The Predictive Value of Urinary Vanillylmandelic Acid Testing in the Diagnosis of Phaeochromocytoma at The University Hospital of the West Indies

SN Chin[1,2], MS Boyne[3], D McGrowder[2], TN Gibson[2], CA McKenzie[3]

ABSTRACT

Objective: *To investigate the positive predictive value (PPV) of urinary vanillylmandelic acid (VMA) testing in the diagnosis of phaeochromocytoma and to describe the features associated with phaeochromocytoma at the University Hospital of the West Indies (UHWI).*

Subjects and Methods: *There were 551 VMA tests performed from January 2003 to June 2009 and 122 tests in 85 patients were elevated (ie ≥ 35 μmol/24 hr). The study patients were categorized as: (i) 'surgical' (5 patients who underwent surgery) or (ii) 'non-surgical' (remaining 80 patients). Forty medical charts (out of 85) were reviewed using a standardized data extraction form.*

Results: *The median age for patients in the non-surgical group (with charts reviewed, n = 35) was 36 years (range 9–70) and the median VMA was 43 μmol/24 hr (IQR 38–51). Of these patients, 83% had one or no symptom typical of phaeochromocytoma. In the surgical group the median VMA was 58 μmol/24 hr (IQR 44-101); phaeochromocytoma was confirmed histologically in 3 patients, all of whom had several symptoms typical of catecholamine excess. VMA testing had a PPV of 8%, specificity of 79% and sensitivity of 100%.*

Conclusions: *VMA testing at UHWI has poor specificity and high sensitivity. These results contrast with international data showing that VMA testing is poorly sensitive but highly specific. The use of assays with higher specificity (eg plasma or urinary metanephrines) may represent a more cost-effective approach to biochemical screening at UHWI.*

Keywords: Blood pressure, diagnosis, metanephrines, phaeochromocytoma, vanillylmandelic acid.

El Valor Predictivo de la Prueba del Ácido Vanilmandélico en Orina Para el Diagnóstico de la Feocromositoma en el Hospital Universitario de West Indies

SN Chin[1,2], MS Boyne[3], D McGrowder[2], TN Gibson[2], CA McKenzie[3]

RESUMEN

Objetivo: *Investigar el valor predictivo positivo (VPP) de las pruebas del ácido vanilmandélico urinario (VMA) en el diagnóstico de la feocromositoma y describir las características asociadas con la feocromositoma en el Hospital de la Universidad de West Indies (HUWI).*

Sujetos y Métodos: *Se realizaron unas 551 pruebas de VMA de enero de 2003 a junio de 2009, y 122 de las pruebas en 85 pacientes tuvieron resultados elevados (ie ≥ 35 μmol/24 hr). Los pacientes del estudio fueron clasificados como: (i) "quirúrgicos" (5 pacientes que se sometieron a cirugía) ó (ii) "no quirúrgicos" (los 80 pacientes restantes). Se revisaron cuarenta historias clínicas (de 85) mediante un formulario estandarizado de extracción de datos.*

Resultados: *El promedio de edad de los pacientes en el grupo no quirúrgico (con historias clínicas, n = 35) fue de 36 años (rango 9–70) y la mediana VMA fue 43 μmol/24 h (IQR 38-51). De estos pacientes, 83% tenían uno o ningún síntoma típico de la feocromositoma. En el grupo quirúrgico la mediana VMA fue 58 μmol/24 h (IQR 44-101). La feocromositoma fue confirmada histológicamente en 3 pacientes, cada uno de los cuales presentó síntomas típicos de exceso de catecolaminas. Las pruebas de VMA tuvieron un VPP de 8%, una especificidad de 79%, y una sensibilidad de 100%.*

From: [1]Departments of Medicine, [2]Pathology, and [3]Tropical Medicine Research Institute, The University of the West Indies, Kingston 7, Jamaica, West Indies.

