

**Overview****Useful For**

In conjunction with, or as an alternative to first-order test in the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing (5-HIAA or serum chromogranin A measurements are first-line tests)

Second-order test in the follow-up of patients with known or treated carcinoid tumors in serum specimens

**Method Name**

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

**NY State Available**

Yes

**Specimen****Specimen Type**

Serum

**Additional Testing Requirements**

First-line testing for the diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome consists of urinary serotonin (SERU / Serotonin, 24 Hour, Urine), urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum).

**Specimen Required**

**Patient Preparation:** Patient should be off of medications that may affect serotonin concentrations including lithium, monoamine oxidase inhibitors, methyl dopa, morphine, and reserpine.

**Collection Container/Tube:**

**Preferred:** Red top

**Acceptable:** Serum gel

**Submission Container/Tube:** Plastic vial

**Specimen Volume:** 2.5 mL

**Collection Instructions:** Centrifuge as soon as blood has clotted and aliquot into plastic vial.

**Specimen Minimum Volume**

1.1 mL

**Reject Due To**

Gross hemolysis	OK
Gross lipemia	OK
Gross icterus	OK

### Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	21 days	
	Frozen	90 days	
	Ambient	4 days	

### Clinical and Interpretive

#### Clinical Information

Serotonin (5-hydroxytryptamine; 5-HT) is synthesized from the essential amino acid tryptophan via the intermediate 5-hydroxytryptophan (5-HTP). 5-HT production sites are the central nervous system (CNS), where it acts as a neurotransmitter, and neuroectodermal cells, chiefly gastrointestinal (GI) enterochromaffin cells (EC-cells). The CNS and peripheral 5-HT pools are isolated from each other. EC-cell production accounts for 80% of the body's 5-HT content.

Many different stimuli can release 5-HT from EC-cells. Once secreted, in concert with other gut hormones, 5-HT increases GI blood flow, motility, and fluid secretion. On first pass through the liver 30% to 80% of 5-HT is metabolized, predominately to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted by the kidneys. Ninety-percent of the remainder is metabolized in the lungs, also to 5-HIAA. Of the remaining 10%, almost all is taken up by platelets, where it remains until it is released during clotting, promoting further platelet aggregation.

The main diseases that may be associated with measurable increases in 5-HT are neuroectodermal tumors, in particular tumors arising from EC-cells, which are termed carcinoids. They 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. The majority of carcinoid tumors do not cause significant clinical disease. Those tumors that behave more aggressively tend to cause nonspecific GI disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines, chiefly 5-HT, and peptide hormones secreted, as to local and distant spread. The symptoms of this so-called carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. All of these symptoms are at least partly caused by 5-HT. The carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far less 5-HT. Since midgut tumors drain into the portal circulation, which passes into the liver, symptoms do not usually occur until liver or other distant metastases have developed, bypassing the extensive hepatic first-pass 5-HT degradation.

Serotonin production by disseminated carcinoid tumors can sometimes be so substantial that body tryptophan stores become depleted and clinical tryptophan deficiency, resembling pellagra (triad of diarrhea, dementia, and dermatitis), develops.

Diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome rests on measurements of circulating and urinary 5-HT, urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells.

#### Reference Values

< or =230 ng/mL

### Interpretation

Metastasizing midgut carcinoid tumors usually produce blood or serum 5-hydroxytryptamine (5-HT) concentrations greater than 1,000 ng/mL. However, elevations above 400 ng/mL are suggestive of carcinoid tumors as the cause of carcinoid syndrome-like symptoms. Lesser increases may be nonspecific or drug-related (see Cautions).

Only a minority of patients with carcinoid tumors will have elevated 5-HT levels. It is usually impossible to diagnose small carcinoid tumors (>95% of cases) without any symptoms suggestive of carcinoid syndrome by measurement of 5-HT, 5 hydroxyindoleacetic acid (5-HIAA), or chromogranin A.

