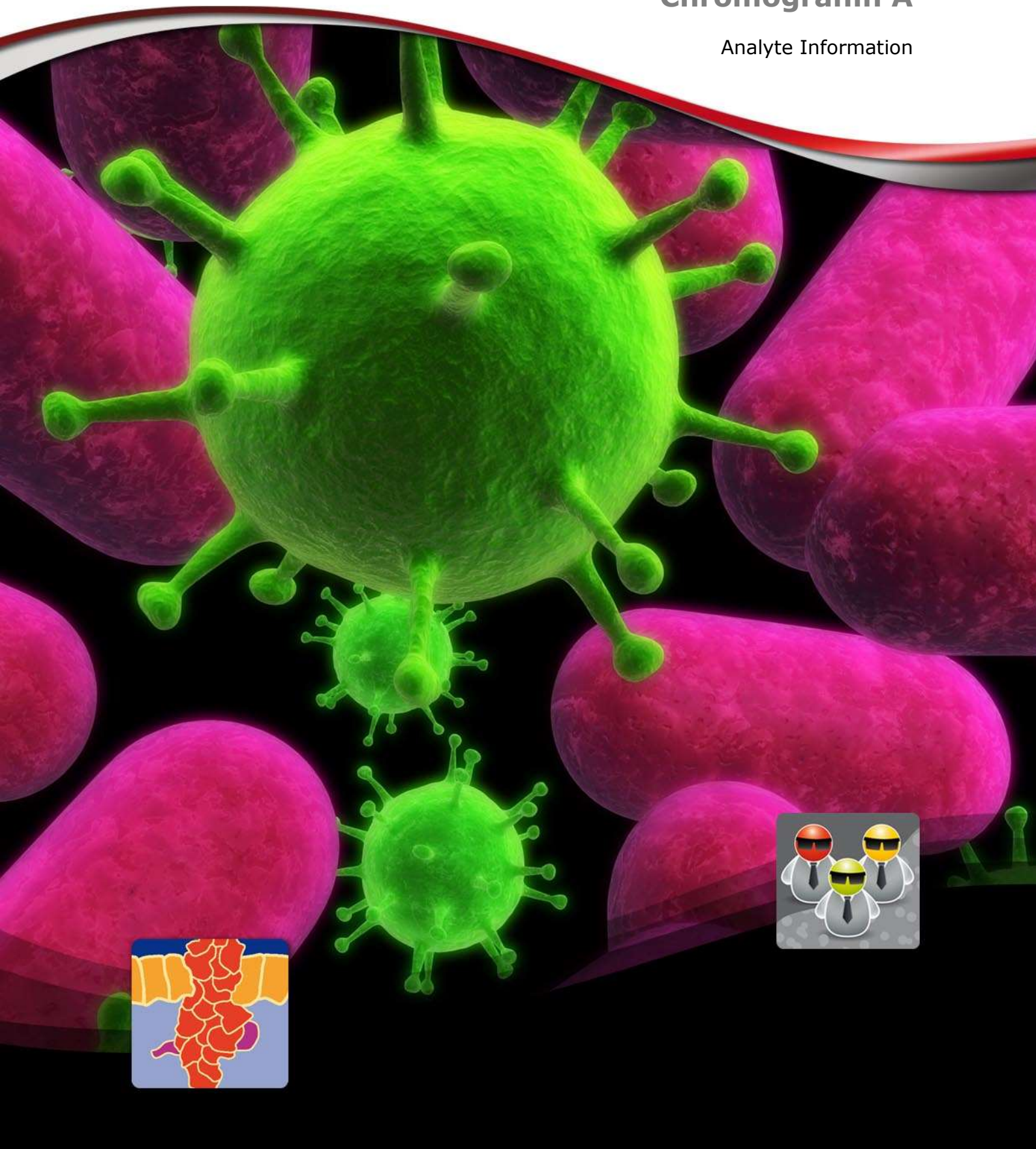
