

## Overview

### Useful For

Second-order testing when cortisol measurement by immunoassay (eg, CORT / Cortisol, Serum) gives results that are not consistent with clinical symptoms, or if patients are known to, or suspected of, taking exogenous synthetic steroids. For confirming the presence of synthetic steroids, order SGSS / Synthetic Glucocorticoid Screen, Serum.

An adjunct in the differential diagnosis of primary and secondary adrenal insufficiency

An adjunct in the differential diagnosis of Cushing syndrome

### Testing Algorithm

See [Steroid Pathways](#) in Special Instructions.

### Special Instructions

- [Steroid Pathways](#)

### Method Name

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

### NY State Available

Yes

## Specimen

### Specimen Type

Serum Red

### Specimen Required

**Container/Tube:** Red top

**Specimen Volume:** 0.6 mL

**Collection Instructions:** Morning (8 a.m.) and afternoon (4 p.m.) specimens are preferred.

### Additional Information:

1. Include time of draw.
2. If multiple specimens are drawn, send separate order for each specimen.

### Specimen Minimum Volume

0.25 mL

### Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	OK

Other	Serum gel tube
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### Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum Red	Refrigerated (preferred)	28 days	
	Ambient	28 days	
	Frozen	28 days	

### Clinical and Interpretive

#### Clinical Information

Cortisol, the main glucocorticoid (representing 75%-95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism and hypocortisolism can cause disease.

Cortisol levels are regulated by adrenocorticotrophic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6-8 a.m.) and nadirs (11 p.m.) in plasma ACTH and cortisol levels.

The majority of cortisol circulates bound to corticosteroid-binding globulin and albumin. Normally, <5% of circulating cortisol is free (unbound). Free cortisol is the physiologically active form, and is filterable by the renal glomerulus.

Pathological hypercortisolism due to endogenous or exogenous glucocorticoids is termed Cushing syndrome. Signs and symptoms of pathological hypercortisolism may include central obesity, hypertension, hyperglycemia, hirsutism, muscle weakness, and osteoporosis. However, these symptoms and signs are not specific for pathological hypercortisolism. The majority of individuals with some or all of the symptoms and signs will not suffer from Cushing syndrome.

When Cushing syndrome is present, the most common cause is iatrogenic, due to repeated or prolonged administration of, mostly, synthetic corticosteroids. Spontaneous Cushing syndrome is less common and results from either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made.

Hypocortisolism most commonly presents with nonspecific lassitude, weakness, hypotension, and weight loss. Depending on the cause, hyperpigmentation may be present. More advanced cases and patients submitted to physical stress (ie, infection, spontaneous or surgical trauma) also may present with abdominal pain, hyponatremia, hyperkalemia, hyperglycemia, and in extreme cases, cardiovascular shock and renal failure.

The more common causes of hypocortisolism are:

Primary adrenal insufficiency:

-Addison disease

-Congenital adrenal hyperplasia, defects in enzymes involved in cortisol synthesis

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Secondary adrenal insufficiency:

- Prior, prolonged corticosteroid therapy
- Pituitary insufficiency
- Hypothalamic insufficiency

See [Steroid Pathways](#) in Special Instructions.

### Reference Values

5-25 mcg/dL (a.m.)

2-14 mcg/dL (p.m.)

Pediatric reference ranges are the same as adults, as confirmed by peer-reviewed literature.

Petersen KE: ACTH in normal children and children with pituitary and adrenal diseases. I. Measurement in plasma by radioimmunoassay-basal values. *Acta Paediatr Scand* 1981;70:341-345

### Interpretation

In primary adrenal insufficiency, adrenocorticotrophic hormone (ACTH) levels are increased and cortisol levels are decreased; in secondary adrenal insufficiency both ACTH and cortisol levels are decreased.

When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is <10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. The 3 most frequently used tests are the ACTH (cosyntropin) stimulation test, the metyrapone test, and insulin-induced hypoglycemia test. First, the basal plasma ACTH concentration should be measured and the short cosyntropin stimulation test performed.

