East Kent Hospitals University NHS Foundation Trust

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Foundation Trust

PHAEOCHROMOCYTOMAS AND PARAGANGLIOMAS:

GUIDELINES FOR REQUESTING PLASMA FREE METANEPHRINES

Version:	2
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Target audience:	Healthcare professionals in primary and secondary care

Version Control Schedule

Version	Date	Author	Status	Comment
1.0	June2020	D Fan	Archived	
1.1	Dec2020	D Fan	Archived	updated the drug list for CCB and test indication
2	Mar2022	D Fan		updated the interfering drug list and comments; added diagnostic sensitivity and specificity; updated sample stability

Consultation and Ratification Schedule

Name and Title of Individual	**Date Consulted**
Dr T Doulton, Consultant Nephrologist/Hypertension Specialist	**Jun 2020&2022**
Dr C Dr McGettigan Endocrinology Consultant	**Jul 2022**
Dr S Joseph, Endocrinology Consultant	**May 2020**
Dr E Grigoras, Specialist Endocrinology	**Apr 2020&2022**
Dr L Faghahati, Endocrinology Consultants	**May 2020&2022**
Dr E Rfidah, Consultant Paediatrician	**May 2020&2022**

Name of Committee	**Date Ratified**
PMGC	Nov 2022
CSS Quality and Risk Committee	Jan 2023
Clinical Biochemistry Senior staff meeting	Jan 2023

Contents

1. Introduction, Background and Purpose

Phaeochromocytomas and paragangliomas (PPGLs) are rare catecholamine-producing tumours of the sympathetic and parasympathetic nervous system. Phaeochromocytomas arise in the adrenal medulla from adrenomedullary chromaffin cells that commonly produce one or more catecholamine: adrenaline, noradrenaline, and dopamine. Metanephrine, normetanephrine, and 3-methoxytyramine are corresponding degradation product of the adrenaline, noradrenaline and dopamine. Rarely phaeochromocytomas are silent. Paragangliomas arise in chromaffin cells outside of the adrenal gland, such as from the sympathetic paravertebral ganglia of thorax, abdomen and pelvis. Paragangliomas could also be derived from parasympathetic ganglia in the neck and at the base of the skull, but these do not produce catecholamines. Up to 85% of chromaffin-cell tumours are phaeochromocytomas, whereas approximately 15 % are paragangliomas.

PPGLs can occur in families as part of the autosomal dominant conditions multiple endocrine neoplasia Type 2 (MEN-2) and von Hippel-Lindau disease. Prompt diagnosis using the most appropriate laboratory tests and strategies for screening are crucial to reduce the morbidity and mortality of PPGLs.

Measurement of pfMETs is the test of choice for detection of PPGLs with the highest specificity and sensitivity, and is replacing the measurement of 24-hour urinary catecholamines for the screening PPGLs. The pfMETs test provides the analysis of metanephrine, normetanephrine, and 3-methoxytyramine.

Neuroblastoma is a cancer of immature nerve cells arising from the adrenal gland, nerve ganglia or the neck. The role of pfMETs test in the investigation of neuroblastoma has not been established. Urinary homovanillic acid (HVA) and vanillylmandelic acid (VMA) on a spot urine is the recommended test instead for screening neuroblastoma in paediatric patients.

This document gives guidance on requesting plasma free metanephrine (pfMETs) measurement for investigation and monitoring of catecholamine-secreting phaeochromocytoma and paragangliomas in adults.

2. Definitions

PPGLs: phaeochromocytomas and paragangliomas

pfMETs: plasma free metanephrines

3. Scope

This guideline outlines the signs and symptoms that support a request for pfMETs measurement. It may be used for patients both within the Trust and in primary care and the community. All staff involved in the requesting of pfMETs measurements, whether clinical or laboratory, must adhere to this guideline.