Correspondence: Dr CA Mckenzie, Tropical Metabolism Research Unit, Tropical Medicine Research Institute, The University of the West Indies, Kingston 7, Jamaica, West Indies. Fax (876) 977-0632, e-mail: colin.mckenzie02@uwimona.edu.jm

Conclusiones: *Las pruebas de VMA en HUWI poseen pobre especificidad y alta sensibilidad. Estos resultados contrastan con los datos internacionales que muestran que la prueba de VMA es pobremente sensible pero altamente específica. El uso de ensayos con mayor especificidad (por ejemplo, metanefrinas plasmáticas o urinarias) puede representar un método costo-efectivo a la hora de realizar el pesquisaje bioquímico en HUWI.*

Palabras claves: Presión arterial, diagnosis, metanefrinas, feocromositoma, ácido vanilmandélico

West Indian Med J 2011; 60 (2): 142

INTRODUCTION

Phaeochromocytomas are neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. They are characterized by excessive production of catecholamines, often leading to hypertension and other symptoms of catecholamine excess. In general medical outpatient clinics, the prevalence of phaeochromocytoma in patients with hypertension has been estimated to be 0.1–0.6% (1). Although phaeochromocytoma is a rare cause of secondary hypertension in the population [0.8 per 100 000 person-years] (2), a high index of suspicion of these tumours is important in the appropriate clinical setting since surgical resection can be curative. Conversely, if not diagnosed and treated appropriately, the excessive secretion of catecholamines can have such consequences as arrhythmias and cardiogenic shock (3, 4).

While the diagnosis of phaeochromocytoma depends on demonstrating excessive production of catecholamines, the best diagnostic test has not been determined conclusively (5). At the University Hospital of the West Indies (UHWI), urinary vanillylmandelic acid (VMA) tests are often done as part of evaluation of hypertension, for example, in young patients with hypertension and in patients with treatment-resistant hypertension. Several investigators have questioned the utility of screening protocols that rely on the VMA assay because of the reported low sensitivity of the assay (46–72%) although its specificity (86–99%) is high (1, 6, 7). It has been our anecdotal experience, however, that VMA testing in our setting has a high sensitivity and a relatively low specificity, which reduces the practical value of the test.

In this retrospective study, the test characteristics (positive predictive value, specificity, sensitivity) of the VMA assay were examined in a group of patients undergoing evaluation for phaeochromocytoma at UHWI. We also describe the clinical features of these patients and the differences between the patients who had a phaeochromocytoma at surgery and the patients who did not have a phaeochromocytoma.

SUBJECTS AND METHODS

A record of all urinary VMA tests performed at the Chemical Pathology Department, The University of the West Indies (UWI) Kingston, Jamaica, from January 1, 2003 to June 30, 2009 was obtained. From this list, we identified all patients with at least one elevated result (*ie* VMA ≥ 35 μmol/24 hr) and conducted a search for their medical charts (dockets) through the Medical Records Department.

Data extraction from the available patients' medical records was performed using a standardized data extraction template. The items recorded were: patient demographics (age, sex, date of birth), age at time of investigations, date investigations commenced, specialty of requesting doctor (or clinic from which the request for testing was sent), symptoms suggestive of catecholamine excess, hypertension history, medication history, blood pressure readings, VMA test results, results of imaging investigations and period of follow-up. Each of the patients (all of whom had at least one elevated VMA result) was assigned to one of two groups: (1) surgical group (these patients underwent surgery for a suspected diagnosis of phaeochromocytoma) and (2) a much larger non-surgical group (patients who did not undergo surgery).

The archives of the Pathology Department of the UHWI were hand-searched for histopathology reports on adrenal specimens from patients in the surgical group in order to ascertain the final histological diagnosis.

This study was approved by the Ethics Committee, Faculty of Medical Sciences, UWI/UHWI. Summary descriptive values are presented for VMA results and for patient characteristics by patient group (*ie* non-surgical *vs* surgical). Summary descriptive values are also presented for hypertensive patients in the non-surgical group. Values are presented as counts or medians (with interquartile ranges) as appropriate. The significance of differences between groups for continuously-distributed traits was examined using the Wilcoxon rank sum test. The significance of differences between groups was assessed using either the chi-squared test or Fisher's exact test.

Sensitivity, specificity and positive predictive values were computed. Vanillylmandelic acid (VMA) results were considered to be false positive for patients who had an elevated VMA result and who were not proven to have a phaeochromocytoma at sur-gery or had no intervention after two years of follow-up. Statistical tests were performed with the Statistical Package for the Social Sciences® (SPSS) v 12.0 (Chicago, IL, USA) and with Stata 10 (College Station, TX, USA).

