MAYO CLINIC LABORATORIES

Test Definition: CGAK

Chromogranin A, Serum

Overview

Useful For

Aiding in monitoring disease progression during the course of disease and treatment in patients with gastroenteropancreatic neuroendocrine tumors (grade 1 and grade 2) when used in conjunction with other clinical methods

This test is **not indicated for use** as a stand-alone monitoring assay.

Method Name

Immunofluorescent Assay (IFA)

NY State Available

Yes

Specimen

Specimen Type

Serum

Specimen Required

Patient Preparation: For at least 2 weeks before specimen collection, patient should stop taking proton pump inhibitor medications.
Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Collection Container/Tube:
Preferred: Serum gel
Acceptable: Red top
Submission Container/Tube: Plastic vial
Specimen Volume: 0.5 mL Serum
Collection Information: Centrifuge and aliquot serum into plastic vial. **Do not submit in original tube**.

Forms

If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
-General Request (T239)
-Oncology Test Request (T729)

Specimen Minimum Volume

Serum: 0.2 mL

Reject Due To

Gross	Reject

hemolysis	
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Frozen (preferred)	90 days	
	Ambient	48 hours	
	Refrigerated	48 hours	

Clinical & Interpretive

Clinical Information

Chromogranin A (CgA) is a 439-amino acid protein with a molecular weight of 48 to 60 kDa, depending on glycosylation and phosphorylation status. It is a member of the granin family of proteins and polypeptides. Granins are widespread in endocrine, neuroendocrine, peripheral, and central nervous tissues, where they are found in secretory granules alongside the tissue-specific secretion products. The role of granins within the granules is to maintain the regulated secretion of these signaling molecules. This includes:
-Facilitating the formation of secretory granules
-Calcium- and pH-mediated sequestration and re-solubilization of hormones or neurotransmitters
-Regulation of neuropeptide and peptide hormone processing through modulation of prohormone convertase activity

In addition, granins contain multiple protease and peptidase cleavage sites and, upon intra- or extracellular cleavage, give rise to a series of peptides with distinct extracellular functions. Some of these have defined functions, such as pancreastatin, vasostatin, and catestatin, while others are less well characterized.(1)

Because of its ubiquitous distribution within neuroendocrine tissues, CgA can be a useful diagnostic marker for neuroendocrine neoplasms, including carcinoids, pheochromocytomas, neuroblastomas, medullary thyroid carcinomas, some pituitary tumors, functioning and nonfunctioning islet cell tumors, and other amine precursor uptake and decarboxylation tumors. It can also serve as a sensitive means for detecting residual or recurrent disease in treated patients.(2-4)

Carcinoid tumors in particular almost always secrete CgA along with a variety of specific modified amines, chiefly serotonin (5-hydroxytryptamine) and peptides.(1-4) Carcinoid tumors are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). Serum CgA and urine 5-hydroxyindolacetic acid (5-HIAA) are considered the most useful biochemical markers and are first-line tests in disease surveillance of most patients with carcinoid tumors.(2-4) Serum CgA measurements have been used in conjunction with, or alternative to, measurements of serum or whole blood serotonin, urine serotonin and 5-HIAA, and imaging studies in the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular, flushing.

A number of tumors that are not derived from classical endocrine or neuroendocrine tissues but contain cells with partial neuroendocrine differentiation, such as small-cell carcinoma of the lung or prostate carcinoma, may also display elevated CgA levels. However, the role of CgA measurement is not well defined in these tumors.

Reference Values

<93 ng/mL
Reference values apply to all ages.

Interpretation

Follow-up/surveillance:
In patients diagnosed with gastroenteropancreatic neuroendocrine tumors (GEP-NET) grade 1 and grade 2, when used in combination with clinical symptoms and/or other laboratory parameters, the change of chromogranin A (CgA) concentration over time provides diagnostic information whether a tumor progression has occurred.