In patients with more advanced tumors, circulating 5-HT is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors. Foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little if any 5-HT. Urinary 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though 5-HT and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with foregut and midgut tumors. Therefore, to achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, 5-HT in serum/blood, 5-HIAA in urine, and serum chromogranin A should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urinary 5-HT measurement will be required. An example would be a nonchromogranin-secreting foregut tumor that only produces 5-HTP, rather than 5-HT. In this case, circulating chromogranin, 5-HT levels, and urinary 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to 5-HT, leading to high urinary 5-HT levels.

Disease progression can be monitored in patients with serotonin-producing carcinoid tumors by measurement of 5-HT in blood. However, at levels above approximately 5,000 ng/mL, the serotonin storage capacity of platelets becomes limiting, and there is no longer a linear relationship between tumor burden and blood 5-HT levels. Urinary 5-HIAA and serum chromogranin A continue to increase in proportion to the tumor burden to much higher 5-HT production levels, and are therefore better suited for follow-up in patients with extensive disease.

### Cautions

Since most circulating 5-hydroxytryptamine (5-HT) is contained in platelets, the preferred specimens for measurement either include all or most of the platelets (ie, whole blood and platelet-rich plasma) or consist of serum from completely clotted specimens, a process that releases nearly all 5-HT from platelets. "Ordinary" or platelet-poor plasma specimens are not suitable.

Medications that may elevate serotonin concentrations include lithium, monoamine oxidase inhibitors, methyl dopa, morphine, and reserpine. The observed levels are usually less than 400 ng/mL. Selective serotonin reuptake inhibitors (eg, fluoxetine) can lead to depletion of platelet serotonin levels and result in false-negative serum and blood 5-HT tests. The effects of drugs are more marked on urinary 5-HT and 5 hydroxyindoleacetic acid (5-HIAA) levels than on blood and serum 5-HT levels.

Serotonin- or tryptophan-rich foods (avocados, bananas, plums, walnuts, pineapple, eggplant, plantain, tomatoes, hickory nuts, kiwi, dates, grapefruit, cantaloupe, and honeydew melon) do not contribute significantly to serum or blood 5-HT measurements, but can elevate platelet-poor plasma 5-HT, urinary 5-HT, and urinary 5-HIAA levels markedly (up to 10-fold).

### Clinical Reference

1. Kema IP, Schellings AM, Meibotg G, et al: Influence of a serotonin and dopamine-rich diet on platelet serotonin content and urinary excretion of biogenic amines and their metabolites. *Clin Chem* 1992;38:1730-1736

2. Kema IP, de Vries EG, Muskiet FA: Clinical chemistry of serotonin and metabolites. J Chromatogr B Biomed Sci Appl 2000;747:33-48

3. Meijer W, Kema I, Volmer M, et al: Discriminating capacity of indole markers in the diagnosis of carcinoid tumors. Clin Chem 2000;46:1588-1596

4. Ganim RB, Norton JA: Recent advances in carcinoid pathogenesis, diagnosis and management. Surg Oncol 2000;9:173-179

## Performance

### Method Description

Serotonin is removed from serum using reversed-phase solid-phase extraction (SPE). Separation is completed using a Bond Elut C18 SPE cartridge, and is eluted with 40% acetonitrile/1 mM ammonium acetate/0.1% formic acid. The eluate is analyzed using liquid chromatography/tandem mass spectrometry (LC-MS/MS) and quantified using a stable isotope-labeled internal standard, d(4)-serotonin.(Carling RS, Degg TS, Allen KR, et al: valuation of whole blood serotonin and plasma and urine 5-hydroxyindole acetic acid in diagnosis of carcinoid disease. Ann Clin Biochem 2002;39:577-582)

### PDF Report

No

### Day(s) and Time(s) Test Performed

Monday, Wednesday, Friday; 10 a.m.

### Analytic Time

4 days

### Maximum Laboratory Time

6 days

### Specimen Retention Time

3 months

### Performing Laboratory Location

Rochester

## Fees and 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 Regional Manager. 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. This test has not been cleared or approved by the U.S. Food and Drug Administration.

### CPT Code Information

84260

**LOINC® Information**

Test ID	Test Order Name	Order LOINC Value
SER	Serotonin, S	27057-9

Result ID	Test Result Name	Result LOINC Value
84395	Serotonin, S	27057-9