RESULTS

There were 551 VMA tests performed during the study period. Of these, 122 tests (performed on 85 patients) were defined as elevated according to the reference limit of the Chemical Pathology Laboratory, UHWI (*ie* normal < 35 μmol/24 hr). Of the 85 patients, five underwent surgery for the excision of a phaeochromocytoma. These patients comprised the "Surgical Group" and the remaining 80 formed the "Non-Surgical Group." Table 1 shows the distribution of tests and test results by patient group. The median VMA of the 122 test results was 44 μmol/24 hr with an interquartile range (IQR) of 39–58 μmol/24 hr. Among the 85 patients, the median number of tests per patient was 1 (IQR 1.0–2.0). When elevated VMA results were considered on a per patient basis, with only one elevated VMA result included for each patient (*ie* including only the higher/highest VMA for patients with more than one elevated test result), the median VMA was 45 (IQR 41–61).

Table 1: Urinary vanillylmandelic acid (VMA) results of 85 patients who had at least one elevated VMA according to patient group.

	Patient Group				
	Both groups	Non-Surgical	Surgical		
			All	Phaeochromocytoma	Other
No of patients with ≥ 1 VMA ≥ 35 μmol/24 h	85	80	5	3	2
No of tests with VMA ≥ 35 μmol/24 h	122	109	13	8	5
Median VMA, μmol/24	44	44	58	49.5	101
hr, (IQR)	(39 – 58)	(39 – 56)	(44 – 101)	(41.5 – 78.5)	(58 – 123)

The median VMA of the elevated VMA results for patients in the non-surgical group was 44 μmol/24 hr (IQR 39–56). When elevated VMA results were considered on a per patient basis, with only one elevated VMA result included for each patient (*ie* including only the higher/highest VMA for patients with more than one elevated test result), the median VMA in the non-surgical group was 45 (IQR 41.0–58.5). In the surgical group the median VMA was 58 (IQR 44–101) and when considered on a per patient basis the median VMA was 91 (IQR 46–133). Phaeochromocytoma was confirmed in three patients; these patients had a total of eight tests performed, with median VMA 49.5 μmol/24 hr (IQR 41.5–78.5). The highest VMA result observed for each of these patients was 91, 44 and 133. The two additional patients in the surgical group did not have phaeochromocytoma – one had a neuroblastoma and the other had reactive lymphadenopathy. These two patients had four tests performed (median VMA 101, IQR 58–123); the patient with neuroblastoma had VMA results of 101, 123 and 309 μmol/24 hr and the patient with reactive lymphadenopathy had a VMA result of 46 μmol/24 hr.

Of the 85 patients with at least one elevated urinary VMA result, we were able to retrieve medical records for 40 (35 patients in the non-surgical group and 5 patients in the surgical group) giving a retrieval rate of 47% (~44% for the non-surgical group; 100% for the surgical group). Table 2 shows the clinical characteristics of these patients. There were no significant differences for age at the time of initiation of investigations or for the proportion of men between groups. The majority of patients (40%) in the non-surgical group were referred from the Hypertension Clinic whereas the distribution of the sources of referral for the much smaller surgical group was more uniform. The median follow-up

Table 2: Clinical characteristics of 40 patients with at least one elevated urinary vanillylmandelic acid result.

Characteristic	Non-surgical group	Surgical group
Number (% men)	35 (63)	5 (40)
Median Age, years (IQR)	36 (28–42)	31 (18–42)
Service requesting test, No. (%)		
Hypertension Clinic	14 (40)	1 (20)
Other Medicine subspecialties	6 (17)	2 (40)
Surgical services	3 (9)	1 (20)
Obstetrics ward	3 (9)	0 (0)
Casualty	3 (9)	0 (0)
Haematology Clinic	1 (3)	1 (20)
Unknown	5 (14)	0 (0)
Number with Hypertension, No. (%)	32 (91)	4 (80)
Symptoms, No. (%)		
Headache	11 (31)	5 (100)
Palpitations	7 (20)	5 (100)
Diaphoresis	3 (9)	4 (80)
'Spells'	2 (6)	2 (40)
Fatigue	1 (3)	0 (0)
Anxiety	1 (3)	0 (0)
Weight loss	1 (3)	1 (20)
Number of symptoms stated, No. (%)		
0–1	29 (83)	0 (0)
2–3	5 (14)	2 (40)
4–5	1 (3)	3 (60)

after the first elevated VMA test was two years (IQR 1–3.5) with no patient receiving additional intervention. Median VMA was 43 μmol/24 hr (IQR 38–51) which was not significantly different from the patients in the non-surgical group for whom medical records were not available.

