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**Overview****Useful For**

Diagnosis and follow-up of glucagonomas and other glucagon-producing tumors

Assessing diabetic patients with problematic hyper- or hypoglycemic episodes (extremely limited utility)

**Method Name**

Immunoassay

**NY State Available**

Yes

**Specimen****Specimen Type**

Plasma EDTA

**Specimen Required**

**Patient Preparation:** Fasting (8 hours)

**Supplies:** Aliquot Tube, 5 mL (T465)

**Collection Container/Tube:** Lavender top (EDTA)

**Submission Container/Tube:** Plastic vial

**Specimen Volume:** 2 mL

**Collection Instructions:**

1. Pre-chill tube at 4 degrees C before drawing the specimen.
2. Draw into the pre-chilled tube, and process as follows:
  - a. After drawing specimen, chill tube in wet ice for 10 minutes.
  - b. Centrifuge in a refrigerated centrifuge or in chilled centrifuge carrier.

c. Immediately after centrifugation, aliquot plasma into a plastic vial, and freeze.

**Forms**

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

**Reject Due To**

Gross hemolysis	Reject
Gross lipemia	OK
Gross icterus	OK

**Specimen Minimum Volume**

0.45 mL

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Plasma EDTA	Frozen (preferred)	90 days	

**Clinical & Interpretive****Clinical Information**

Glucagon is a single-chain polypeptide of 29 amino acids that is derived from a larger precursor peptide (big plasma glucagon) that is cleaved upon secretion. The main sites of glucagon production are the hypothalamus and pancreatic alpha-islet cells. The function of hypothalamic glucagon is incompletely understood and currently no clinical disorders of hypothalamic glucagon function have been defined. Pancreatic islet glucagon is secreted in response to hypoglycemia, with resultant increases in blood glucose concentration. Glucagon's hyperglycemic effect is produced by stimulating hepatic glycogenolysis and gluconeogenesis; it has no effect on muscle glycogen. Once blood glucose levels have normalized, glucagon secretion ceases.

Excessive glucagon secretion can lead to hyperglycemia. Excessive and inappropriate glucagon secretion can sometimes be observed in diabetes, in particular during ketoacidosis, and can complicate management of the disorder. In rare cases, it also can occur in tumors of the pancreatic islets (glucagonoma), carcinoid tumors and other neuroendocrine neoplasms, and hepatocellular carcinomas. Patients with glucagon-secreting tumors may present with classic glucagonoma syndrome, consisting of necrolytic migratory erythema, diabetes, and diarrhea but can also have more subtle symptoms and signs.

Decreased or absent glucagon response to hypoglycemia can be seen in type I diabetes (insulin-dependent diabetes) and can contribute to severe and prolonged hypoglycemic responses.

Glucagon is routinely measured along with serum glucose, insulin, and C-peptide levels, during the mixed-meal test employed in the diagnostic workup of suspected postprandial hypoglycemia. However, it plays only a minor role in the interpretation of this test.

**Reference Values**

< or =6 hours: 100-650 pg/mL

1-2 days: 70-450 pg/mL

2-4 days: 100-650 pg/mL

4-14 days: declining gradually to adult levels

>14 days: < or =80 pg/mL (range based on 95% confidence limits)

Glucagon levels are inversely related to blood glucose levels at all ages. This is particularly pronounced at birth and shortly thereafter, until regular feeding patterns are established. This explains the higher levels immediately after birth, which then first fall as the glucagon release mobilizes the infant's glucose stores, then rise again as stores are depleted, finally normalizing towards adult levels as regular feeding patterns are established.

For SI unit Reference Values, see <https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html>

**Interpretation**

Elevated glucagon levels in the absence of hypoglycemia may indicate the presence of a glucagon-secreting tumor. Successful treatment of a glucagon-secreting tumor is associated with normalization of glucagon levels.

Inappropriate elevations in glucagon levels in hyperglycemic type I diabetic patients indicate that paradoxical glucagon release may contribute to disease severity. This can be observed if insulin treatment is inadequate and patients are ketotic. However, glucagon measurement plays little, if any, role in the diagnostic workup of diabetic ketoacidosis, which is based on demonstrating significantly elevated plasma or serum glucose (>250 mg/dL), circulating ketones (beta-hydroxy butyrate), and acidosis (typically with increased anion gap).

