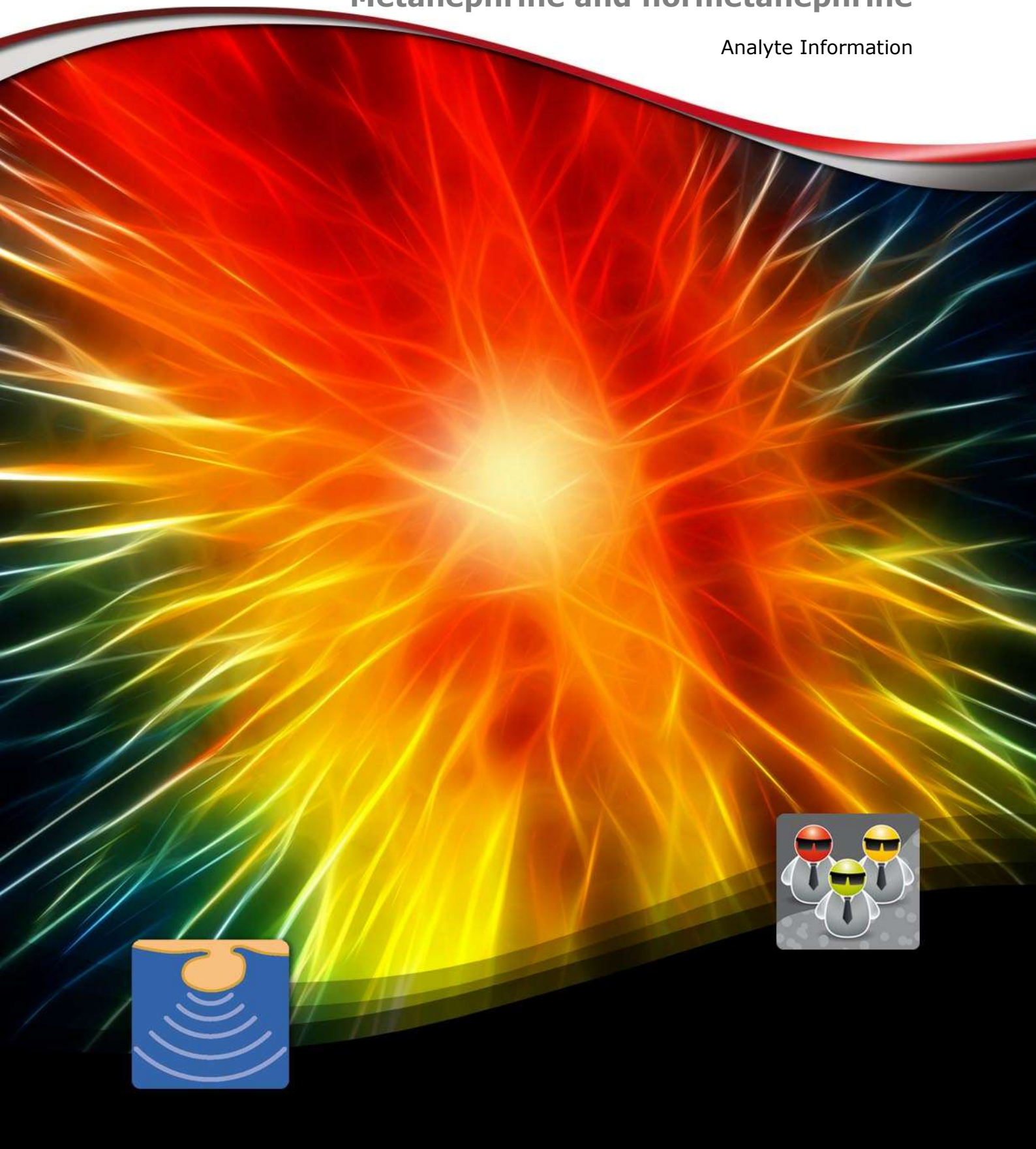
Adrenal Function

Metanephrine and normetanephrine

Analyte Information



Metanephrine and normetanephrine

Introduction

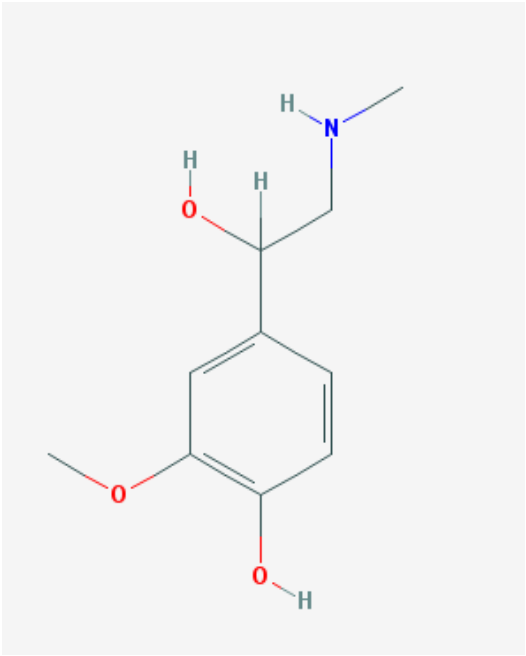
Metanephrine and normetanephrine (collectively referred to as metanephrines) are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively.

Epinephrine and norepinephrine are hormones called catecholamines that are released into the blood in response to physical or emotional stress and help regulate the flow and pressure of blood throughout the body. They also help to control many other body functions, such as heart rate and blood sugar.

