MAYO CLINIC LABORATORIES

# Test Definition: PMET

Metanephrines, Fractionated, Free, Plasma

## Overview

### Useful For

Screening test for presumptive diagnosis of catecholamine-secreting pheochromocytomas or paragangliomas

### Method Name

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

### NY State Available

Yes

## Specimen

### Specimen Type

Plasma EDTA

### Specimen Required

**Patient Preparation:** Use of an Epi-pen within the last 7 days may produce inaccurate results.
**Supplies:** Sarstedt Aliquot Tube, 5 mL (T914)
**Collection Container/Tube:** Lavender top (EDTA)
**Submission Container/Tube:** Plastic vial
**Specimen Volume:** 1 mL
**Collection Instructions:** Within 2 hours of collection centrifuge and aliquot plasma into a plastic vial.

### Forms

If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
-General Request (T239)
-Oncology Test Request (T729)
-Renal Diagnostics Test Request (T830)

### Specimen Minimum Volume

0.3 mL

### Reject Due To

| | |
|---|---|
| Gross hemolysis | OK |
| Gross lipemia | OK |
| Gross icterus | OK |

### Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---|---|---|---|
| Plasma EDTA | Frozen (preferred) | 28 days | |
| | Ambient | 7 days | |
| | Refrigerated | 14 days | |

## Clinical & Interpretive

### Clinical Information

Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating ("spells"). Patients with pheochromocytoma may also be asymptomatic and present with sustained hypertension or an incidentally discovered adrenal mass.

Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine, norepinephrine, and dopamine). Metanephrine and normetanephrine (collectively referred to as metanephrines) are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. The metanephrines are stable metabolites and are cosecreted directly with catecholamines by pheochromocytomas and other neural crest tumors. This results in sustained elevations in plasma free metanephrine levels, making them more sensitive and specific than plasma catecholamines in the identification of pheochromocytoma patients.(1) Metanephrine and normetanephrine are both further metabolized to conjugated metanephrines and vanillylmandelic acid.

### Reference Values

METANEPHRINE, FREE
<0.50 nmol/L

NORMETANEPHRINE, FREE
<0.90 nmol/L

### Interpretation

In the normal population, plasma metanephrine and normetanephrine levels are low, but in patients with pheochromocytoma or paragangliomas, the concentrations may be significantly elevated. This is due to the relatively long half-life of these compounds, ongoing secretion by the tumors and, to a lesser degree, peripheral conversion of tumor-secreted catecholamines into metanephrines.

Measurement of plasma free metanephrines appears to be the best test for excluding pheochromocytoma. The test's sensitivity approaches 100%, making it extremely unlikely that individuals with normal plasma metanephrine and normetanephrine levels suffer from pheochromocytoma or paraganglioma.(1,2)

Due to the low prevalence of pheochromocytomas and related tumors (<1:100,000), it is recommended to confirm elevated plasma free metanephrines with a second, different testing strategy in order to avoid large numbers of false-positive test results.(3) The recommended second-line test is measurement of fractionated 24-hour urinary metanephrines (METAF / Metanephrines, Fractionated, 24 Hour, Urine). In most cases this strategy will suffice in confirming or excluding the diagnosis. Occasionally, it will be necessary to extend this approach if there is a very high

clinical index of suspicion or if test results are nonconclusive. In these cases, repeat plasma and urinary metanephrines testing, additional measurement of plasma or urinary catecholamines, or imaging procedures might be indicated.

Elevated results are reported with appropriate comments.

## Cautions

While most circulating metanephrines are derived directly from adrenal secretion, peripheral conversion of catecholamines makes a small contribution. Therefore, substances that increase endogenous catecholamine levels can result in borderline elevations of plasma metanephrines. These include:
-Monoamine oxidase inhibitors (MAOI-a class of antidepressants with marked effects on catecholamine levels, particularly if the patient consumes tyrosine-rich foods such as nuts, bananas, or cheese)
-Catecholamine reuptake inhibitors including cocaine and synthetic cocaine derivatives such as many local anesthetics, some of which also are antiarrhythmic drugs (eg, lidocaine)
-Some anesthetic gases, particularly halothane
-Withdrawal from sedative drugs, medical or recreational, particularly alcohol, benzodiazepines (eg, Valium), opioids, and some central acting antihypertensive drugs, particularly clonidine, but generally not cannabis or other hallucinogens such as lysergic acid diethylamide, mescal, or peyote

The observed elevations of plasma metanephrines are usually minor.

We are currently not aware of any substances that interfere directly with the assay.

Artifactually decreased plasma metanephrine levels may be observed when patients are already receiving metyrosine treatment. This drug may be administered in suspected or confirmed cases of pheochromocytoma while awaiting definitive treatment. It inhibits tyrosine hydroxylase, the enzyme that catalyzes the first step in catecholamine synthesis.

## Supportive Data

This liquid chromatography tandem mass spectrometry (LC-MS/MS) method replaces the in-house high-performance liquid chromatography with electrochemical detection (HPLC-EC) method. The HPLC-EC method was labor intensive, with a complicated extraction and lengthy run time, and was prone to interferences. The LC-MS/MS method correlates well with Mayo Clinic Laboratories previously performed HPLC-EC method: N=92, slope=0.87, intercept=0.05, r(2)=0.95. The reference ranges remain the same as the HPLC-EC method and were validated by method comparison between these methods. LC-MS/MS also correlates with the National Institutes of Health's HPLC-EC method.

## Clinical Reference

1. Eisenhofer G. Free or total metanephrines for diagnosis of pheochromocytoma: what is the difference? Clin Chem. 2001;47(6):988-989
2. Lenders JW, Pacek K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA. 2002;287(11):1427-1434
3. Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared to the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab. 2003;88(2):553-558
4. Algeciras-Schimnich A, Preissner CM, Young WF Jr, et al. Plasma chromogranin A or urine fractionated metanephrines follow-up testing improves the diagnostic accuracy of plasma fractionated metanephrines for pheochromocytoma. J Clin Endocrinol Metab. 2008;93(1):91-95. doi:10.1210/jc.2007-1354
5. Eisenhofer G, Deutschbein T, Constantinescu G, et al. Plasma metanephrines and prospective prediction of tumor

location, size and mutation type in patients with pheochromocytoma and paraganglioma. Clin Chem Lab Med. 2020;59(2):353-363. doi:10.1515/cclm-2020-0904
6. Taylor RL, Singh RJ. Validation of liquid chromatography-tandem mass spectrometry method for analysis of urinary conjugated metanephrine and normetanephrine for screening of pheochromocytoma. Clin Chem 2002;48(3):533-539

## Performance

### Method Description
Free metanephrine (MN) and normetanephrine (NMN) are extracted from plasma using solid phase extraction. The concentrated eluate is analyzed using liquid chromatography tandem mass spectrometry and quantified using stable isotope labeled internal standards, d3-MN and d3-NMN . Analytes and internal standards are ionized using electro spray ionization and are detected in the multiple reaction-monitoring mode. The specific transitions for MN, NMN, d3-MN, and d3-NMN are m/z 180.2 to m/z 148.2, 166.2 to m/z 134.2, 183.2 to m/z 151.2, and m/z 169.2 to m/z 137.2, respectively.(Unpublished Mayo method)

### PDF Report
No

### Day(s) Performed
Monday through Saturday

### Report Available
2 to 5 days

### Specimen Retention Time
2 weeks

### Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Superior Drive

## 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

83835

## LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| PMET | Metanephrines, Fract., Free, P | 57772-6 |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| 10140 | Normetanephrine, Free | 40851-8 |
| 10139 | Metanephrine, Free | 49700-8 |