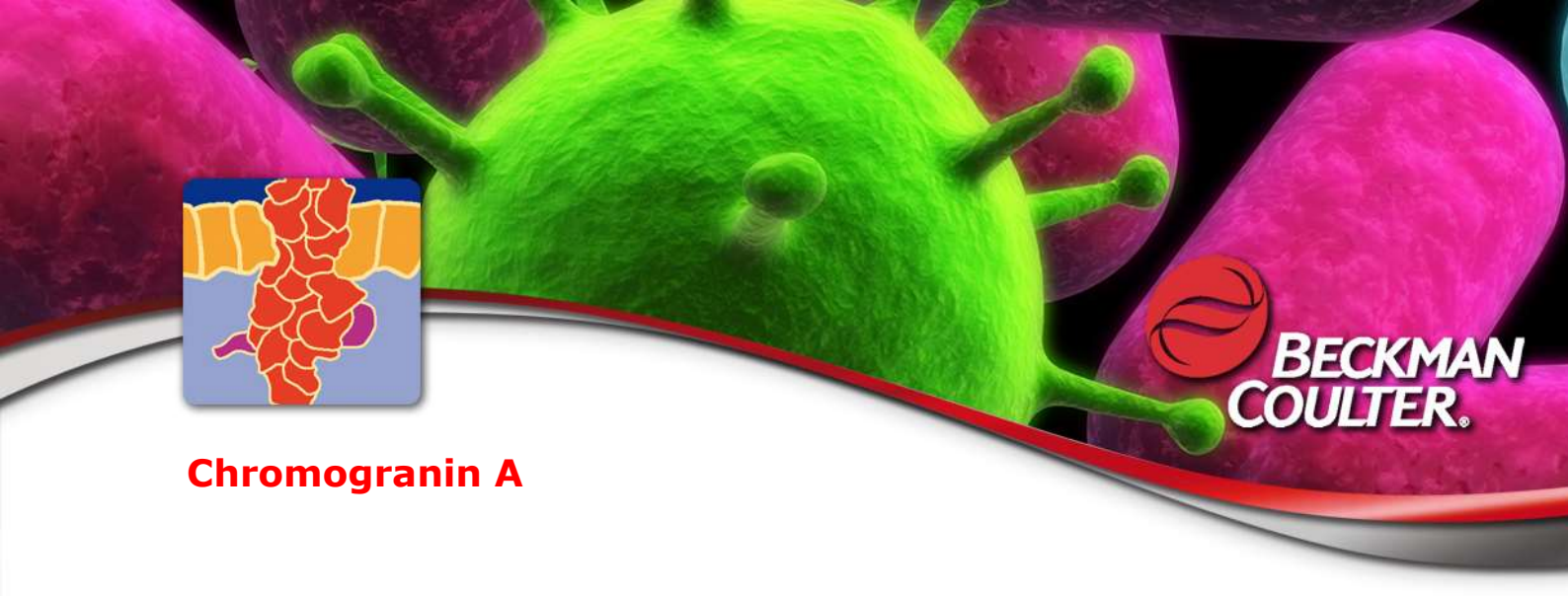
Tumor markers