The majority (83%) of the patients in the non-surgical group had only one symptom or no symptoms associated with phaeochromocytoma (headaches, palpitations and sweating). Headache was the most common symptom (31%). Only two patients were recorded as having the classical 'spells' described for phaeochromocytoma. In the surgical group, the majority of patients (60%) had at least four symptoms associated with phaeochromocytoma and all patients had more than one symptom. All patients experienced headache and palpitations, and most (80%) also reported diaphoresis. Two patients (40%) were recorded as having the classical 'spells' described for phaeochromocytoma. Both the number of symptoms reported, and the frequency of occurrence of the three most common symptoms (headache, palpitations and diaphoresis) were significantly different between groups ($p < 0.001$ and $p < 0.05$ corrected for multiple tests, respectively).

Adrenal imaging was performed in 19 of the 35 non-surgical patients with available medical records – abdominal ultrasound in 17 patients and computed tomography (CT) in the other two patients. Only one abnormal result was recorded ("enlarged adrenal fossa, with no definite mass seen" on non-contrast CT scan) but this patient defaulted from follow-up without further investigation and the outcome is unknown.

Thirty-two (91%) of the patients in the non-surgical group for whom records were available were diagnosed with hypertension. Their characteristics are shown in Table 3. All had sustained hypertension, with the majority (78%) taking anti-hypertensive medications on first presentation. The median number of anti-hypertensive medications was 2 (IQR 1-2); blood pressure readings were categorized as Stage II hypertension under the JNC 7 classification (8) – median systolic blood pressure of 160 mm Hg (IQR 143–171) and median diastolic pressure of 100 mm Hg (IQR 94–112). The median duration of hypertension at the time of presentation was five years (IQR 1–8). The three normotensive patients in this group had no symptoms indicative of catecholamine excess. The recorded indications for ordering VMA tests in these patients were: (1) to rule out the possibility of phaeochromocytoma in a patient with neurofibromatosis, (2) to rule out the possibility of phaeochromocytoma in a patient with congenital adrenal hyperplasia (adrenalectomy was contemplated) and (3) investigation of palpitations in pregnancy. The median systolic (110, IQR 100–120 mm Hg) and diastolic (73, IQR 70–76 mm Hg) blood pressure readings were both significantly ($p = 0.05$) lower than the blood pressure levels of the hypertensive patients.

Phaeochromocytoma was confirmed histologically in 3 of the 5 surgical patients (1 male and 2 females, ages 12, 31 and 44 years, respectively), all of whom had typical symptoms of catecholamine excess (headaches, palpitations, diaphoresis and "spells"). The 12 and 31-year old patients were investigated because they had early-onset hypertension, with elevated VMA results and adrenal masses identified on subsequent computed tomography (CT) of the abdomen. The other patient was investigated after an adrenal incidentaloma was discovered on CT of the abdomen.

Neither of the two patients who underwent surgery and did not have phaeochromocytoma had any of the typical symptoms of catecholamine excess. One was an 18-year old female, being investigated for a large adrenal mass and who had markedly elevated VMA results. Adrenal histology confirmed that she had a neuroblastoma. The other patient was a 42-year old man with severe treatment-resistant hypertension, elevated VMA levels on only one occasion and an infrarenal mass demonstrated on CT of the abdomen. The histological diagnosis in his case was reactive lymphadenopathy.

Table 3: Clinical characteristics of 32 non-surgical patients with hypertension and at least one elevated urinary vanillylmandelic acid result.