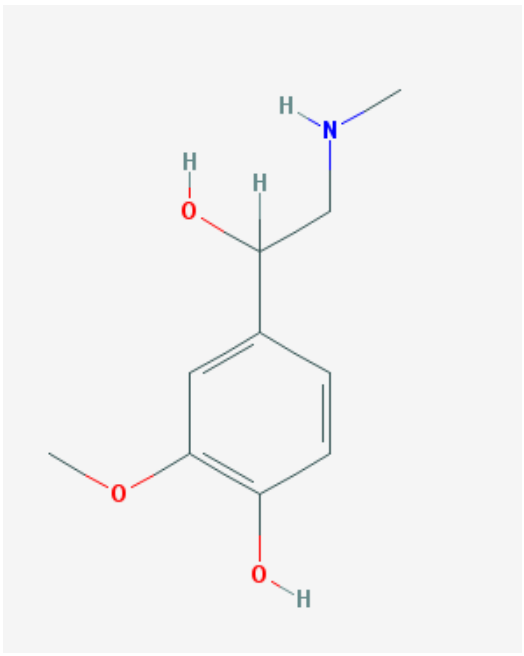
Increased metanephrine and normetanephrine levels are found in patients with pheochromocytoma and tumors derived from neural crest cells.

Metanephrine and normetanephrine are both further metabolized to vanillylmandelic acid all three compounds are excreted in urine.

Metanephrine, $C_{10}H_{15}NO_3$



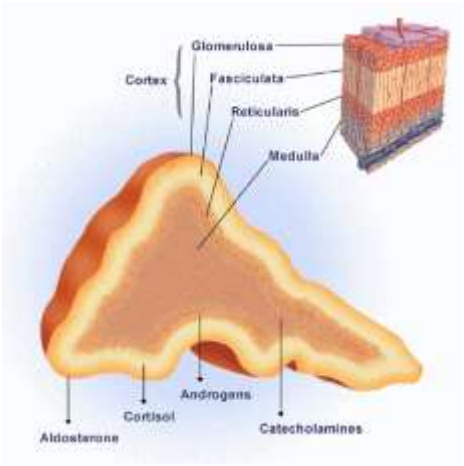
Normetanephrine, $C_9H_{13}NO_3$



Adrenal gland

The adrenal glands are small, bilateral structures that weigh approximately 4-5 g, regardless of age, weight or gender. Each gland consists of a yellow outer cortex, and a grey inner medulla (see Fig.1).