Chromogranin A

Analyte Information





Chromogranin A

Introduction

Chromogranin A (CgA) is a 439-amino acid protein with a molecular weight of 48 to 60 kDa, depending on glycosylation and phosphorylation status.

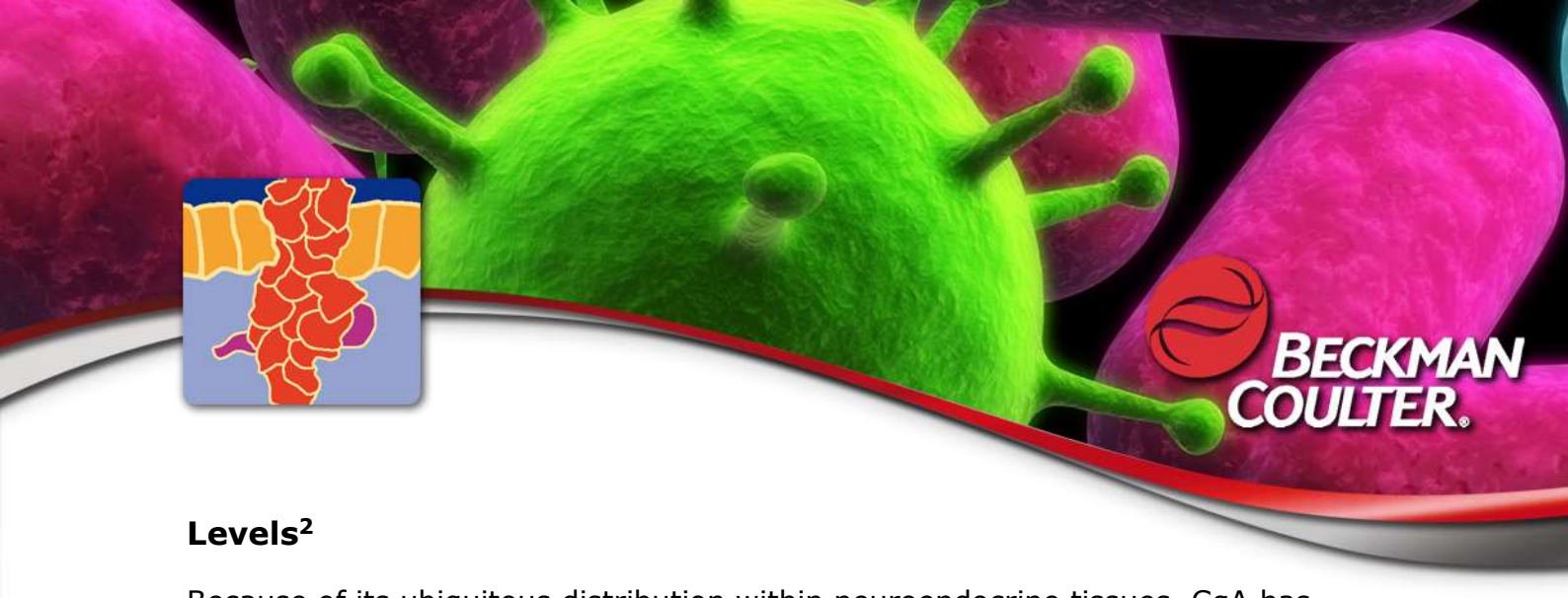
It is a member of the granin family (chromogranins or secretogranins) which is a family of acid proteins present in the secretory granules of a wide variety of endocrine and neuro-endocrine cells with numerous pairs of basic amino acids as potential cleavage sites.

Granins are precursors of biologically active peptides, which may act as helper proteins in the packaging of peptide hormones and neuropeptides. Granins exert similar subcellular location.

The granin family[1] of acid secretory proteins consists of the three „classic" granins - chromogranin A, which was first isolated from chromaffin cells of the adrenal medulla, chromogranin B (secretogranin I, 657 amino acids long protein), and chromogranin C (617 amino acids), also known as secretogranin II. Four other acidic-secretory proteins considered to be the members of the granin family are secretogranin III, secretogranin IV, secretogranin V, and secretogranin VI.

CgA is a precursor of biologically active peptides, which act as autocrine or paracrine negative modulators of the neuroendocrine system. To these peptides belong vasostatin 1 with antiadrenergic effects, pancreastatin, which is a strong inhibitor of glucose induced insulin release from the pancreas, parastatin (parathyroid secretory protein) inhibiting low Ca^{2+} - stimulated parathyroid secretion, and catestatin, which is a catecholamine release-inhibitory peptide.

The proteolysis of CgA is tissue specific, for example pancreastatin was found in alpha cells of pancreas, chromostatin in beta cells of pancreas, but neither pancreastatin nor chromostatin were observed in adrenal chromaffin cells.



