The Association for Clinical Biochemistry & Laboratory Medicine

Better Science, Better Testing, Better Care

Summary of Endocrinology Society Guidelines for Phaeochromocytoma and Paraganglioma

Title	Phaeochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline
Journal Reference	Lenders JWM, Duh Q-Y, Eisenhofer G, Gimenez-Roqueplo A-P, Grebe SKG, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915–42. The consensus process involved members of the Endocrine Society (USA), the European Society of Endocrinology, and American Association for Clinical Chemistry.
Date of Review:	11th of September 2018
Summary of Condition	Phaeochromocytomas/Paragangliomas (PPGL) are rare neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. Most produce catecholamines. Presentation is highly variable: signs/symptoms include headaches hyperhidrosis, tachycardia, and hypertension. PPGL should be considered in individuals presenting with; signs/ symptoms, associated syndromes (e.g. MEN2, VHL), known PPGL associated mutations (e.g. SDHB), adrenal incidentalomas and patients with a previous history of PPGL. The biochemical tests of choice are plasma free metanephrines or 24-hour urinary fractionated metanephrines. These metabolites are continuously produced by the tumour unlike the episodic release of catecholamines. Elevated results should be reviewed carefully giving due consideration to potential sampling errors and interfering medications. For borderline elevated results a clonidine suppression test with measurement of plasma normetanephrine may be helpful. PPGL are more likely if normetanephrine or metanephrine results are >3 ULN, or if both metabolites are elevated. Appropriate imaging techniques should be used to locate the tumour such as MRI, CT, MIBG, FDOPA. Shared decision making is recommended for genetic testing in all PPGL patients with appropriate pre and post counselling available. SDHB mutations are noted to confer increased risk of malignancy. Genetic testing may be targeted rather than universal in those with syndromic presentations. Where surgery is planned, alpha-blockade should be performed 1-2 weeks prior to beta-blockade. Patients may also be given a high salt diet and a high fluid intake. BP, heart rate and glucose should be monitored post-operatively. Surgical success should be confirmed biochemically within 2-4 weeks and patients followed up annually for recurrence.
Overview of assays	The guidelines point to the high diagnostic accuracy of plasma free metanephrine analysis, suggesting a slight advantage for plasma over

	urine testing. However, they acknowledge the lack of direct head-to-head comparisons using mass spectrometry-based measurements and so stop short of recommending one methodology over the other. LC/MS or HPLC with electrochemical detection are the recommended analytical techniques. Immunoassays have been shown to be less precise and significantly negatively biased in comparison to these methods. For measurements of plasma metanephrines supine-sampling with reference intervals established in the same position is recommended. While the practicalities of seated-sampling is accepted, it is mandated that reference intervals (supine) that do not compromise diagnostic accuracy be used. This approach mitigates false-negative screens but increases the likelihood of false-positive results, hence the suggestion that positive tests be repeated using supine-sampling. If this cannot be done, measurements of urinary fractionated metanephrines provide a useful alternative.
Lab professionals to be made aware *Please select/highlight appropriate choices*	✓ **Chemical Pathologist** ✓ **Clinical Scientist** ✓ **Biomedical Scientist**
Impact on Lab	☐ **Moderate**
Please detail the impact of this guideline	The guidelines detail the many signs and symptoms where PPGL should be considered. They state that plasma free metanephrines or 24-hour urinary fractionated metanephrines, using HPLC coupled with electrochemical detection or mass spectrometry should be used as the initial biochemical screen. Therefore, laboratories should no longer be using urinary catecholamines alone, or immunoassay methods. All elevated results must be carefully reviewed taking pre-analytical factors (sampling procedures and medications) into account. Various imaging techniques may be appropriate for localising and follow-up. Genetic testing should be considered in all confirmed cases, and targeted where appropriate. Successful surgical removal should be confirmed biochemically 2-4 weeks post-operatively with annual follow-up for recurrence. ***Note 1:*** *European Society of Endocrinology Guidelines on the on the Long-Term Follow-Up of Patients Operated on for PPGL recommend annual follow-up for at least 10 years following surgery for a PPGL. Ref: European Journal of Endocrinology (2016) 174,G1-G10.* ***Note 2:*** *Since the publication of the 2014 Guidelines, plasma 3-Methoxytyramine has been shown to be a sensitive biomarker of dopamine production in patients with mutations in SDHB gene and more closely associated with malignant PPGL.*

Impact on Lab

- **None**: This guideline has no impact on the provision of laboratory services
- **Moderate**: This guideline has information that is of relevance to our pathology service and may require review of our current service provision.
- **Important:** This guideline is of direct relevance to our pathology service and will have a direct impact on one or more of the services that we currently offer.

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