4. Guidance

As with any other laboratory investigation full and explicit clinical details should be provided. All requests will be reviewed before analysis and inappropriate requests will not be processed

4.1. Plasma free metanephrines analysis

4.1.1 Suspected PPGLs

Requests for pfMETs measurement when PPGLs are suspected in patients will only be processed if at least **one** of the following criteria is satisfied:

a) Classic triad of symptoms: palpitations, headaches and diaphoresis (sweating).
b) Hypertension, in particular paroxysmal hypertension (30%) or orthostatic hypotension
c) Adrenal incidentaloma which is not clearly an adenoma on imaging (*See Bio-NO-455 Adrenal Incidentaloma: guidelines for investigation*)
d) Asymptomatic patients with an inherited disorder associated with an increased risk of PPGLs such as multiple endocrine neoplasia (MEN) 2A and 2B, Von Hippel-Lindau disease, and neurofibromatosis type 1.
e) Medications listed in Table 1 have been reported to be associated with adverse reactions in patients with PPGLs and can precipitate a crisis. Screening for PPGLs should be considered if there are signs/symptoms before introducing these drugs.

Drug class	Examples
Dopamine D2 receptor antagonists (including some antiemetic agents and antipsychotics)	Metoclopramide, sulpiride, amisulpride, tiapride, chlorpromazine, prochlorperazine, droperidol
β-Adrenergic receptor blockers	Propranolol, sotalol, timolol, nadolol, labetalol
Sympathomimetics	Ephedrine, pseudoephedrine, fenfluramine, methylphenidate, phentermine, dexamfetamine
Opioid analgesics	Morphine, pethidine, tramadol
Norepinephrine reuptake inhibitors (including tricyclic antidepressants)	Amitriptyline, imipramine,
Serotonin reuptake inhibitors (rarely reported)	Paroxetine, fluoxetine
Monoamine oxidase inhibitors	Tranylcypromine, moclobemide, phenelzine
Corticosteroids	Dexamethasone, prednisone, hydrocortisone, betamethasone
Peptides	ACTH, glucagon
Neuromuscular blocking agents	Succinylcholine, tubocurarine, atracurium

Table 1: Medications that are implicated in adverse reactions in patients with PPGLs and that can precipitate a crisis

4.1.2 Monitoring PPGLs

Patients with a personal history of a PPGLs need at least annual screening for up to 10 years after resection.

4.2 Testing strategies

4.2.1 Screening test – plasma free metanephrines (seated)

Seated sample collection is used for initial screening to rule out low risk patients. Patients must attend phlebotomy outpatients at one of the three acute hospital sites (i.e. at K&CH, QEQMH or WHH) for sample collection. Patients must be seated for a minimum of 10 minutes prior to sample collection.

This test can be requested by primary care or secondary care.

A fasting sample is required and patients should not eat any food for 8-14 hours before the test.

4.1.1 Follow-up test - plasma free metanephrines (supine)

Supine sample collection should be reserved for high risk patients or those giving equivocal results in the initial screening (seated sample collection). Supine sample collection cannot be undertaken in phlebotomy. Patients must attend Medical Day Unit (MDU) at the K&CH; the requestor must liaise with MDU. Patients must be supine for 30 minutes before sample collection.

This test can only be requested by secondary care.

Supine collection of samples with dietary and drug restrictions gives increased sensitivity and specificity. If a repeat testing is performed in supine position when initial test results are increased or equivocal, dietary and drug restrictions should be applied. Fasting status and the impact of dietary catecholamines have minimal impact on concentrations of plasma free normetanephrine and metanephrine. However, dietary catecholamine intake (and potentially intake of some non-catecholamine rich foods) can significantly increase plasma 3-methoxytyramine concentrations.

The interfering dietary factors and drugs are listed below:

- Avoid caffeinated and decaffeinated foods and drinks (e.g. coffee, tea and cola, chocolate) for 24 hours.

- Avoid any catecholamine rich foods (e.g. bananas, plums, pineapples, walnuts, tomatoes, avocados, aubergines, alcoholic drinks, vinegar) for 24 hours.
- Avoid nicotine 9 hours prior to testing e.g. no smoking or other nicotine replacement therapy, such as patches and gum.
- Ideally patient should be taken off all drugs which have pharmacological effects on secretion, metabolism or excretion of catecholamines and their metabolites. The list of drugs in Table 2 have been shown to cause false positive increases in pfMETs.

