Test Definition: META3

Metanephrines with 3-Methoxytyramine, 24 Hour, Urine

Overview

Useful For

A first- and second-tier screening test for the presumptive diagnosis of catecholamine-secreting pheochromocytomas and paragangliomas

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
3MT1	3-Methoxytyramine, U	Yes, (Order 3MT)	Yes
METAF	Metanephrines, Fractionated, 24h, U	Yes	Yes

Special Instructions

- Urine Preservatives-Collection and Transportation for 24-Hour Urine Specimens

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Urine

Necessary Information

24-Hour volume (in milliliters) is required.

Specimen Required

Patient Preparation: Tricyclic antidepressants, labetalol, and sotalol medications may elevate levels of metanephrines producing results that cannot be interpreted. If clinically feasible, it is optimal to discontinue these medications at least 1 week before collection. For advice on assessing the risk of removing patients from these medications and alternatives, consider consultation with a specialist in endocrinology or hypertension.
Supplies: Urine Tubes, 10 mL (T068)
Submission Container/Tube: Plastic urine tube
Specimen Volume: 10 mL
Collection Instructions:

1. Complete 24-hour urine collections are preferred, especially for patients with episodic hypertension; ideally the collection should begin at the onset of a "spell."
2. Add 10 g (pediatric: 3 g) of boric acid or 25 mL (pediatric: 15 mL) of 50% acetic acid as preservative **at start of collection**.
3. Collect urine for 24 hours.

Additional Information: See Urine Preservatives-Collection and Transportation for 24-Hour Urine Specimens for multiple collections.

Urine Preservative Collection Options

Note: Preservatives must be added or temperature controls applied at the start of the collection.

Ambient (no additive)	OK
Refrigerate (no additive)	OK
Frozen (no additive)	OK
50% Acetic Acid	Preferred
Boric Acid	Preferred
Diazolidinyl Urea	No
6M Hydrochloric Acid	OK
6M Nitric Acid	No
Sodium Carbonate	OK
Toluene	OK

Specimen Minimum Volume

4 mL

Reject Due To

Gross hemolysis	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Urine	Refrigerated (preferred)	28 days	
	Ambient	21 days	
	Frozen	28 days	

Clinical & Interpretive

Clinical Information

Pheochromocytomas and paragangliomas (Pheo/PGL) are rare, usually benign, tumors of chromaffin cells in the adrenal

medulla or paragangliomas (estimated population prevalence rates of 1 in 200,000 with a yearly incidence rate of 1-2/1000) that are potentially lethal because they secrete excessive, uncontrolled amounts of catecholamines (dopamine, epinephrine, and norepinephrine), resulting in often severe hypertension and many cardiac abnormalities. A subgroup of these patients will also suffer tumor recurrence and sometimes malignant behavior. Untreated, these tumors have substantial morbidity and mortality.

Key symptoms are episodes of hypertension with palpitations, severe headaches, and sweating (spells). However, some patients might be asymptomatic, have mild symptoms that might be missed, or have sustained hypertension, which is frequently observed in these patients. Finally, due to the high frequency of medical imaging for unrelated ailments, increasing numbers of occult small adrenal tumors are often incidentally discovered, some of which might be Pheo/PGLs.

3-Methoxytyramine (3MT), metanephrine, and normetanephrine are the metabolites of dopamine, epinephrine, and norepinephrine, respectively. These metabolites are further metabolized to vanillylmandelic acid. Pheochromocytoma cells also have the ability to oxymethylate catecholamines into metanephrines, which are secreted into circulation and urine. 3MT is only elevated in a small proportion of patients with Pheo/PGL. Because of its low levels testing is performed using only 24-hour urine specimens at this time, while epinephrine, and norepinephrine can be measured in plasma or 24-hour urine specimens.

An early childhood malignancy that arises from immature neuroendocrines in the adrenals, called neuroblastoma, shares many features of Pheo/PGL but has the added threat of a high malignancy rate; however, there are also frequent spontaneous remissions, particular in very young infants.