Characteristic	
Nature of hypertension, N (%)	
Sustained	32 (100)
Paroxysmal	0
Taking anti-hypertensive medications, N (%)	25 (78)
Median number of medication (range)	2 (0–4)
Median systolic blood pressure, mm Hg (range)	160 (120–240)
Median diastolic blood pressure, mm Hg (range)	100 (70–160)
Median duration of hypertension (for 30 documented), years (range)	5.0 (0.1–27)

Table 4: Clinical utility of urinary vanillylmandelic acid in the diagnosis of phaeochromocytoma utilizing different analytical approaches

	Upper limit of normal ≥ 35 μmol/24 hr		**Upper limit of normal ≥ 52 μmol/24 hr**	
	Per test basis	**Per patient basis**	**Per test basis**	**Per patient basis**
Sensitivity	100% (8/8)	100% (3/3)	50% (4/8)	67% (2/3)
Specificity	79% (429/543)	68% (172/254)*	93% (506/543)	90% (229/254)*
Positive predictive value	8% (8/122)	4% (3/85)	10% (4/41)	7% (2/27)

Notes:
*Assuming 172 patients contributed 429 normal vanillylmandelic acid test results

We first considered all test results as being independent of each other. Under this scenario, VMA testing had a specificity of 79% (429/543), a positive predictive value (PPV) of 7% (8/122) and a sensitivity of 100% (8/8). Results were considered to be false positive for patients who had levels above the reference limit for the Chemical Pathology Laboratory (*ie* ≥ 35 umol/24 hr) and who were not demonstrated to have a phaeochromocytoma after a median follow-up period of two years. Under a more relaxed case definition of "catecholamine-secreting tumour", we included among the true cases, a patient who was shown to have a neuroblastoma at surgery. Under this broader definition, urinary VMA testing had a specificity of 80% (429/539), a positive predictive value (PPV) of 10% (12/122) and a sensitivity of 100% (12/12).

Treating the VMA results as independent of each other may give rise to misleading inferences when considered from the patient perspective. We thus examined the sensitivity and the PPV of VMA testing by considering results on a per patient basis rather than a per test basis. If we use only the higher/highest VMA value for each of the 85 patients, we find that the sensitivity remains at 100% (3/3) but the PPV declines to 4% (3/85). Under the broader heading of catecholamine-secreting tumour, the sensitivity is still 100% (4/4) and the PPV is 5% (4/85), which is still lower than the PPV on a per test basis. The specificity was not formally considered on a per patient basis as the number of patients who contributed the 429 non-elevated VMA results was unknown. However, one can make a conservative assumption of 172 patients contributing the 429 normal VMA test results (this assumes that the number of tests performed per patient is higher for these patients than for those with at least one elevated result). Using these conservative figures, the specificity on a per patient basis is 68% (172/254).

The possibility that a higher threshold might improve the test characteristics of the VMA assay was explored and a cut-off at 1.5 times the laboratory reference was arbitrarily chosen. An increase to this value *(ie* ≥ 52 μmol/24 hr) would result in a 66% reduction in the number of elevated VMA assays (from 122 to 41). This reduction corresponds to a 68% reduction in the number of patients who would have at least one elevated result according to the usual reference limit. On a per test basis, the median VMA was 75 μmol/24 hr (IQR 58–98) while on a per patient basis (n = 27), the median of the higher/highest VMA was 79 μmol/24 hr (IQR 63–104). On a per test basis, the sensitivity falls to 50% (4/8), specificity increases to 93% (506/543), and the PPV increases to 10% (4/41). On a per patient basis with the higher threshold, the sensitivity was 67% (2/3) and the PPV was 7% (2/27). The sensitivity and PPV for identifying a catecholamine-secreting tumour were 75% (3/4) and 11% (3/27) respectively.

Finally, the specificity under the higher threshold was examined. If the same number of patients with VMA results below the previous threshold is assumed (see above), then on a per patient basis, the specificity would be 90% (229/254).

DISCUSSION

Biochemical tests of catecholamine excess include measurements of 24-hour urinary excretion of metanephrines, catecholamines (epinephrine and norepinephrine) and VMA (1). More recently, the measurement of plasma-fractionated metanephrines has become available as a highly sensitive screening test (9, 10) and has been advocated as the single best test of choice, although this remains controversial (11). Goldstein *et al* concluded that plasma free metanephrines is the first line diagnostic test due to its sensitivity, with negative results ruling out the diagnosis (12). However, some investigators have found that plasma metanephrines lack the specificity necessary to recommend it as a first line test (13). They concluded that measurements of 24-hour urinary total metanephrines and catecholamines yield fewer false-positive results and are more useful in patients who do not have a relatively high clinical prior probability.