Fig.1: Structure of adrenal gland[1]



The catecholamines, such as dopamine, epinephrine and norepinephrine, are secreted in the medulla - inner portion of the adrenal gland and also in the sympathetic nervous system.

Norepinephrine and epinephrine trigger our body's fight-or-flight response to a perceived threat. The hormones prompt higher blood pressure, a faster heart rate and a boost in other body systems that enable us to react quickly.

The cortex forms the bulk of the adrenal gland and is responsible for the secretion of three types of hormones that possess a wide range of biological functions: the glucocorticoids, the mineralocorticoids and the adrenal sex hormones.

Adrenal cortical function is essential for life; total loss of it is fatal within 4 to 14 days if left untreated. This is not the case of medullary function, as dopamine, epinephrine and norepinephrine are also secreted by sympathetic nervous system.

Table 1: Adrenal synthetic products and primary functions in the body

Medulla		Catecholamines adrenaline (epinephrine) and noradrenaline (norepinephrine)	Response to stress (fight-or-flight response)
Cortex	Zona glomerulosa (outer)	Mineralocorticoids, mainly aldosterone	Long-term regulation of blood pressure
	Zona fasciculata	Glucocorticoids, mainly cortisol	Response to stress, influence on metabolism of proteins, carbohydrates and fats
	Zona reticularis (inner)	Androgens, mainly DHEA and DHEA-S	Androgen effects

Levels

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.

Elevated metanephrines levels are associated with the following disorders:

- pheochromocytoma
- paraganglioma

Decreased metanephrines levels may be observed:

- patients receiving metyrosine treatment (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)

Pheochromocytoma and paragaglioma

Pheochromocytoma (PCC) is a neuroendocrine tumor of the medulla of the adrenal glands (originating in the chromaffin cells).

While most chromaffin cells reside in the adrenal glands, small clusters of these cells are also in the heart, head, neck, bladder, back wall of the abdomen and along the spine. Tumors in these chromaffin cells are called paragangliomas and may result in the same effects on the body as in pheochromocytoma. Consequently, paragangliomas (often described as extra-adrenal pheochromocytomas) are closely related tumors to pheochromocytoma. They originate in the ganglia of the sympathetic nervous system and are named based upon the primary anatomical site of origin.

The causes of pheochromocytoma and paragaglioma are unknown.

A pheochromocytoma and paraganglioma result in the irregular and excessive release of these catecholamines, mostly norepinephrine, plus epinephrine to a lesser extent, and their metabolites.

Clinical application

The metanephrines are stable metabolites and are secreted 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

Recent studies and publications have shown that the quantification of plasma free Metanephrine and plasma free Normetanephrine is the most accurate biochemical marker for the clinical diagnosis of pheochromocytoma and follow-up of pheochromocytoma patients.