In diabetic patients, low glucagon levels (undetectable or in the lower quartile of the normal range) in the presence of hypoglycemia indicate impairment of hypoglycemic counter-regulation. These patients may be particularly prone to recurrent hypoglycemia. This can be a permanent problem due to islet alpha-cell destruction or other, less well understood processes (eg, autonomous neuropathy). It can also be functional, most often due to over tight

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blood-glucose control, and may be reversible after decreasing insulin doses.

**Cautions**

Results obtained with different glucagon assays can differ substantially. This can be caused by use of different calibration standards. Different glucagon assays may also exhibit variable cross-reactivity with different isoforms of glucagon, not all of which are biologically active. Some assays, including this one, remove biologically inactive isoforms before measurement, while others do not. All these factors contribute to the differences between different assays. Therefore, serial measurements should always be performed using the same assay.

The heterogeneity of plasma glucagon is well established. It has at least 3 major components. In addition to the biologically active glucagon (MW 3500) and its possible precursor (MW 9000), there also is big plasma glucagon (BPG) of unknown biological significance. By using ethanol extraction, BPG (considered to be an interfering factor in the glucagon assay) is removed. Therefore, the assay measures only biologically active glucagon and its precursors.

Precise reference ranges for appropriate glucagon responses for given blood glucose ranges are not well established and vary widely from assay to assay. Expert advice should be sought when interpreting inappropriately low glucagon levels or when interpreting glucagon, insulin, and C-peptide levels obtained during mixed-meal testing.

Diabetics, obese subjects, acromegalics, and patients with Cushing syndrome have higher glucagon levels.

Tumor marker tests, including glucagon, are not specific for malignancy. All immunometric assays can, on rare occasions, be subject to hooking at extremely high analyte concentrations (false-low results), heterophilic antibody interference (false-high results), or autoantibody interference (unpredictable effects). If the laboratory result does not fit the clinical picture, these possibilities should be considered.

**Clinical Reference**

1. Tomassetti P, Migliori M, Lalli S, et al: Epidemiology, clinical features and diagnosis of gastroenteropancreatic endocrine tumours. *Ann Oncol.* 2001;12 Suppl 2:S95-99
2. Jhiang G, Zhang BB: Glucagon and regulation of glucose metabolism. *Am J Physiol Metab.* 2003;284:E671-E678
3. vanBeek AP, de Haas ER, van Vloten WA, et al: The glucagonoma syndrome and necrolytic migratory erythema: a clinical review. *Eu J Endocrinol.* 2004;151:531-537
4. [Cruz-Bautista I](#), [Lerman I](#), [Perez-Enriquez B](#), et al: Diagnostic challenge of glucagonoma: case report and literature review. *Endocr Pract.* 2006 Jul-Aug;12(4):422-426
5. Falconi M, Eriksson B, Kaltsas G, et al: [ENETS Consensus guidelines update for the management of patients with](#)

[functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors.](#)

Neuroendocrinology. 2016;103(2):2153-2171

## Performance

### Method Description

Big plasma glucagon (BPG), which is considered to be biologically inactive, is extracted using ethanol prior to assay of the specimen. Following ethanol extraction, glucagon reacts with an anti-glucagon antibody that is attached to magnetic beads. After incubation and washing, a second detection antibody is added and attaches to any bead-bound glucagon, forming a sandwich assay. A streptavidin-phycoerythrin (SPE) tag binds to the glucagon-antibody complex. Laser-based fluorescent analysis of the resulting glucagon-antibody-SPE complex is performed on the Luminex 200 instrument. (Package insert: Human Glucagon Magnetic Bead Kit, Millipore Sigma; Rev. 12/26/2018)

### PDF Report

No

### Specimen Retention Time

90 days

### Performing Laboratory Location

Rochester

## Fees & Codes

### 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 US Food and Drug Administration.

### CPT Code Information

82943

### LOINC® Information

Test ID	Test Order Name	Order LOINC Value
GLP	Glucagon, P	2338-2

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Result ID	Reporting Name	LOINC®
9358	Glucagon, P	2338-2