Biochemical testing for neuroblastoma differs from Pheo/PGL because of many specific issues in testing infants and young children, using urine tests rather than blood tests.

For all Pheo/PGL, the preferred initial testing is by plasma metanephrine testing, as it has the highest clinical sensitivity thus facilitating ruling out Pheo/PGL, if the test results are within the healthy population reference range. However, in potential familial cases or monitoring of treated patients, some additional and repeated testing may be required.

Testing for 24-hour urine metanephrine plus urinary catecholamine levels may be used as a confirmatory study in patients with less than a 2-fold elevation in plasma free fractionated catecholamines. This is highly desirable, as the very low population incidence rate of Pheo/PGL (<1:200,000 population per year) will otherwise result in large numbers of unnecessary, costly, and sometimes risky imaging procedures.

Finally, familial Pheo/PGL probably accounts for a higher proportion of cases than previously thought; at least 30% are now believed to be familial. The corollary of this is that about 20 to 30 seemingly sporadic cases are likely familial. Given these statistics, genetic testing for index cases and family members should be considered.

Treatment consists of surgical tumor removal after pharmaceutical alpha-adrenergic blockade, which may be supplemented with beta blockade once the alpha blockade has been established. The aim of this preparation is to prevent massive catecholamine surges during surgery.

Reference Values

3-METHOXYTYRAMINE:
Males: < or =306 mcg/24 h
Females: < or =242 mcg/24 h

METANEPHRINE:
Males
Normotensives
3-8 years: 29-92 mcg/24 h
9-12 years: 59-188 mcg/24 h
13-17 years: 69-221 mcg/24 h
> or =18 years: 44-261 mcg/24 h
Reference values have not been established for patients younger than 36 months.

Hypertensives: <400 mcg/24 h

Females
Normotensives
3-8 years: 18-144 mcg/24 h
9-12 years: 43-122 mcg/24 h
13-17 years: 33-185 mcg/24 h
> or =18 years: 30-180 mcg/24 h
Reference values have not been established for patients younger than 36 months.

Hypertensives: <400 mcg/24 h

NORMETANEPHRINE:
Males
Normotensives
3-8 years: 34-169 mcg/24 h
9-12 years: 84-422 mcg/24 h
13-17 years: 91-456 mcg/24 h
18-29 years: 103-390 mcg/24 h
30-39 years: 111-419 mcg/24 h
40-49 years: 119-451 mcg/24 h
50-59 years: 128-484 mcg/24 h
60-69 years: 138-521 mcg/24 h
> or =70 years: 148-560 mcg/24 h
Reference values have not been established for patients younger than 36 months.

Hypertensives: <900 mcg/24 h

Females
Normotensives
3-8 years: 29-145 mcg/24 h

9-12 years: 55-277 mcg/24 h
13-17 years: 57-286 mcg/24 h
18-29 years: 103-390 mcg/24 h
30-39 years: 111-419 mcg/24 h
40-49 years: 119-451 mcg/24 h
50-59 years: 128-484 mcg/24 h
60-69 years: 138-521 mcg/24 h
> or =70 years: 148-560 mcg/24 h
Reference values have not been established for patients younger than 36 months.

Hypertensives: <900 mcg/24 h

TOTAL METANEPHRINE:
Males
Normotensives
3-8 years: 47-223 mcg/24 h
9-12 years: 201-528 mcg/24 h
13-17 years: 120-603 mcg/24 h
18-29 years: 190-583 mcg/24 h
30-39 years: 200-614 mcg/24 h
40-49 years: 211-646 mcg/24 h
50-59 years: 222-680 mcg/24 h
60-69 years: 233-716 mcg/24 h
> or =70 years: 246-753 mcg/24 h
Reference values have not been established for patients younger than 36 months.