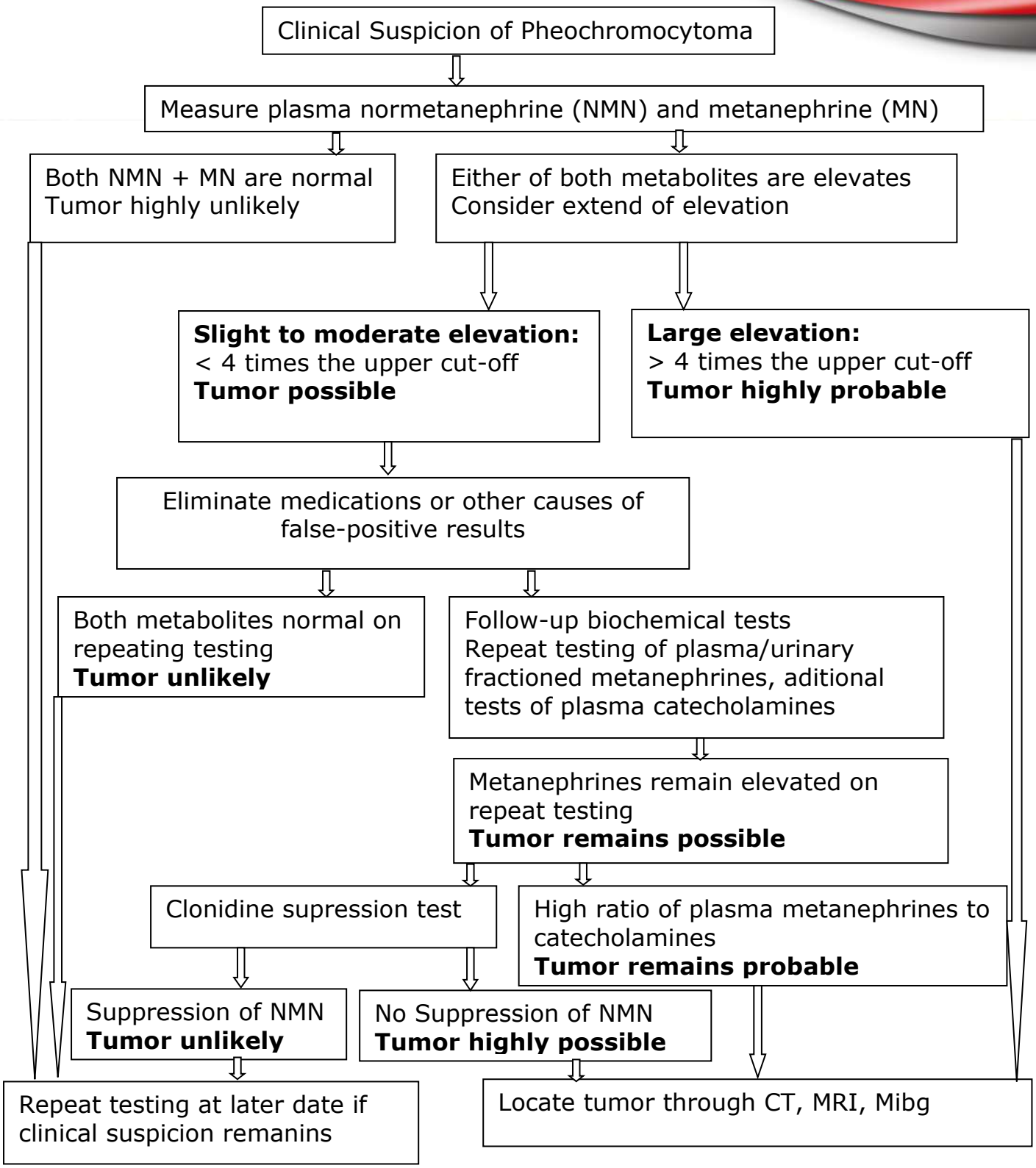
The test's sensitivity approaches 100%, making it extremely unlikely that individuals with normal plasma metanephrine and normetanephrine levels suffer from pheochromocytoma or paraganglioma[2,3].

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[4].

For the interpretation of the results, a grey area has to be considered. This grey area does not depend on the methodology used and is reflected in a slight to mediate increase in Metanephrine and Normetanephrine up to 4 times the upper cut-off[5]. Approx. 20 % of the tumors are found in this grey area, especially in the case of the Hereditary Syndrome, incidental tumors and in sporadic cases of Pheochromocytomas with a diameter less than 1 cm. In case of a result in the grey area, it is recommended to collect a new sample together with an anamnesis concerning especially influences like the medication and age of the patient.

The recommended second-line test is measurement 24-hour urinary metanephrines test. Patients with pheochromocytoma or other tumors derived from neuroendocrine cells show elevated urinary levels of total metanephrines. As catecholamine secretion from neuroendocrine cells show high variations, urine samples collected over a period of 24 hours are used to average these fluctuations.

Pheochromocytoma Diagnosis Decision Tree



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