

# Plasma Metanephrines



Health  
Pathology

## Fact Sheet

### Test name

Metanephrine, normetanephrine, 3-methoxytyramine (3-MT).

### Test indication

Metanephrine, normetanephrine and 3-methoxytyramine (3-MT) are the O-methylated metabolites of the catecholamines adrenaline, noradrenaline and dopamine, respectively. They are produced by neuroendocrine tissue, including chromaffin cells of the adrenal medulla and sympathetic ganglia.

Measurement of plasma metanephrine, normetanephrine and 3-MT is recommended as a first line test for the diagnosis of pheochromocytoma and paraganglioma in adults.<sup>1</sup> Plasma 3-MT is superior to urinary dopamine and urinary 3-MT for the detection of dopamine-producing tumours.<sup>2</sup>

3-MT is a metabolite of dopamine. When measured in conjunction with plasma metanephrine and normetanephrine, 3-MT improves the diagnostic sensitivity for the diagnosis of pheochromocytoma and paraganglioma in specific circumstances:

- Patients with extra-adrenal disease
- Patients with recurrent disease post-surgery
- Patients with head and neck paraganglioma
- Patients with mutations in SDHB and SDHD tumour suppressor genes

In children, measurement of plasma normetanephrine and 3-MT appears to have superior diagnostic accuracy than urine homovanillic acid (HVA) and vanillylmandelic acid (VMA) in the diagnosis of neuroblastoma.<sup>3</sup>

### Specimen requirements

*Sample type:* Lithium heparin blood

*Minimum volume:* 0.5mL plasma (approx. 1mL whole blood)

#### *Collection requirements*

- Samples should be collected after an overnight fast
- **Supine collection is preferred.** The patient should be lying down for a minimum of 30 minutes before collection, and during collection.
- Consider withdrawing medications known to interfere with results (see below) if safe to do so.
- Stimulants such as caffeine should be avoided.
- Please indicate collection posture and fasting status on the request form
- The sample should be put on ice after collection

#### *Transport*

- Send to the laboratory on ice
- Separate and freeze plasma within 6 hours of collection
- Transport plasma on dry ice

*Stability* Heparinised plasma is stable for 7 days at 4°C and up to 30 days at -20°C

## Test performance

*Method:* Liquid chromatography-mass spectrometry (LCMS/MS)

*Frequency of testing:* Once per week

## Decision limits

Plasma metanephrine	
>2 yrs	<447pmol/L

Plasma normetanephrine	
2-14 yrs	<540 pmol/L
14-20 yrs	<550 pmol/L
20-23 yrs	<560 pmol/L
23-26 yrs	<570 pmol/L
26-28 yrs	<580 pmol/L
28-30 yrs	<590 pmol/L
30-32 yrs	<600 pmol/L
32-34 yrs	<610 pmol/L
34-35 yrs	<620 pmol/L
35-36 yrs	<630 pmol/L
36-37 yrs	<640 pmol/L
37-39 yrs	<650 pmol/L
39-40 yrs	<660 pmol/L
40-41 yrs	<670 pmol/L
41-42 yrs	<680 pmol/L
42-43 yrs	<690 pmol/L
43-44 yrs	<700 pmol/L
44-45 yrs	<720 pmol/L
45-46 yrs	<730 pmol/L

Plasma normetanephrine (cont)	
46-47yrs	<740 pmol/L
47-48yrs	<760 pmol/L
48-49 yrs	<770 pmol/L
49-50yrs	<780 pmol/L
50-51yrs	<800 pmol/L
51-52yrs	<820 pmol/L
52-53yrs	<830 pmol/L
53-54yrs	<850 pmol/L
54-55yrs	<870 pmol/L
55-56yrs	<890 pmol/L
56-57yrs	<900 pmol/L
57-58yrs	<920 pmol/L
58-59yrs	<940 pmol/L
59-60yrs	<970 pmol/L
60-61yrs	<990 pmol/L
61-62yrs	<1010 pmol/L
62-63yrs	<1030 pmol/L
63-64yrs	<1060 pmol/L
>64 yrs	<1080 pmol/L

Plasma 3-methoxytyramine	
>2 yrs	<100 pmol/L

Decision limits for metanephrine and normetanephrine are sourced from a study of 1226 reference individuals.<sup>4</sup> These decision limits have been verified locally. The 3-MT decision limit is sourced from a study of 423 reference individuals.<sup>5</sup> The authors of the study demonstrated the appropriateness of the decision limit in a prospective examination of a second population.<sup>5</sup>

Decision limits for patients under the age of 2 years are not currently available. However, published data suggest that normetanephrine and 3-MT would be expected to be higher, and metanephrine would be expected to be lower in this age group.<sup>6</sup>

## Interpretation of results

The plasma test panel is designed to have a high diagnostic sensitivity so that there is a low probability of a tumour being missed. When samples are collected supine the panel has been shown to have a sensitivity of 98% and specificity of 94%.<sup>2</sup> Therefore, a negative result makes the above diagnoses very unlikely, although very small and/or non-functional tumours can be missed on occasion.

Despite the high specificity of the test, in practice false positive results are reasonably common. This is normally due to suboptimal collection conditions (see below).

## Potential causes of false positive results

### Posture

The reference intervals above are based on supine sampling, as is recommended for the diagnosis of pheochromocytoma, to maximise diagnostic sensitivity. Upright posture has a stimulating effect on the release of noradrenaline with metabolism to normetanephrine, meaning that decision limits established in seated patients are up to two-fold higher than when the patient is supine. Therefore if blood is collected from a seated patient, the chance of a false positive result is increased.

### Medications

Medications that block the neuronal uptake of catecholamines, including drugs used to treat depression, insomnia, neuropathic pain and other medical conditions, are a cause of false positive results which may need to be considered when interpreting results. Monoamine oxidase inhibitors block deamination pathways causing substantial increases in plasma and urinary metanephrines and so these medications should be withdrawn before testing, if possible. Sympathomimetics and stimulants, such as caffeine, also increase catecholamine release and are therefore best avoided before testing.

The following medications and drugs of abuse have been shown to interfere with one or more of the tests included in this panel:

- Tricyclic antidepressants
- Phenoxybenzamine
- Monoamine oxidase inhibitors
- Sympathomimetics (e.g. ephedrine)
- Dopamine analogues (e.g. L-DOPA) (*primarily interferes with measurement of 3-MT*)
- Cocaine
- Amphetamines

### Physiological stress

Physiological stress (e.g. recent illness, emotional upset) may activate the sympathoadrenal system resulting in increased release of catecholamines and production of metanephrines. Samples should be collected when the physiological stress has resolved.

A cold environment may also cause false positive results.

## Investigation of elevated results

- The nature and pattern of elevation should be considered when interpreting the results. False positives are common and the diagnostic cut-offs are designed to maximise sensitivity at the expense of specificity. Nonetheless, all elevated results should be followed up.
- A borderline-high result should be repeated in a supine position.
- Measurement of 24 hour urine metanephrines may also be helpful in these circumstances.
- Results obtained in a supine position which meet the following criteria have a higher likelihood of clinical significance and are more likely to represent a pheochromocytoma or paraganglioma:
  - Elevation of one metabolite  $\geq 2x$  the age-specific decision limit: this corresponded to a positive predictive value of 76%.<sup>2</sup>
  - Elevation of more than one metabolite above the decision limit (and by  $>2$ -fold for any one metabolite): the positive predictive value of the panel reaches 99% when two or more metabolites are elevated.

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