Hypertensives: <1300 mcg/24 h

Females
Normotensives
3-8 years: 57-210 mcg/24 h
9-12 years: 107-394 mcg/24 h
13-17 years: 113-414 mcg/24 h
18-29 years: 142-510 mcg/24 h
30-39 years: 149-535 mcg/24 h
40-49 years: 156-561 mcg/24 h
50-59 years: 164-555 mcg/24 h
60-69 years: 171-616 mcg/24 h
> or =70 years: 180-646 mcg/24 h
Reference values have not been established for patients younger than 36 months.

Hypertensives: <1300 mcg/24 h

For International System of Units (SI) conversion for Reference Values, see

www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Interpretation

Further clinical investigation (eg, radiographic studies) and genetic studies might be warranted in patients whose 3-methoxytyramine (3MT), metanephrine, or normetanephrine are elevated or when there is a very high clinical index of suspicion.

Increased 3MT levels are found in patients with pheochromocytoma and dopamine-secreting tumors.

3-Methoxytyramine levels of 306 mcg/24 h or less in male patients and 242 mcg/24 h or less in female patients can be detected in non-pheochromocytoma hypertensive patients.

Cautions

Tricyclic antidepressants, labetalol, and sotalol medications may elevate levels of metanephrines producing results that cannot be interpreted. If clinically feasible, it is optimal to discontinue these medications at least 1 week before collection.

This test utilizes a liquid chromatography tandem mass spectrometry method and is not affected by the interfering substances that affected older spectrophotometric (Pisano reaction) methods (ie, diatrizoate, chlorpromazine, hydrazine derivatives, imipramine, monoamine oxidase inhibitors, methyldopa, phenacetin, ephedrine, or epinephrine) or high-performance liquid chromatography methods (acetaminophen).

Clinical Reference

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2. 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.
3. Roden M, Raffesberg W, Raber W, et al. Quantification of unconjugated metanephrines in human plasma without interference by acetaminophen. Clin Chem. 2001;47(6):1061-1067
4. Sawka AM, Singh RJ, Young WF Jr. False positive biochemical testing for pheochromocytoma caused by surreptitious catecholamine addition to urine. The Endocrinologist. 2001;11(5):421-423
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6. Le Jacques A, Abalain JH, Le Saos F, Carre JL. Interet du dosage urinaire de la 3-methoxytyramine dans le diagnostic des pheochromocytomes et paragangliomes: a propos de 28 cas [Significance of 3-methoxytyramine urine measurement in the diagnosis of pheochromocytomas and paragangliomas: about 28 patients]. Ann Biol Clin (Paris). 2011;69(5):555-559. doi:10.1684/abc.2011.0612
7. Lam L, Woollard GA, Teague L, Davidson JS. Clinical validation of urine 3-methoxytyramine as a biomarker of neuroblastoma and comparison with other catecholamine-related biomarkers. Ann Clin Biochem. 2017;54(2):264-272
8. 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
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Performance

Method Description
Urine samples are acidified and hydrolyzed in a heat block, then metanephrine and normetanephrine are extracted from the specimens utilizing extraction cartridges. Analyte concentrations are determined through analysis performed by a liquid chromatography tandem mass spectrometry method.(Unpublished Mayo method)

Urinary 3-methoxytyramine is determined by reverse-phase liquid chromatography tandem mass spectrometry with stable isotope dilution analysis.(Unpublished Mayo method)

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
82542
83835

Test Definition: META3

Metanephrines with 3-Methoxytyramine, 24 Hour, Urine

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
META3	Metanephrines with 3-MT, 24h, U	101400-0

Result ID	Test Result Name	Result LOINC® Value
8552	Metanephrine, U	104629-1
21545	Normetanephrine, U	104631-7
83006	Total Metanephrines, U	104630-9
TM50	Collection Duration (h)	13362-9
VL48	Volume (mL)	3167-4
2434	Comment	48767-8
609422	3-Methoxytyramine, U	32618-1