The change of CgA is calculated from measurements at consecutive routine monitoring visits within a typical interval of 3 to 6 months and is considered test-positive if the serum CgA concentration increases by more than 50% to an absolute value greater than 100 ng/mL. A positive CgA-change test was shown to be significantly associated with tumor progression ($p < 0.001$).

Calculation and interpretation of delta CgA in G1/G2 GEP-NET:
Delta CgA = ([CgA concentration of current visit-CgA concentration of previous visit]/CgA concentration of previous visit) x 100%

For delta CgA above 50% and CgA concentrations above 100 ng/mL:
An increase of CgA serum concentrations of more than 50% to a value of greater than 100 ng/mL between consecutive monitoring visits defines a positive test result representing a higher probability that tumor progression has occurred with an observed sensitivity of 34%.

For delta CgA less than or equal to 50% or CgA concentrations less than or equal to 100 ng/mL:
A change of CgA serum concentrations of a less than or equal to 50% increase between monitoring visits or to a value of 100 ng/ml or less defines a negative test result representing a lower probability that tumor progression has occurred with an observed specificity of 93%.

CgA in other tumors:
Urine 5-hydroxyindolacetic acid (5-HIAA) and serum CgA levels increase in proportion to carcinoid tumor burden. Because of the linear relationship of CgA to tumor burden, its measurement also may provide prognostic information.

Most mid- and hindgut tumors secrete CgA even if they do not produce significant amounts of serotonin or serotonin metabolites (eg, 5-HIAA). Guidelines recommend 3 to 12 monthly measurements of CgA or 5-HIAA in follow-up of midgut carcinoids.(2,3) Patients with foregut tumors can also be monitored with CgA or 5-HIAA measurements if they were positive for these markers at initial diagnosis. Hindgut tumors usually do not secrete serotonin and consequently, only CgA monitoring is recommended.(1-4)

As is typical for tumor marker use in follow-up and surveillance, a 50% change in serum CgA concentrations should be considered potentially clinically significant in the absence of confounding factors (see Cautions). Much smaller changes in CgA concentrations might be considered significant if they occur over several serial measurements and are all in the

same direction.

Adjunct in diagnosis of carcinoid tumors:
CgA is elevated in most patients (approximately 90%) with symptomatic or advanced carcinoids (carcinoid syndrome), usually to levels several times the upper limit of the reference interval. Serum CgA measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. CgA is also elevated in 80% to 90% of patients with symptomatic foregut and midgut tumors.

To achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, serum CgA, serotonin in serum or blood, and 5-HIAA in urine should all be measured. In most cases, if none of these analytes are elevated, carcinoids can usually be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urine serotonin measurement, will be required. An example would be a foregut tumor that does not secrete CgA and only produces 5-hydroxytryptophan (5-HTP) rather than serotonin. In this case, circulating chromogranin, serotonin, and urine 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to serotonin, leading to high urine serotonin levels.

Adjunct in the diagnosis of other neuroendocrine tumors:
In patients with suspected neuroendocrine tumors other than carcinoids, CgA is often elevated alongside any specific amine and peptide hormones or neurotransmitters that may be produced. The CgA elevations are less pronounced than in carcinoid tumors, and measurement of specific tumor secretion products is considered of greater utility. However, CgA measurements can occasionally aid in diagnosis of these tumors if specific hormone measurements are inconclusive. This is the case with pheochromocytoma and neuroblastoma, where CgA levels may be substantially elevated and can, therefore, provide supplementary and confirmatory information to measurements of specific hormones. In particular, CgA measurements might provide useful diagnostic information in patients with mild elevations in catecholamines and metanephrines;(5) such mild elevations often represent false-positive test results.

