# Test Definition: SERU

Serotonin, 24 Hour, Urine

## Overview

### Useful For

Diagnosis of a small subgroup of carcinoid tumors that produce predominately 5-hydroxytryptophan (5-HTP) but very little serotonin and chromogranin A

Follow-up for patients with known or treated carcinoid tumors that produce predominately 5-HTP but very little serotonin and chromogranin A

### Special Instructions

- Urine Preservatives-Collection and Transportation for 24-Hour Urine Specimens

### Method Name

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

### NY State Available

Yes

## Specimen

### Specimen Type

Urine

### Additional Testing Requirements

First-line testing for the diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome consists of urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid, 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum). Serotonin in whole blood (SERWB / Serotonin, Blood), serum (SER / Serotonin, Serum), and urine (SERU / Serotonin, 24 Hour, Urine) are useful in conjunction with these first-line tests.

### Necessary Information

**24-Hour volume (in milliliters) is required.**

### Specimen Required

**Patient Preparation:**

1. For 48 hours before and during specimen collection, patient should **not** eat avocados, bananas, butternuts, cantaloupe, dates, eggplant, grapefruit, hickory nuts, honeydew melon, kiwifruit, melon, nuts, pecans, pineapple, plantains, plums, tomatoes, or walnuts, which are high in serotonin or tryptophan.
2. Patient **should not** take medications that may elevate serotonin levels, including lithium, monoamine oxidase inhibitors, methyldopa, morphine, and reserpine, or selective serotonin reuptake inhibitors (SSRI, eg, PROZAC) which can lead to depletion of platelet serotonin levels and result in false-negative serotonin results for a minimum of 72 hours before specimen collection. Some drugs with longer half-lives (i.e. fluoxetine) can require months after discontinuation

for serotonin levels to return to baseline.

**3. Patient should avoid heavy nicotine consumption during the 24-hour collection period.**

**Supplies:** Urine Tubes, 10 mL (T068)

**Container/Tube:** Plastic, 10-mL urine tube

**Specimen Volume:** 5 mL

**Collection Instructions:**

1. Add 25 mL of 50% acetic acid as preservative at start of collection.
2. Collect urine for a full 24 hours (required) and record the total volume.
3. Refrigerate specimen during collection.

**Additional Information:** See Urine Preservatives-Collection and Transportation for 24-Hour Urine Specimens for multiple collections.

## Forms

If not ordering electronically, complete, print, and send an Oncology Test Request (T729) with the specimen.

## Urine Preservative Collection Options

**Note:** The addition of preservative must occur **prior to beginning the collection**.

| | |
|---|---|
| Ambient (no additive) | OK |
| Refrigerate (no additive) | OK |
| Frozen (no additive) | OK |
| 50% Acetic Acid | Preferred |
| Boric Acid | No |
| Diazolidinyl Urea | No |
| 6M Hydrochloric Acid | No |
| 6M Nitric Acid | OK |
| Sodium Carbonate | No |
| Toluene | OK |

## Specimen Minimum Volume

2.5 mL

## Reject Due To

| | |
|---|---|
| Gross hemolysis | OK |

## Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---|---|---|---|
| Urine | Refrigerated (preferred) | 28 days | |
| | Ambient | 48 hours | |
| | Frozen | 28 days | |

## Clinical & Interpretive

### Clinical Information

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

Many different stimuli can release serotonin from EC cells. Once secreted, in concert with other gut hormones, serotonin increases GI blood flow, motility, and fluid secretion. On first pass through the liver, 30% to 80% of serotonin is metabolized, predominately to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted by the kidneys. Ninety percent of the remainder is metabolized to 5-HIAA in the lungs. 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 serotonin are neuroectodermal tumors, particularly those 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). The enzyme 5-HTP decarboxylase, which converts the intermediate 5-HTP to serotonin, is present in midgut tumors but is absent or present in low concentrations in foregut and hindgut tumors.

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 tract 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 serotonin, 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. These symptoms are at least partly caused by serotonin. Carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far lesser amounts of serotonin. Because midgut tumors drain into the portal circulation, which passes into the liver, undergoing extensive hepatic (first pass) serotonin degradation, symptoms do not usually occur until liver or other distant metastases have developed, producing serotonin that bypasses the hepatic 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 whole blood, serum, and urine serotonin, urine 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid, 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells. Urine serotonin is, in most circumstances, the least likely marker to be elevated (see Interpretation).