Drug class	**Examples**
Tricyclic antidepressants	Amitriptyline, clomipramine, dosulepin
Selective serotonin reuptake inhibitors	Citalopram, fluoxetine, sertraline
Serotonin/noradrenaline reuptake inhibitors	Venlafaxine, duloxetine
α-adrenergic receptor blockers	Phenoxybenzamine, doxazosin, indoramin
β- adrenergic receptor blockers	Atenolol, labetalol, propanolol
Calcium-channel blockers	Amlodipine, diltiazem, nifedipine
Monoamine-oxidase inhibitors	Isocarboxazid, moclobamide, phenelzine
Dopa- related	Levo(l)-dopa, methyldopa
Stimulant / Sympathomimetic drugs	Ephedrine, amphetamine, cocaine, nicotine, caffeine

Table 2: A list of drugs that have been shown to cause false positive increases in pfMETs

- Avoid drugs causing analytical interference to the testing method, including metaraminol, nadolol, sotalol, metformin, midodrine, procainamide, and ranitidine.
- A study showed no significant changes in pfMETs were seen at the end of the low dose dexamethasone test (LDDST) compared to baseline. However caution should be exercised in patients with adrenal masses with imaging characteristics compatible with phaeochromocytoma

4.3 Sample requirements

4 mL EDTA whole blood sample

Whole blood samples must be transported to clinical biochemistry (pathology) immediately and centrifuged within 1 hour of collection to be viable for analysis. Any blood samples not fulfilling these collection criteria will not be assayed.

The separated samples should not be left on the bench for prolonged lengths of time to minimise light exposure. Cover the samples with paper tissue if prolonged light exposure is anticipated.

Separated plasma samples sent from other laboratories should be stored frozen prior to dispatch where light exposure is minimal. Separated plasma samples sent from other laboratories should be stored frozen prior to dispatch and must be sent to K&CH laboratory frozen, packed with dry ice or ice packs, in a timely manner. Plasma samples that arrive thawed and at room temperature in the postage box are NOT suitable for analysis.

4.4 Interpretation of tests for PPGLs

The reference ranges in Table 3 are based on an adult population. A study showed that for seated pMETs, by applying the reference below, the diagnostic sensitivity was 93% and specificity was 90% (12).

	Seated	**Supine**
Plasma metanephrine	<510 pmol/L	<450 pmol/L
Plasma normetanephrine	< 1180 pmol/L	< 730 pmol/L
Plasma 3-methoxytyramine	<180 pmol/L	< 180 pmol/L

Table 3 Reference ranges for adult patients in seated and supine positions.

Specific reference ranges for paediatric patients are not available. The Duty Biochemist is available to discuss these results on 01233 616060 (x723 6060/6287) if required.

A summary of our interpretive guidance on seated collection for primary care and non-specialised secondary care is shown in Tables 4&5. All results must be interpreted in the context of symptoms and other clinical and imaging findings. When a neuroendocrine tumour cannot be excluded, patients should be referred into secondary care (Endocrinology or Hypertension clinics) for further investigation.

Interpretive comments for **Seated collection**	**Adult Reference Range** **(>16 years)**	**Borderline**	**Possible Phaeo**	**Consistent with Phaeo**
Plasma metanephrine or normetanephine	**Within reference range**	**Up to 2X ULRR**	**2 to 4X ULRR**	**>4X ULRR**
Comments	Results do not suggest the presence of phaeochromocytoma/ paraganglioma.	Borderline increase in plasma metanephrine / normetanephrine, but not in the range normally associated with phaeochromocytoma. See guidelines at http://tinyurl.com/ekhuftbiochem for list of drugs that may cause increased concentrations. Consider discussion with endocrinologist	Plasma metanephrine / normetanephrine in a range which suggests possible phaeochromocytoma. See guidelines at http://tinyurl.com/ekhuftbiochem for list of drugs that may cause increased concentrations. Suggest discussion with endocrinologist	Grossly increased plasma metanephrine / normetanephrine, in range consistent with phaeochromocytoma. Suggest urgent discussion with endocrinologist

Table 4 Interpretation of metanephrine and normetanephrine results for primary care and non-specialised secondary care .