Possible adjunct in outcome prediction and follow-up of prostate cancer:
Prostate cancers often contain cells with partial neuroendocrine differentiation. These cells secrete CGA. The amounts secreted are insufficient in most cases to make this a useful marker for prostate cancer diagnosis. However, if patients with advanced prostate cancer are found to have elevated CGA levels, this indicates the tumor contains a significant neuroendocrine cell subpopulation. Such tumors are often resistant to antiandrogen therapy and have a worse prognosis. These patients should be monitored particularly closely.(6)

Cautions

This test should not be used for cancer screening or cancer diagnosis. Furthermore, chromogranin A (CgA) is not indicated to be used as a stand-alone monitoring assay and should be used in conjunction with clinical signs and symptoms and other diagnostic evidence. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed.

Test results cannot be interpreted as absolute evidence for the presence or absence of malignant disease.

Drugs that stimulate secretion of neuroendocrine cells can lead to artifactual CgA elevations. In particular, proton pump inhibitors (PPI; eg, omeprazole), which are used in the treatment of esophageal and gastroduodenal ulcer disease and dyspepsia, will result in significant elevations of serum CgA levels, often to many times above the normal reference interval. PPI should therefore be discontinued for at least 2 weeks before CgA measurements because the biological

effects of PPI persist for a significant time period after the drugs are discontinued. If absolutely necessary, H2-receptor antagonists at modest doses can be substituted for PPI in such patients without risking significant false-elevations in CgA.(7)

Atrophic gastritis and pernicious anemia also lead to false elevations in serum CgA levels by the same mechanism as PPI, lack of feedback inhibition of gastrin production due to gastric achlorhydria.

CgA and its peptide fragments are cleared by a combination of hepatic metabolism and kidney excretion. Impaired kidney function is associated with elevated serum CgA to similar concentrations to those observed in patients on PPI, making single serum CgA measurements uninterpretable.(8) Serial measurements may have some value in selected patients if the impaired kidney function remains stable, in particular because CgA does not seem to change significantly following dialysis (in-house data, 24 patients; p=0.32). However, results must be interpreted with extreme caution.

Various non-neuroendocrine tumors might be associated with elevations, usually modest, in serum CgA concentrations. This possibility should be considered in patients who are evaluated or followed for neuroendocrine tumors and who show serum CgA elevations that are discordant to the clinical assessment or other biochemical and imaging tests.

Values obtained with different assay methods or kits may be different and cannot be used interchangeably.
In rare cases, some individuals can develop antibodies to mouse or other animal antibodies (often referred to as human anti-mouse antibodies [HAMA] or heterophile antibodies), which may cause interference in some immunoassays. Caution should be used in interpretation of results, and the laboratory should be alerted if the result does not correlate with the clinical presentation.

A "hook effect" can occur at extremely high CgA concentrations, resulting in a lower measured CgA concentration than is actually contained in the specimen. This assay is unlikely to be subject to hooking unless CgA concentrations in excess of 1,000,000 ng/mL are present. However, if there is a strong clinical suspicion of hooking, then retesting after further sample dilutions should be requested.

Occasional patient specimens will contain mixtures of CgA fragments that lead to nonlinearity of measurement in specimens with high concentrations of CgA that need to be diluted. It might not be possible to provide an accurate result in some of these individuals.

Supportive Data

Reference values were derived from 162 donors (68 [42%] male and 94 [58%] female), ages 21 to 79. There was no age (p>0.17) or sex (p>0.85) association at the 97.5th percentile, so the overall reference range of <93 ng/mL (97.5% CI: 86, 99) was calculated.

A previous study in 148 pediatric patients (F=66, M=82; age range 1 day to 18 years) demonstrated that there is no significant difference in serum chromogranin A concentrations between children and adults.

A prospective, multi-center, observational study with 153 evaluable neuroendocrine tumor patients was performed to validate the performance of B·R·A·H·M·S CgA (chromogranin A)II KRYPTOR assay in monitoring grade 1 and grade 2 GEP-NET progressive or non-progressive disease within 32 months.(9) Course of disease was assessed by standard imaging (CT/MRI scans) and tumors were classified by RECIST 1.1 criteria for progression (progressive disease) vs. no progression (complete response, partial response, or stable disease).