Levels[2]

Because of its ubiquitous distribution within neuroendocrine tissues, CgA has become the most important circulating tumour marker for different kinds of neuroendocrine tumours.

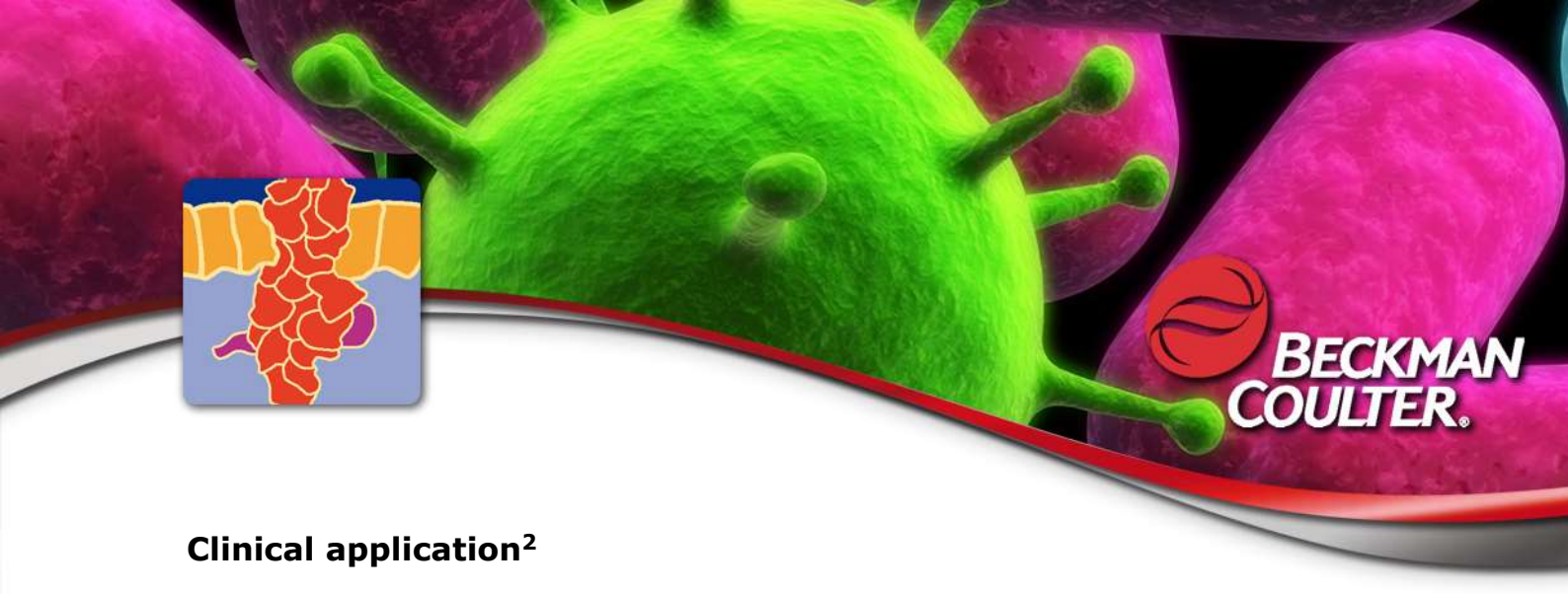
CgA levels are increased in carcinoid tumours, neuroblastoma, pheochromocytoma, and gastro-entero-pancreatic tumours such as gastrinoma, glucagonoma, insulinoma.

In pheochromocytomas, chromogranin A-levels show a high correlation to the tumour mass and are therefore widely used to monitor the outcome of therapies. Moreover, there is a relationship between CgA concentrations and PASS (Pheochromocytoma of the Adrenal Gland Scaled Score) score rating the malignity of pheochromocytoma.

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. An increase of CgA levels in patients with prostate carcinoma is a hint for an unfavourable outcome of the disease.

