

**Overview****Useful For**

As part of the diagnostic workup of suspected insulinoma

As part of the diagnostic workup of patients with suspected prohormone convertases1/3 deficiency

As part of the diagnostic workup of patients with suspected proinsulin variations

**Method Name**

Electrochemiluminescent Assay

**NY State Available**

Yes

**Specimen****Specimen Type**

Plasma EDTA

**Specimen Required****Patient Preparation:**

1. Patient should be fasting for 8 hours.
2. Infants under 2 years of age should fast a maximum of 6 hours.

**Collection Container/Tube:** Ice-cooled, lavender top (EDTA)

**Submission Container/Tube:** Plastic vial

**Specimen Volume:** 0.5 mL

**Collection Instructions:** After collection, place the whole blood on ice for at least 10 minutes, then centrifuge at refrigerated temperature.

**Specimen Minimum Volume**

0.25 mL

**Reject Due To**

Gross hemolysis	Reject
Gross lipemia	OK
Gross icterus	OK

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Plasma EDTA	Frozen	30 days	

## Clinical and Interpretive

### Clinical Information

Proinsulin is the precursor of insulin and C-peptide (connecting peptide). Following synthesis, proinsulin is packaged into secretory granules, where it is processed to C-peptide and insulin by prohormone convertases (PC1/3 and PC2) and carboxypeptidase E. Only 1% to 3% of proinsulin is secreted intact. However, because proinsulin has a longer half-life than insulin, circulating proinsulin concentrations are in the range of 5% to 30% of circulating insulin concentrations on a molar basis, with the higher relative proportions seen after meals and in patients with insulin resistance or early type 2 diabetes. Proinsulin can bind to the insulin receptor and exhibits 5% to 10% of the metabolic activity of insulin.

Proinsulin levels might be elevated in patients with insulin-producing islet cell tumors (insulinomas). These patients suffer from hypoglycemic attacks due to inappropriate secretion of insulin by the tumors. The biochemical diagnosis rests primarily on demonstrating non-suppressed insulin levels in the presence of hypoglycemia (blood glucose <45 mg/dL). The diagnosis can be difficult, as tumors might be small or secrete insulin only episodically. Insulin injections or hypoglycemic drugs can also mimic insulinoma. Evaluation of these patients frequently requires a prolonged fast (72 hours), as well as supplementary tests in addition to insulin and glucose measurements, including a sulfonylurea screen, and measurement of C-peptide, proinsulin, and beta-hydroxybutyrate. The inappropriate oversecretion of insulin by insulinomas causes the release of an increased numbers of secretory granules with incompletely processed insulin, resulting in elevated serum/plasma proinsulin concentrations. This oversecretion of proinsulin in insulinomas is accentuated during fasting, when proinsulin normally does not account for more than 5% of the insulin concentrations.

Proinsulin is strikingly elevated in PC1/3 deficiency. These patients have defects in the processing of multiple peptide hormones and suffer from diabetes, adrenal insufficiency, infertility, and obesity. Affected individuals typically have red hair regardless of racial background. Variants in the proinsulin molecule have been reported that affect PC cleavage efficiency or subsequent proinsulin metabolism. These variants can also lead to markedly elevated proinsulin levels, but are usually not accompanied by diabetes, or any other hormonal abnormalities.

### Reference Values

3.6-22 pmol/L

### Interpretation

Normal individuals will have proinsulin concentrations below the upper limit of the normal fasting reference range (22 pmol/L) when hypoglycemic (blood glucose <60 mg/dL). Conversely, most (>80%) insulinoma patients will have proinsulin concentrations above the upper limit of the reference range. The sensitivity and specificity for a diagnosis of insulinoma during hypoglycemia are approximately 75% and near 100%, respectively, at the 22 pmol/L cutoff. A higher sensitivity (>95%) can be achieved using a 5 pmol/L cutoff, and this is the cutoff recommended by Mayo Clinic's highly experienced hypoglycemia team to avoid missing cases. However, the lower cutoff results in a reduced specificity (approximately 40%), emphasizing the need for a combination of different tests to assure accurate biochemical diagnosis.

Patients with PC1/3 deficiency have low, or sometimes undetectable, insulin levels and substantially elevated proinsulin levels, exceeding the upper limit of the reference range substantially in the fasting state and rising even higher after food intake. Many other hormonal abnormalities are also present, including cortisol deficiency (because of lack of processing of pro-opiomelanocortin to adrenocorticotrophic hormone and other peptides), infertility, and,

often, obesity.

### Cautions

To avoid misdiagnoses, all proinsulin measurements used in the diagnostic workup of patients with hypoglycemia must be interpreted in the context of coexisting illnesses, blood glucose concentration at the time of sampling, and other tests, namely, insulin, C-peptide, beta-hydroxybutyrate measurements, and a sulfonylurea drug screen. Patients with chronic renal failure and type II diabetes mellitus can have increased proinsulin, C-peptide, and insulin values, but usually without suppressed (<45 mg/dL) blood glucose.

### Clinical Reference

1. Murtha TD, Lupsa BC, Majumdar S, et al: A Systematic Review of Proinsulin-Secreting Pancreatic Neuroendocrine Tumors. *J Gastrointest Surg* 2017 Aug;21(8):1335-1341
2. Placzkowski KA, Vella A, Thompson GB, et al: Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. *J Clin Endocrinol Metab* 2009 Apr;94(4):1069-1073
3. Vezzosi D, Bennet A., Fauvel J, Caron P: Insulin, C-peptide and proinsulin for the biochemical diagnosis of hypoglycemia related to endogenous hyperinsulinism. *Eur J Endocrinol* 2007;157(1):75-83
4. Service FJ: Hypoglycemic disorders. *N Engl J Med* 1995;322(17):1144-1152
5. Steiner DF: The proprotein convertases. *Cur Opin Chem Biol* 1998;2(1):31-39

### Performance

#### Method Description

Sequential 2-site electrochemiluminescent immunoassay performed on the MesoScale Discovery instrument. The assay uses a monoclonal biotinylated anti-insulin capture antibody and an anti-C-peptide detection antibody labeled with SULFO-TAG. The signal is directly proportional to the amount of proinsulin in the sample. Assay calibration is traceable to the WHO 1st International Standard for human Proinsulin NIBSC code: 09/296. This assay demonstrates no cross-reactivity with insulin or C-peptide.(Unpublished Mayo method)

#### PDF Report

No

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

Varies

#### Analytic Time

1 day

#### Maximum Laboratory Time

6 days

#### Specimen Retention Time

3 months

#### Performing Laboratory Location

Rochester

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**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**

84206

**LOINC® Information**

Test ID	Test Order Name	Order LOINC Value
PINS	Proinsulin, P	27882-0

Result ID	Test Result Name	Result LOINC Value
80908	Proinsulin, P	27882-0