

Overview

Useful For

A second-order screening test for the presumptive diagnosis of pheochromocytoma in patients with non-episodic hypertension

Confirming positive plasma metanephrine results in patients with non-episodic hypertension

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
METAU	Metanephrines, Fractionated, U	No	Yes
CRETR	Creatinine, Random, U	Yes, (Order RCTUR)	Yes

Method Name

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

CRETR: Enzymatic Colorimetric Assay

NY State Available

Yes

Specimen

Specimen Type

Urine

Specimen Required

Patient Preparation:

- For at least 48 hours prior to test, patient should avoid use of cold medicines, nose drops, and nasal sprays.
- Patients taking tricyclic antidepressants and labetalol and sotalol (beta blockers) may have falsely elevated levels of metanephrines. If medically feasible, for at least 1 week before specimen collection, the patient should not take these medications.

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

**Collection Container/Tube:** Clean, plastic urine collection container

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

**Specimen Volume:** 10 mL

Collection Instructions:

- Collect a random urine specimen.
- No preservative.

Forms

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

Specimen Minimum Volume

3 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Urine	Refrigerated (preferred)	28 days	
	Ambient	14 days	
	Frozen	28 days	

Clinical & Interpretive

Clinical Information

Pheochromocytoma is a rare, potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating ("spells").

Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine and norepinephrine).

Metanephrine and normetanephrine are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. Both are further metabolized to vanillylmandelic acid.

Pheochromocytoma cells are also able to oxymethylate catecholamines into metanephrines that are secreted into circulation.

Reference Values

METANEPHRINE/CREATININE

Normotensives

- 0-2 years: 82-418 mcg/g creatinine
- 3-8 years: 65-332 mcg/g creatinine
- 9-12 years: 41-209 mcg/g creatinine
- 13-17 years: 30-154 mcg/g creatinine
- > or =18 years: 29-158 mcg/g creatinine

NORMETANEPHRINE/CREATININE

Males

Normotensives

- 0-2 years: 121-946 mcg/g creatinine

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3-8 years: 92-718 mcg/g creatinine  
9-12 years: 53-413 mcg/g creatinine  
13-17 years: 37-286 mcg/g creatinine  
18-29 years: 53-190 mcg/g creatinine  
30-39 years: 60-216 mcg/g creatinine  
40-49 years: 69-247 mcg/g creatinine  
50-59 years: 78-282 mcg/g creatinine  
60-69 years: 89-322 mcg/g creatinine  
> or =70 years: 102-367 mcg/g creatinine

Females

Normotensives

0-2 years: 121-946 mcg/g creatinine  
3-8 years: 92-718 mcg/g creatinine  
9-12 years: 53-413 mcg/g creatinine  
13-17 years: 37-286 mcg/g creatinine  
18-29 years: 81-330 mcg/g creatinine  
30-39 years: 93-379 mcg/g creatinine  
40-49 years: 107-436 mcg/g creatinine  
50-59 years: 122-500 mcg/g creatinine  
60-69 years: 141-574 mcg/g creatinine  
> or =70 years: 161-659 mcg/g creatinine

TOTAL METANEPHRINE/CREATININE

Males

Normotensives

0-2 years: 241-1,272 mcg/g creatinine  
3-8 years: 186-980 mcg/g creatinine  
9-12 years: 110-582 mcg/g creatinine  
13-17 years: 78-412 mcg/g creatinine  
18-29 years: 96-286 mcg/g creatinine  
30-39 years: 106-316 mcg/g creatinine  
40-49 years: 117-349 mcg/g creatinine  
50-59 years: 130-386 mcg/g creatinine  
60-69 years: 143-427 mcg/g creatinine  
> or =70 years: 159-472 mcg/g creatinine

Females

Normotensives

0-2 years: 241-1,272 mcg/g creatinine  
3-8 years: 186-980 mcg/g creatinine  
9-12 years: 110-582 mcg/g creatinine  
13-17 years: 78-412 mcg/g creatinine  
18-29 years: 131-467 mcg/g creatinine  
30-39 years: 147-523 mcg/g creatinine

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40-49 years: 164-585 mcg/g creatinine  
50-59 years: 184-655 mcg/g creatinine  
60-69 years: 206-733 mcg/g creatinine  
> or =70 years: 230-821 mcg/g creatinine

**Interpretation**

Increased metanephrine and normetanephrine levels are found in patients with pheochromocytoma and tumors derived from neural crest cells.

Increased urine metanephrines can be detected in non-pheochromocytoma hypertensive patients; quantification may help distinguish these patients from those with tumor-induced symptoms.