### Reference Values

< or =210 mcg/24 h

Reference values apply to all ages.

## Interpretation

It is usually impossible to diagnose asymptomatic, small carcinoid tumors by measurement of serum or urine serotonin, urine 5 hydroxyindoleacetic acid (5-HIAA), or serum chromogranin A. By contrast, 1 or more of these markers are elevated in most patients with more advanced and symptomatic tumors, usually to levels several times the upper limit of the reference interval.

In patients with advanced and symptomatic tumors the following patterns of tumor marker elevations are observed:
-Serum or whole blood serotonin 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, because foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little, if any, serotonin.
-Urine 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 serotonin and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with symptomatic foregut and midgut tumors.
-Urine serotonin is in most circumstances the least likely marker to be elevated. The exception is tumors (usually foregut tumors) that produce predominately 5-HTP, rather than serotonin, and also secrete little, if any, chromogranin A. In this case, circulating chromogranin A, circulating serotonin levels, and urine 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to serotonin, leading to high urine serotonin levels.

Urine serotonin measurements are not commonly employed in carcinoid tumor follow-up. The exceptions are patients with tumors that almost exclusively secrete 5-HTP, as summarized above. In these individuals, urine serotonin is the tumor marker of choice to monitor disease progression.

In all other patients, disease progression is monitored best using urinary 5-HIAA and serum chromogranin A measurements. These markers are usually proportional to the patient's tumor burden over a wide range of tumor extent and tumor secretory activity.

## Cautions

Serotonin or tryptophan-rich foods (eg, avocados, bananas, plums, walnuts, pineapple, eggplant, plantain, tomatoes, hickory nuts, kiwi, dates, grapefruit, cantaloupe, or honeydew melon) will elevate urinary serotonin and urinary 5-hydroxyindoleacetic acid (5-HIAA) levels markedly. Serum and blood serotonin and chromogranin A levels are not significantly affected by diet.(1)

Medications that may elevate urine and serum serotonin concentrations include lithium, monoamine oxidase-inhibitors, methyldopa, morphine, and reserpine. Selective serotonin reuptake inhibitors (SSRI; eg, PROZAC) can lead to depletion of platelet serotonin levels and result in false-negative urine, serum, and blood serotonin tests. The effects of drugs are more marked on urine serotonin and 5-HIAA levels than on serum serotonin levels.

Heavy nicotine consumption, in particular heavy smoking, can result in false elevations of urinary serotonin levels as measured with this assay. This is due to about 1% measurement cross-reactivity of the major nicotine metabolite cotinine with serotonin. While this has no significant impact on serum or whole blood serotonin, the renal elimination of cotinine means that this metabolite is highly concentrated in urine, resulting in potential elevations in urine serotonin of

10 to 80 mcg/24 hours above the true urine serotonin level.

### Clinical Reference

1. Kema IP, Schellings AM, Meibotg G, Hoppenbrouwers CJ, Muskiet FA. 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(9):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(10):1588-1596
4. Eisenhofer G, Grebe S, Cheung NKV. Monamine-producing tumors. In: Rifai N, Horvath AR, Wittwer C, eds Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2017: chap 63
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8. Carling RS, Degg TS, Allen KR, Bax ND, Barth JH. Evaluation of whole blood serotonin and plasma and urine 5-hydroxyindole acetic acid in diagnosis of carcinoid disease. Ann Clin Biochem. 2002;39(Pt 6):577-582
9. Stiefel R, Lehmann K, Winder T, Siebenhüner AR. What have we learnt from the past - would treatment decisions for GEP-NET patients differ between 2012 to 2016 by the new recommendations in 2022?. BMC Cancer. 2023;23(1):148. Published 2023 Feb 13. doi:10.1186/s12885-023-10567-1

## Performance

### Method Description

Isotopically labeled internal standard (serotonin-D4) is added to the sample. Serotonin and the internal standard are enriched using solid phase extraction and analyzed using liquid chromatography-tandem mass spectrometry.(Unpublished Mayo method)

### PDF Report

No

### Day(s) Performed

Monday, Wednesday, Friday

### Report Available

5 to 8 days

### Specimen Retention Time

2 weeks

### Performing Laboratory Location

## 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

84260

### LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| SERU | Serotonin, 24 Hr, U | 18253-5 |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| 26603 | Serotonin, 24 Hr, U | 18253-5 |
| TM80 | Collection Duration (h) | 13362-9 |
| VL67 | Volume (mL) | 3167-4 |