MAYO CLINIC LABORATORIES

Test Definition: CGAK

Chromogranin A, Serum

Overview

Useful For

Follow-up or surveillance of patients with known or treated carcinoid tumors

An adjunct in the diagnosis of carcinoid tumors

An adjunct in the diagnosis of other neuroendocrine tumors, including pheochromocytomas, medullary thyroid carcinomas, functioning and nonfunctioning islet cell and gastrointestinal amine precursor uptake and decarboxylation tumors, and pituitary adenomas

A possible adjunct in outcome prediction and follow-up in advanced prostate cancer

Method Name

Immunofluorescent Assay (IFA)

NY State Available

Yes

Specimen

Specimen Type

Serum

Specimen Required

Patient Preparation: Proton pump inhibitor medications should be discontinued for at least 2 weeks before collection.
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
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

0.2 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Frozen (preferred)	90 days	
	Ambient	7 days	
	Refrigerated	24 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 resolubilization 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 daughter 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). Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines and peptide hormones secreted, as to local and distant spread. The symptoms of this carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. 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 are used in conjunction with, or alternative to, measurements of serum or whole blood serotonin, urine serotonin and 5-HIAA, and imaging studies. This includes the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing.

Finally, 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. The role of CGA measurement is not well defined in these tumors, with the possible exception of prognostic information in advanced prostate cancer.(5)

Reference Values

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

Interpretation

Follow-up/Surveillance:
Urine 5-hydroxyindolacetic acid (5-HIAA) and serum chromogranin A (CGA) increase in proportion to carcinoid tumor burden. Because of the linear relationship of CGA to tumor burden, its measurement also provides prognostic information.

Most mid- and hindgut tumors secrete CGA even if they do not produce significant amounts of serotonin or serotonin metabolites (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 40% to 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 3 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 in particular 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;(6) 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.(5)

Cautions

Causes of Elevations of Serum Chromogranin A Concentration Unrelated to Carcinoids or Other Neuroendocrine Tumors.

Proton Pump Inhibitor Drugs:
Drugs that stimulate secretion of neuroendocrine cells can lead to artifactual chromogranin A (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 range. In-house data from 1760 specimens suggest that PPI elevate CGA level on average by 757 ng/mL, but a wide range of responses is observed, with some patients showing either lesser or far greater elevations. 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)

The use of PPI also compounds the effects of other conditions, listed below, that can result in false elevations of CGA. In every case, we found that PPI caused additional CGA elevations.

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.

Impaired Hepatic or Kidney Function:
CGA and its peptide fragments are cleared by a combination of hepatic metabolism and kidney excretion. The effects of hepatic failure are relatively minor in the absence of hepatocellular carcinoma or fulminant liver failure. However, even modest kidney impairment can elevate serum CGA, and end-stage kidney failure is associated with elevations (in-house data: mean 471 ng/mL) similar 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 renal 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.

Non-neuroendocrine Tumors:

As indicated in the Clinical Information, 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. One example is testicular cancer, which in the in-house study was associated with a mean CGA increase of 189 ng/mL.

General Assay Issues of Note:
Limited Agreement Among Different CGA Immunoassays:
There is no universal calibration standard for serum CGA assays. In addition, different CGA assays that use different antibodies or antibody combinations will display different cross-reactivity with the various CGA fragments. Therefore, reference intervals and individual patient results differ significantly between different CGA assays and cannot be directly compared. Serial measurements should be performed with the same assay or, if assays are changed, patients should have their baseline re-established.

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

Heterophilic Antibody Interference:
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.

Spurious False-Low Results Due to "Hook Effect":
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 as it is capable of measuring CGA concentrations in excess of 1,000,000 ng/mL accurately. However, if there is a strong clinical suspicion of hooking, then retesting after further sample dilution should be requested.

CGA Fragments Interfering with Accurate Quantification:
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 gender ($p>0.85$) 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.

Clinical Reference

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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.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Monday through Saturday

Report Available

1 to 3 days

Specimen Retention Time

3 months

Performing Laboratory Location

Rochester

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 was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

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