Elevated Chromogranin A levels are associated with the following disorders:

- Carcinoid tumours
- Neuroendocrine tumours
    - Pheochromocytoma
    - Medullary thyroid carcinomas (MTC)
    - Gastro-entero-pancreatic tumours such as gastrinoma, glucagonoma, insulinoma
    - Pituitary adenomas
- Prostate cancer (follow up in advanced cancers)



Clinical application[2]

First-line tests in disease surveillance of most patients with carcinoid tumors

Carcinoid tumors in particular almost always secrete CgA along with a variety of specific modified amines, chiefly serotonin (5-hydroxytryptamine: 5-HT) and peptides. 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);

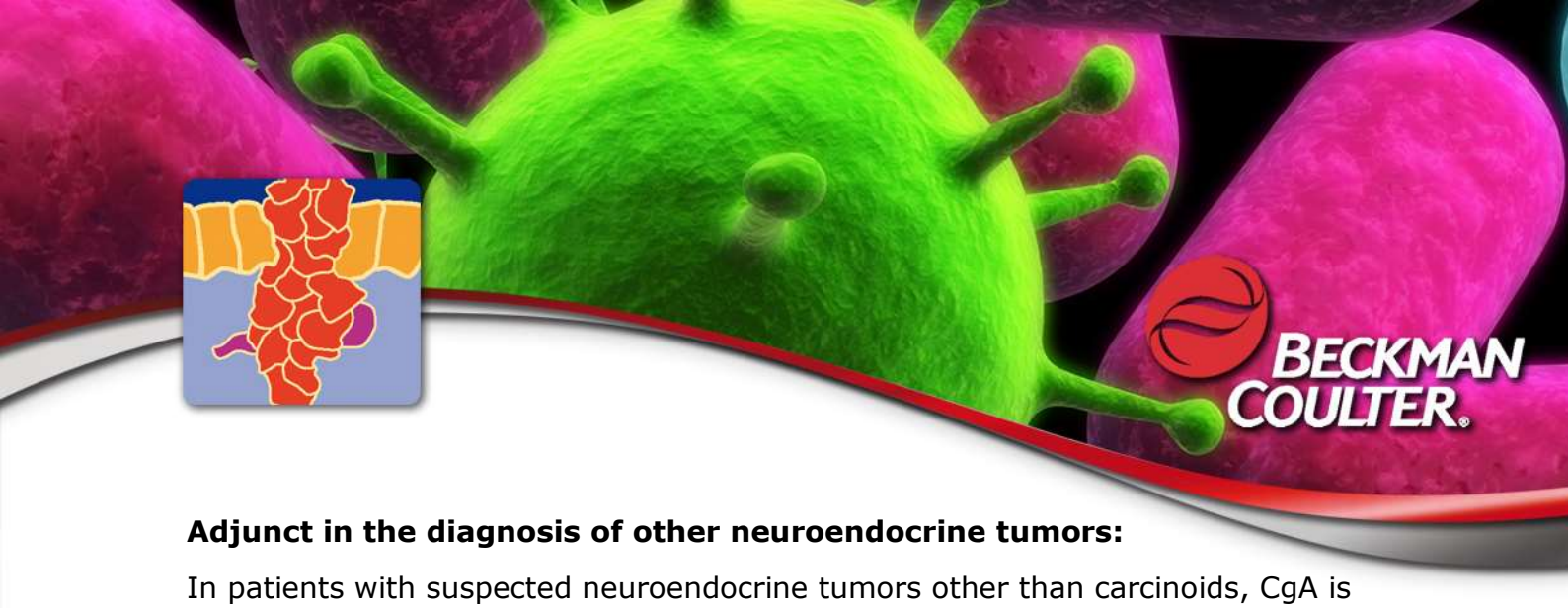
and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases).

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.

Serum CgA measurements are used in conjunction with, or alternative to, measurements of serum or whole blood serotonin, urine serotonin, and urine 5-HIAA and imaging studies. This includes the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing.