Clinical Reference

1. Bartolomucci A, Possenti R, Mahata SK, Fischer-Colbrie R, Loh YP, Salton SR. The extended granin family: structure, function, and biomedical implications. Endocr Rev. 2011;32(6):755-797
2. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas. 2010;39(6):753-766
3. Anthony LB, Strosberg JR, Klimstra DS, et al. The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (nets): well-differentiated nets of the distal colon and rectum. Pancreas. 2010;39(6):767-774
4. Kullke MH, Benson AB, Bergsland E, et al. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines): NCCN Guidelines Version 1. Neuroendocrine Tumors. 2012:1-94
5. Algeciras-Schimnich A, Preissner CM, Young WF Jr, Singh RJ, Grebe SK. Plasma chromogranin A or urine fractionated metanephrines follow-up testing improves the diagnostic accuracy of plasma fractionated metanephrines for pheochromocytoma. J Clin Endocrinol Metab. 2008;93(1):91-95
6. Ploussard G, Rozet F, Roubaud G, Stanbury T, Sargos P, Roupret M. Chromogranin A: a useful biomarker in castration-resistant prostate cancer. World J Urol. 2023;41(2):361-369. doi:10.1007/s00345-022-04248-0
7. Korse CM, Muller M, Taal BG. Discontinuation of proton pump inhibitors during assessment of chromogranin A levels in patients with neuroendocrine tumours. Br J Cancer. 2011;105(8):1173-1175
8. Bech PR, Ramachandran R, Dhillo WS, Martin NM, Bloom SR. Quantifying the effects of renal impairment on plasma concentrations of the neuroendocrine neoplasia biomarkers chromogranin A, chromogranin B, and cocaine- and amphetamine-regulated transcript. Clin Chem. 2012;58(5):941-943
9. B R A H M S CgAII KRYPTOR. Instruction for Use. V1.1us. Thermo Fisher Scientific Inc; 2023
10. Wang YH, Yang QC, Lin Y, Xue L, Chen MH, Chen J. Chromogranin A as a marker for diagnosis, treatment, and survival in patients with gastroenteropancreatic neuroendocrine neoplasm. Medicine (Baltimore). 2014;93(27):e247. doi:10.1097/MD.0000000000000247
11. Ciobanu OA, Martin S, Fica S. Perspectives on the diagnostic, predictive and prognostic markers of neuroendocrine neoplasms (Review). Exp Ther Med. 2021;22(6):1479. doi:10.3892/etm.2021.10914

Performance

Method Description

Chromogranin A (CgA) is measured in a homogeneous automated immunofluorescent assay. This assay uses technology based on a variant of Forster resonance energy transfer, called time-resolved amplified cryptate emission (TRACE). A mouse monoclonal antibody against CgA is labeled with europium cryptate (TRACE donor) and a second mouse monoclonal antibody against CgA is labeled with Alexa Fluor 647 (TRACE acceptor). CgA is sandwiched between the 2 antibodies, bringing them into close proximity. When the antigen-antibody complex is excited with a nitrogen laser at 337 nm, some fluorescent energy is emitted at 620 nm, and the rest is transferred by nonradiative dipole-dipole coupling to Alexa Fluor 647. This energy is then emitted as fluorescence at 647 nm. A ratio of the energy emitted at 647 nm to that emitted at 620 nm (internal reference) is calculated for each sample. Signal intensity is proportional to the number of antigen-antibody complexes formed and, therefore, to antigen concentration.(Package insert: B R A H M S CgAII KRYPTOR Instruction for Use. Thermo Fisher Scientific Inc; V1.1us, 09/2023)

PDF Report

No

Day(s) Performed
Monday through Saturday

Report Available
1 to 3 days

Specimen Retention Time
2 weeks

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Superior Drive

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test has been cleared, approved, or is exempt by the US Food and Drug Administration and is used per manufacturer's instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.

CPT Code Information
86316

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CGAK	Chromogranin A, S	9811-1

Result ID	Test Result Name	Result LOINC® Value
CGAK	Chromogranin A, S	9811-1