**Cautions**

While screening for pheochromocytoma is best accomplished by measuring free fractionated metanephrines in plasma (a more sensitive assay), follow-up testing with urinary fractionated metanephrines (a more specific assay) may identify false-positive results. Twenty-four-hour urine collections are preferred, especially for patients with episodic hypertension; ideally the collection should begin at the onset of a "spell."

This test utilizes a liquid chromatography tandem mass spectrometry method and is not affected by the interfering substances that affected the previously utilized spectrophotometric (Pisano reaction) method (ie, diatrizoate, chlorpromazine, hydrazine derivatives, imipramine, monoamine oxidase inhibitors [MAOI], methyldopa, phenacetin, ephedrine, or epinephrine).

This method is also not subject to the known interference of acetaminophen, which is seen with the plasma metanephrine test using high-performance liquid chromatography with electrochemical detection.

When N-acetylcysteine is administered at levels sufficient to act as an antidote for the treatment of acetaminophen overdose, it may lead to falsely decreased creatinine results.

**Clinical Reference**

1. van Duinen N, Corssmit EPM, de Jong WHA, Brookman D, Kema P, Romijn JA. Plasma levels of free metanephrines and 3-methoxytyramine indicate a higher number of biochemically active HNPGL than 24-h urinary excretion rates of catecholamines and metabolites. *Eur J Endocrinol.* 2013;169(3):377-382 doi:10.1530/EJE-13-0529
2. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. *Ann Intern Med.* 2001;134(4):315-329
3. Sawka AM, Singh RJ, Young WF Jr. False positive biochemical testing for pheochromocytoma caused by surreptitious catecholamine addition to urine. *Endocrinologist.* 2001;11:421-423
4. Eisenhofer G, Grebe S, Cheung NKV. Monoamine-producing tumors. In: Rifai N, Horvath AR, Wittwer CT, eds. *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics.* 6th ed. Elsevier; 2018:1421
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6. Hernandez FC, Sanchez M, Alvarez A, et al. A five-year report on experience in the detection of pheochromocytoma. *Clin Biochem.* 2000;33(8):649-55. doi:10.1016/s0009-9120(00)00172-7
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8. Le Jacques A, Abalain JH, Le Saos F, Carre JL. Significance of 3-methoxytyramine urine measurement in the diagnosis of pheochromocytomas and paragangliomas: about 28 patients. *Ann Biol Clin (Paris)*. 2011;69(5):555-9. French. doi:10.1684/abc.2011.0612
9. Muskiet FA, Thomasson CG, Gerding AM, Fremouw-Ottevangers DC, Nagel GT, Wolthers BG. Determination of catecholamines and their 3-O-methylated metabolites in urine by mass fragmentography with use of deuterated internal standards. *Clin Chem*. 1979;25(3):453-60
10. Hirsch D, Grossman A, Nadler V, Alboim S, Tsvetov G. Pheochromocytoma: Positive predictive values of mildly elevated urinary fractionated metanephrines in a large cohort of community-dwelling patients. *J Clin Hypertens (Greenwich)*. 2019;21(10):1527-1533. doi:10.1111/jch.13657

## Performance

### Method Description

Urinary metanephrines are determined by liquid chromatography tandem mass spectrometry (LC-MS/MS). Urinary metanephrines occur largely in conjugated form. After urine samples are acidified and hydrolyzed in a heat block, metanephrine and normetanephrine are extracted from the specimens utilizing extraction cartridges. The metanephrine, normetanephrine, and 3-methoxytyramine (3MT) are eluted from the cartridge and analyzed by LC/MS/MS using multiple reaction monitoring in positive mode. Deuterated metanephrine (d3-metanephrine), deuterated normetanephrine (d3-normetanephrine), and deuterated 3MT (d4-3MT) are added prior to the hydrolysis as internal standards. The metanephrine, normetanephrine, and 3-MT concentrations are quantified using ratios of the peak areas to deuterium labeled internal standards by LC-MS/MS. (Unpublished Mayo method)

### Creatinine:

The enzymatic method is based on the determination of sarcosine from creatinine with the aid of creatininase, creatinase, and sarcosine oxidase. The liberated hydrogen peroxide is measured via a modified Trinder reaction using a colorimetric indicator. Optimization of the buffer system and the colorimetric indicator enables the creatinine concentration to be quantified both precisely and specifically. (Package insert: Creatinine plus ver 2. Roche Diagnostics; V15.0, 03/2019)

### PDF Report

No

### Day(s) Performed

Monday through Friday

### Report Available

3 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

82570

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
METRN	Metanephrintest, Fractionated, Random, U	68317-7

Result ID	Test Result Name	Result LOINC® Value
21546	Metanephrintest/Creatinine	9645-3
21547	Normetanephrintest/Creatinine	13783-6
21548	Total Metanephrintest/Creatinine	13771-1
CRETR	Creatinine, Random, U	2161-8