a higher apparent value if monitoring raised concentrations.

## 7 Causes and investigation of abnormal results

7.1 High values

7.1.1 Causes

- Malignancy
  - particularly pancreatic carcinoma, cholangiocarcinoma and gallbladder carcinoma
  - also hepatocellular, gastric, colorectal, breast, ovarian and lung cancer.
- Benign gastrointestinal disease, including:
  - acute and chronic pancreatitis
  - cholecystitis

- cirrhosis
- chronic and alcoholichepatitis
- acute hepatic necrosis
- gallstones
- cholestasis of any cause.

- Other
  - lung disorders (cystic fibrosis, pneumonia, tuberculosis, pleural effusion)
  - pelvic inflammatory disease
  - Hashimoto's thyroiditis
  - rheumatoid arthritis
  - renal failure
  - systemic lupus erythematosus (SLE).

7.1.1 Investigation

CA 19-9 testing is usually performed in individuals known to have or suspected of having a pancreatic or biliary malignancy. Results should be interpreted alongside those of other investigations such as imaging and cellular pathology.

7.2 Low values

7.2.1 Causes

Lewis-negative individuals do not express CA 19-9.

7.2.1 Investigation

Not usually required

7.3 Notes

Particularly high values for [CA 19-9] can occur in cholestasis; these should fall to normal with effective treatment.

## 8 Performance

8.1 Sensitivity, specificity etc. for individual conditions

1. Pancreatic carcinoma

Using a cut-off of 37 kU/L, CA 19-9 has been shown to have 81% sensitivity and 90% specificity for pancreatic cancer. At a cut-off of 100 kU/l, specificity is increased to 98%, but sensitivity is reduced to 68%. At a cut-off of 1000 kU/l, specificity is 99.8% but sensitivity only 41%.
The sensitivity varies with the stage of pancreatic cancer. Only 50% of patients with pancreatic cancers of <3 cm diameter will have an elevated CA 19-9. Poorly differentiated cancers produce lower quantities of CA 19-9 compared with well-differentiated cancers.

2. Other malignancies

Sensitivity for other cancers is as follows:

- hepatobiliary: 70%
- gastric: 40-50%
- hepatocellular: 30-50%
- colorectal: 30%
- breast 15%.

For colorectal cancer, sensitivity improves in later disease stages.
Sensitivity and specificity may be further improved by combining measurement of CA 19-9 and CEA.

## 9 Systematic reviews and guidelines

9.1 Systematic reviews

Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. Goonetilleke KS, Siriwardena AK. Eur J Surg Oncol 2007;33:266-270.
*This review concludes that CA 19-9 should be used in diagnostic algorithms for pancreatic cancer, and that elevated values obtained in the setting of obstructive jaundice should be repeated when the jaundice is relieved*

9.2 Guidelines

1. Pancreatic cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Cascinu S, Falconi M, Valentini V, Jelic S. ESMO Guidelines Working Group. Ann Oncol 2010; 21 Suppl 5:v55-58.
*This guideline covers the use of CA 19-9 in pancreatic cancer*
2. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. Khan SA, Davidson BR, Goldin R *et al.* Gut 2002;51(Suppl VI):vi1–vi9
*This guideline covers the use of CA 19-9 in cholangiocarcinoma*

9.3 Recommendations

1. Serum tumour markers: how to order and interpret them. Sturgeon CM, Lai LC, Duffy MJ. BMJ 2009;339:b3527.
*This article reviews the use of serum tumour markers, highlighting their recommended uses and potential pitfalls.*
2. Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report. Duffy MJ, Sturgeon C, Lamerz R *et al.* Ann Oncol 2010;21:441-447
*This review covers the use of CA 19-9 for diagnosis, prognosis, surveillance, and monitoring response to treatment. It also looks at emerging tissue-based markers in pancreatic cancer.*

## 10. Links

10.1 Related analytes

CA 50 is another blood group antigen that is used as a marker for pancreatic and colorectal cancer. The CA 50 monoclonal antibody recognises the same sialylated Lewis-a epitope as the CA 19-9 antibody, but in addition recognises the compound lacking the fucose residue (i.e. that expressed by individuals who are blood type Lewis (a-b-).

10.2 Related tests

CA 19-9 is often measured together with carcinoembryonic antigen (CEA)

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