Reviewer’s report

Title: Measurement of Fractionated Plasma Metanephrines for Exclusion of Pheochromocytoma: Can Specificity be Improved by Adjustment for Age?

Version: 1 Date: 21 December 2004

Reviewer: michael roden

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General
This study reports an age-based algorithm in order to improve the diagnostic efficacy of fractionated plasma metanephrines in the exclusion of non familial pheochromocytoma. The use of this algorithm leads to improvement of the percentage of false positive results in the face of optimal sensitivity of 100%.
This is an interesting paper offering a new approach to improve the role of metanephrines in the diagnosis of pheochromocytoma.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. p.4: acetaminophen interference is not typical for all methods to measure metanephrines. This needs to be made clear (Roden et al. Clin Chem 47:1061, 2001).
2. p.7: it is unclear why a sensitivity of 90.9% was considered to be acceptable. Sensitivity should be as close as possible to 100%, because failure to detect almost 10% with pheochromocytoma renders such a test useless. As the algorithm finally had a 100% sensitivity. The respective statement on p.7 needs to be explained in more detail.
3. One person with a false negative score had Van Hippel Lindau disease, although genetic/familial pheochromocytomas were excluded. Was the diagnosis made latter or clinically and were other patients with genetic defects and familial diseases also present in the derivation and validation cohort?
4. Information on the study populations is not presented in detail, at least age ranges and percentage of clinical symptoms should be presented.
5. p.10: The statement that the physiologic causes for increased normetanephrine are unclear is correct, however, at least some evidence has been provided that particularly hypertensive type 2 diabetic patients who are generally older exhibit exaggerated catecholamine and metanephrine responses. Please check for hypertensive and/or diabetic patients in your cohorts and discuss (Raber et al, Eur J Clin Invest 33:480, 2003).

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Could the authors assess or at least speculate on the impact of their age-based score on rational / economic aspects of pheochromocytoma diagnosis?

Discretionary Revisions (which the author can choose to ignore)
What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No