Cushing syndrome is characterized by increased serum cortisol levels. However, the 24-hour urinary free cortisol excretion is the preferred screening test for Cushing syndrome, specifically CORTU / Cortisol, Free, 24 Hour, Urine that utilizes liquid chromatography-tandem mass spectrometry. A normal result makes the diagnosis unlikely.

Symptoms or signs of Cushing syndrome in a patient with low serum and urine cortisol levels suggest possible exogenous synthetic steroid effects.

### Cautions

When patients are not taking or are not suspected to be taking exogenous glucocorticoids, the regular assay (CORT / Cortisol, Serum) should be used.

When cortisol assays are used for serial monitoring, the same methodology should be used throughout.

There is little, if any, value in an isolated p.m. serum cortisol measurement.

The most common cause of increased plasma cortisol levels in women is a high circulating concentration of estrogen (ie, estrogen therapy, pregnancy) resulting in increased concentration of corticosteroid-binding globulin. This does not result in an increase in the free, bioactive cortisol fraction. For this reason, measurement of 24-hour urinary free cortisol (CORTU / Cortisol, Free, 24 Hour, Urine) or demonstration of absent diurnal variation (ie, by midnight salivary cortisol measurement SALCT / Cortisol, Saliva) are the preferred means of diagnosing spontaneous Cushing syndrome.

Acute stress (including hospitalization and surgery), alcoholism, depression, and many drugs (ie, exogenous cortisones, anticonvulsants) can obliterate normal diurnal variation, affect response to suppression/stimulation tests, and cause elevated baseline levels.

**Not recommended** for evaluating response to metyrapone; DOC / 11-Deoxycortisol, Serum is more reliable.

A low plasma cortisol level does not give conclusive indication of congenital adrenal hyperplasia. DOC / 11-Deoxycortisol, Serum; OHPG / 17-Hydroxyprogesterone, Serum; and DHEA\_ / Dehydroepiandrosterone (DHEA), Serum provide a more accurate and specific determination of the enzyme deficiency.

### Clinical Reference

1. Lin CL, Wu TJ, Machacek DA, et al: Urinary free cortisol and cortisone determined by high-performance liquid chromatography in the diagnosis of Cushing's syndrome. *J Clin Endocrinol Metab* 1997;82:151-155
2. Findling JW, Raff H: Diagnosis and differential diagnosis of Cushing's syndrome. *Endocrinol Metab Clin North Am* 2001;30(3):729-747
3. Buchman AI: Side effects of corticosteroid therapy. *J Clin Gastroenterol* 2001;33(4):289-297
4. Dodds HM, Taylor PJ, Cannell GR, Pond SM: A high-performance liquid chromatography-electrospray-tandem mass spectrometry analysis of cortisol and metabolites in placental perfusate. *Anal Biochem* 1997;247:342-347

### Performance

#### Method Description

Liquid chromatography with triple quadrupole mass spectrometer: deuterated cortisol (d4-cortisol) is added to each specimen as an internal standard. Cortisol and d4-cortisol are extracted from the samples with methylene chloride and analyzed by liquid chromatography-tandem mass spectrometry using multiple reaction monitoring. A calibration curve is included with each batch of patient samples. (Taylor RL, Machacek D, Singh RJ: Validation of a high-throughput liquid chromatography-tandem mass spectrometry method for urinary cortisol and cortisone. *Clin Chem* 2002;1511-1519)

#### PDF Report

No

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

Monday through Friday; 4 p.m.

#### Analytic Time

2 days

#### Maximum Laboratory Time

5 days

#### Specimen Retention Time

14 days

#### 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

82533

### LOINC® Information

Test ID	Test Order Name	Order LOINC Value
CINP	Cortisol, S, LC-MS/MS	87429-7

Result ID	Test Result Name	Result LOINC Value
84279	Cortisol, S, LC-MS/MS	2143-6
23606	AM Cortisol	9813-7
23607	PM Cortisol	9812-9