PHAEOCHROMOCYTOMAS AND PARAGANGLIOMAS: GUIDELINES FOR REQUESTING PLASMA FREE METANEPHRINES

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Name of originator/author:	Danni Fan/Elizabeth Hall
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Version Control Schedule

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1.0	June2020	D Fan	Archived	
1.1	Dec2020	D Fan		updated the drug list for CCB and test indication

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1 Policy Summary

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

2 Introduction

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) is the recommended test instead for screening neuroblastoma in paediatric patients.

3 Purpose and Scope

This policy 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.

4 Definitions

PPGLs: phaeochromocytomas and paragangliomas

pfMETs: plasma free metanephrines

5 Duties

All staff involved in the requesting of pfMETs measurements, whether clinical or laboratory, must adhere to this policy.

6 PPGLs: Guidelines for Requesting Plasma Free Metanephrines

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.

6.1 Plasma free metanephrines analysis

6.1.1 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

6.1.2 Monitoring PPGLs

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

6.2 Testing strategies

6.2.1 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.

6.2.2 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 Ambulatory Care/Day Hospital at the K&CH or QEQMH sites; the requestor must liaise with ambulatory Care. 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 and metformin.

6.3 Sample requirements

4 mL EDTA whole blood sample

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

Separated plasma samples sent from other laboratories should arrive frozen, packed with dry ice or ice packs. Plasma samples that arrive thawed but cold within 3 days of posting are still acceptable. Plasma samples that arrive thawed and at room temperature in the postage box are NOT suitable for analysis.

6.4 Interpretation of tests for PPGLs

The reference ranges in Table 3 are based on an adult population. 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.

	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.

A summary of our interpretive guidance for primary care and the community 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	**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/ paraganglioma. Exclude drug causes e.g. antidepressants and antihypertensives (especially beta-blockers and non-selective alpha-adrenoceptor blockers). Recommend discussion with endocrinologist	Plasma (metanephrine / normetanephrine) in a range which suggests possible phaeochromocytoma/ paraganglioma. Exclude drug causes e.g. antidepressants and antihypertensives (especially beta-blockers and non-selective alpha-adrenoceptor blockers). Recommend discussion with endocrinologist	Plasma normetanephrine in range consistent with phaeochromocytoma/ paraganglioma. Suggest urgent discussion with endocrinologist

Table 4 Interpretation of metanephrine and normetanephrine results.

	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. Suggest consider non-specific cause e.g. diet or medication. Recommend discussion with endocrinologist	Normal plasma metadrenaline and normetadrenaline with elevated 3-methoxytyramine. Suggest Consider non-specific cause e.g. 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. Recommend 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.

7 Key Stakeholders, Consultation, Approval and Ratification Process

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

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 & their teams (including Dr S Joseph, Dr E Grigoras and Dr L Faghahati) and Consultant Paediatrician Dr E Rfidah. Email correspondence is stored on Q-pulse and the S drive.

8 Review and Revision Arrangements

Two years from implementation date, by author.

9 Dissemination and Implementation

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

10 Document Control including Archiving Arrangements

Archive of this document will be through QPulse.

11 Monitoring Compliance

Within the Trust, compliance with this policy 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.

12 References

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, Duh QY, Eisenhofer G, et al; Endocrine Society. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42.
4. Huang KH, Chung SD, Chen SC, et al. Clinical and pathological data of 10 malignant pheochromocytomas: long-term follow up in a single institution. Int J Urol. 2007 Mar;14(3):181-5.
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, Grossman A, Lulsegged A, Gall N. 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

13 Associated Documentation

BIO NO 455 Adrenal Incidentaloma: guidelines for investigation

Appendix A - Equality Impact Assessment

Equality and Human Rights Impact Analysis (EHRIA)

Part One – Screening Tool

Name of the policy, strategy, function or methodology:	Plasma free metanephrines: guidelines for use in screening and monitoring phaeochromocytomas and paragangliomas

Details of person completing the EHRIA	
Name	Danni Fan
Job Title	Principal Clinical Scientist
Department/Specialty	Pathology/Clinical Biochemistry
Telephone Number	

1. Identify the policy, strategy, function or methodology aims

What are the main aims, purpose and outcomes of the policy, strategy, function or methodology?
To ensure appropriate requesting of plasma free metanephrines across the health service in East Kent.
Does it relate to our role as a service provider and/or an employer?
Service provider.

2. Assess the likely impact on human rights and equality

Use this table to check if the policy, strategy, function or methodology:

- could have a negative impact on human rights or on any of the equality groups, or
- could have a positive impact on human rights, contribute to promoting equality, equal opportunities or improve relations.

It is not necessary to complete each box, nor to mark whether it is positive or negative, although you can do this if you find it helpful.

	Protected Characteristic								
	Race	**Sex**	**Disability**	**Sexual Orientation**	**Religion or belief**	**Age**	**Gender reassignment**	**Marriage & Civil Partnership**	**Pregnancy & Maternity**
Could this policy, procedure, project or service affect this group differently from others? **YES/NO**									
Could this policy, procedure, project or service promote equal opportunities for this group? **YES/NO**									
Right to life *e.g. decisions about life-saving treatment, deaths through negligence in hospital*									
Right not to be tortured or treated in an inhuman or degrading way *e.g. dignity in care, abuse or neglect of older people or people with learning disabilities.*									
Right to respect for private and family life e.g. *respecting lgb relationships, confidentiality*									
Right to freedom of thought, conscience and religion *e.g. respect for cultural and religious requirements*									
Right to freedom of expression *e.g. access to appropriate communication aids*									
Right to freedom of assembly and association *e.g., right to representation, to socialise in care settings*									
Right to education *e.g. access to basic knowledge of hygiene and sanitation*									
Right to liberty e.g. informal detention of patients who do not have capacity									

3. How does it impact on people's human rights and equality?

Using the table above, explain anticipated impacts. If a full EHRIA is recommended, you can summarise the impacts - it is not necessary to set these out in detail,

Could people's human rights be impacted negatively? Could the policy, strategy, function or methodology result in inequality or discrimination?
No
Could this policy, strategy, function or methodology result in positive impacts on people's human rights or equality? Could it present opportunities to promote equality?
No

4. Recommendations

Is a full EHRIA recommended? If not, give reasons
No. The policy has equal impact.

5. Publication of EHRIA

Give details of where Screening Tool or the full EHRIA will be published and when this will take place
With document.

Details of person completing the EHRIA	
Name	Danni Fan, Principal Clinical Scientist

Signed …… Date: ……

Approval and sign-off	Name
Head of Department/Director	Dr Sally Stock, Head of Service Clinical Biochemistry

Signed …… Date: ……

	Name
Trust Board approval and sign-off	not applicable

Signed …… Date: ……

Appendix B – Author's Checklist of compliance with the Policy for the Development and Management of Organisation Wide Policies and Other Procedural Documents

POLICY:

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

	Requirement:	Compliant Yes/No/ Unsure	Comments
1.	**Style and format**	Yes	
2.	**An explanation of any terms used in documents developed**	Yes	
3.	**Consultation process**	Yes	
4.	**Ratification process**	Yes	
5.	**Review arrangements**	Yes	
6.	**Control of documents, including archiving arrangements**	Yes	
7.	**Associated documents**	n/a	
8.	**Supporting references**	Yes	
9.	**Relevant NHSLA criterion specific requirements**	n/a	
10.	**Any other requirements of external bodies**	n/a	
11.	**The process for monitoring compliance with NHSLA and any other external and/or internal requirements**	n/a	