	Adult Reference Range (>16 years)	Borderline Up to 4X ULRR	Isolated Raised 3MT	Confirmed Phaeo
Plasma 3-methoxytyramine	**Within reference range**	**Up to 4X ULRR**	**>4X ULRR**	**>4X ULRR**
	n/a	Normal plasma metadrenaline and normetadrenaline. Isolated mild elevation in 3-methoxytyramine might be non-specific. Consider causes such as diet or medication. Suggest discussion with endocrinologist	Normal plasma metadrenaline and normetadrenaline with elevated 3 methoxytyramine. Consider causes such as diet or medication (e.g. L-dopa). Although this may not be clinically significant, please note isolated raised 3-methoxytyramine can be associated with head and neck paraganglioma, SDH-related pathology and neuroblastoma. Suggest discussion with endocrinologist	In cases of confirmed (phaeochromocytoma/ paraganglioma), elevated 3 methoxytyramine may be associated with certain genetic causes of phaeochromocytoma/ paraganglioma or the presence of metastases

Table 5 Interpretation of plasma 3-methoxytyramine results for primary care and non-specialised secondary care.

5. Consultation and Approval

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this guideline.

Consultation has been through e-mail or face-to-face communication between clinical biochemistry staff and trust Consultant Nephrologist/Hypertension Specialist Dr T Doulton, Endocrinology Consultants (including Dr C Dr McGettigan, Dr S Joseph, Dr E Grigoras and Dr L Faghahati) and Consultant Paediatrician Dr P Angelini and Dr E Rfidah. Email correspondence is stored on Q-pulse

6. Review and Revision Arrangements

Two years from implementation date, by author.

7. Training

TrustNet, by proactive implementation through the Care Groups by appropriate clinical leads and by proactive dissemination to primary care partners.

8. Document Control including Archiving Arrangements

Archive of this document will be through QPulse.

9. Monitoring

Within the Trust, compliance with this guideline must rest with the requesting Care Groups with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry.

10. References and Associated Documents

1. BMJ Best Practice: Phaeochromocytoma (Last updated: Jun 14, 2018)
2. National comprehensive cancer network (NCCN) guidelines in oncology-neuroendocrine and adrenal tumours version 4, 2018
3. Lenders JW et al; Endocrine Society. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42.
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5. Eisenhofer G et al. Measurements of plasma methoxytyramine, normetanephrine, and metanephrine as discriminators of different hereditary forms of phaeochromocytoma. Clin Chem 2011; 57: 411-20.
6. Farah G et al Grossly elevated plasma metanephrine levels due to midodrine, an α1 receptor agonist, in a patient presenting with postural orthostatic tachycardia syndrome. Endocrine Abstracts 2015; 37: EP1237
7. Chromsystems MassChrom® Free Metanephrines in plasma manual (EN11/2019 V5)
8. Eisenhofer G et al. Biochemical Diagnosis of pheochromocytoma: How to distinguish true- from false-positive test results. *JCEM* 2003; **88**: 2656-66.
9. de Jong WHA et al. Dietary influences on plasma and urinary metanephrines: Implications for diagnosis of catecholamine-producing tumors. JCEM 2009; 94: 2841-49.
10. Management of adrenal incidentalomas:European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors
11. Chromsystems MassChrom® Free Metanephrines in plasma manual (EN 10/2021 V5.1) Urgent Field Safety Notice \ FSN 1-2022 \ 19.01.2022
12 Boot C, et al Single-centre study of the diagnostic performance of plasma metanephrines with seated sampling for the diagnosis of phaeochromocytoma/paraganglioma. Ann Clin Biochem. 2017 Jan;54(1):143-148

Associated Documentation

BIO NO 455 Adrenal Incidentaloma: guidelines for investigation
BIO NO 842 Measurement of Plasma Free Metanephrines using LC-MS/MS