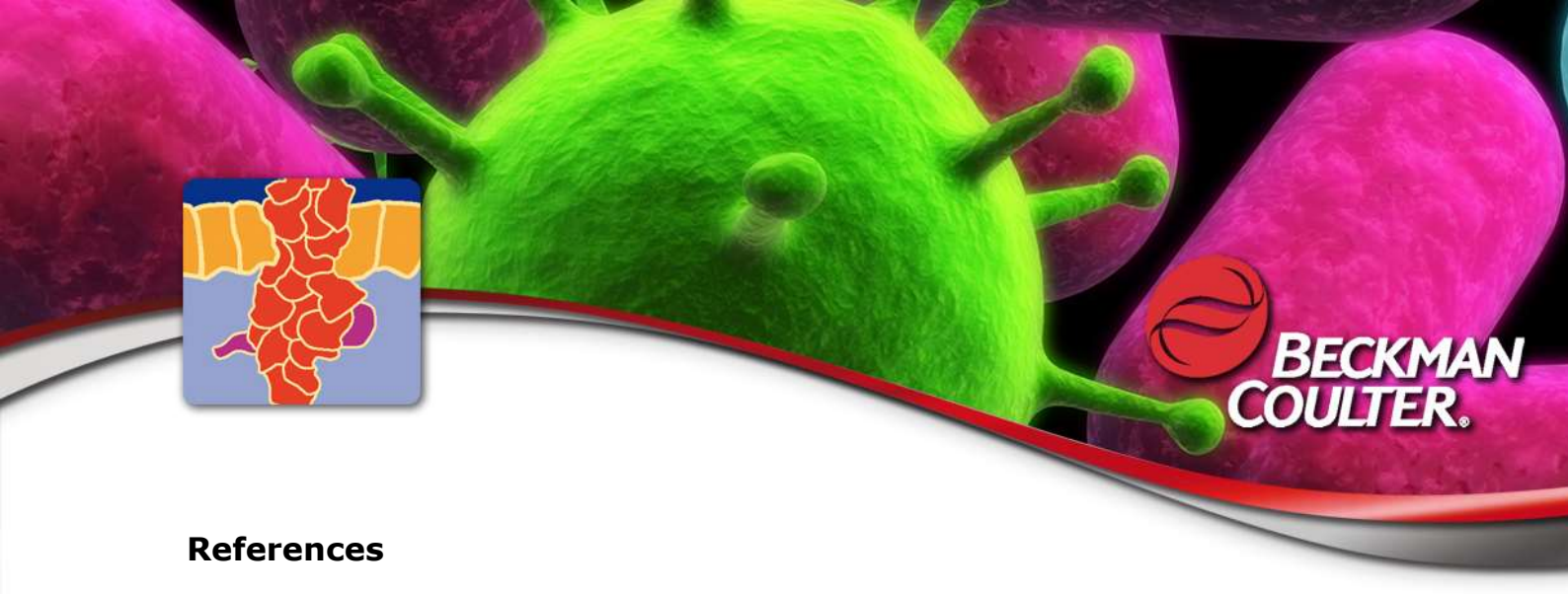


Adjunct in the diagnosis of other neuroendocrine tumors:

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[3]; 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 anti-androgen therapy and have a worse prognosis. These patients should be monitored particularly closely[4].



References

1 Bílek R, Šafařík L, Ciprová V, Vlček P, Lisá L: Chromogranin A, a Member of Neuroendocrine Secretory Proteins as a Selective Marker for Laboratory Diagnosis of Pheochromocytoma. Physiol. Res. 2008; 57 (Suppl.1): S171-S179

2 https://www.mayomedicallaboratories.com

3 Algeciras-Schimnich A, Preissner CM, Young WF, et al: Plasma chromogranin A or urine fractionated metanephrines follow-up testing improves the diagnostic accuracy of plasma fractionated metanephrines for pheochromocytomas. J Clin Endocrinol Metab 2008;93:91-95

4 Tricoli JV, Schoenfeldt M, Conley BA: Detection of prostate cancer and predicting progression: Current and future diagnostic markers. Clin Cancer Res 2004;10:3943-3953