We have found that VMA testing at our institution has a high sensitivity (100% on both a per patient and per test basis) compared to reports (46–72%) previously published (6, 11). The PPV is low whether considered on a per test (7%) or per patient basis (4%). Vanillylmandelic acid testing has lower specificity (79%) in this study when compared to other reports (95–96%) (6, 11). However, it is not possible to be certain about the specificity value as systematic follow-up data were not available on patients who had normal VMAs. It is possible, for instance, that these patients could have had a subsequent diagnosis of phaeochromocytoma made at another institution. It was outside the scope of this study to perform a comprehensive follow-up of these patients.

The median VMA (44 μmol/24 hr) among patients who did not have a phaeochromocytoma was not markedly elevated above the laboratory cut-off of 35 μmol/24 hr and this suggests that a higher threshold might make VMA testing a more discriminating test. In this retrospective dataset, using a higher cut-off resulted in the majority of patients who had false positive results being reclassified as having normal results. The increased threshold would prevent unnecessary further testing in these patients, increase the specificity and PPV, and could have avoided surgery in one patient who did not have a phaeochromocytoma. However, this would have been at the cost of missing one patient with a phaeochromocytoma. Failure to identify a true case may be an unacceptably high cost.

Using a test with higher specificity and more careful patient selection may be a better option than changing the reference limit for VMA assays.

It is interesting to note that the majority (83%) of non-surgical patients had either one or no symptoms that are conventionally attributed to catecholamine excess. Less than one-third had headache, which is reported in the literature

(14, 15) as the most common symptom (72%), followed by sweating (69%) and palpitations (51%). These symptoms make up the classic triad, which was rare in the present review. Clinician assessment of a patient's probability of having phaeochromocytoma is paramount in deciding whether biochemical testing is indicated. Pursuing biochemical testing may be inappropriate in cases where the clinical probability is very low (based on paucity of typical symptoms). In contrast to the non-surgical patients, patients who had phaeochromocytoma were all hypertensive and had multiple symptoms typical of catecholamine excess. Since VMA testing has very high sensitivity but lower specificity, it may be appropriate in these highly symptomatic cases.

Asymptomatic patients undergo testing mainly to rule out phaeochromocytoma as a cause of hypertension. As the prevalence in hypertensive persons is less than 0.5% (1), these patients are considered low risk. Interpretation of an elevated result in these patients is especially difficult due to the low PPV rate. Using plasma or urinary metanephrines may therefore be desirable in the evaluation of these patients.

A non-systematic review of 11 hypertensive patients under our care who had both VMA and plasma metanephrine assays provides some evidence in favour of the suggestions made above. Two patients were tested after the detection of an abdominal mass and 9 patients had biochemical evaluation prior to any imaging being performed. The patients with abdominal masses (highest VMA values were 119 and 146) had elevated plasma metanephrines and were subsequently shown to have phaeochromocytomas. None of the other nine patients (median of highest VMA results 65, IQR 54–79) had elevated metanephrines or were proven to have a phaeochromocytoma. Even from this small sample, the association between plasma metanephrines and presence/absence of phaeochromocytoma is significant (Fisher's exact p = 0.018). These preliminary data support the selection of different tests depending on whether the patient has a high or low clinical probability of having a phaeochromocytoma. So, patients with an abdominal mass and multiple symptoms of catecholamine excess could have VMA testing, whereas patients with hypertension and few, if any, symptoms of catecholamine excess should have a high specificity test (*eg* metanephrines).

False positive results often lead to repeat testing and abdominal imaging, which increase total costs. Although VMA testing is relatively inexpensive, the combination of repeat testing and imaging would be costlier than performing a single highly specific test, such as metanephrines (Table 5). In addition, although difficult to quantify in financial terms, there is the cost of patient anxiety, and loss of productivity with more time off work to facilitate multiple tests. The low PPV rate from our data may be due, in part, to the spectrophotometric test method used (16). This method may yield elevated results due to dietary intake of chocolate, coffee, bananas, foods containing vanilla, citrus fruits, and drugs such as acetaminophen and methyldopa. It is generally recommended that these must be restricted three days prior to and during the 24-hour urine collection. The level of adherence to these recommendations is, however, impossible to ascertain from this retrospective review. However, the restriction of vanilla- and amine-containing foods is debatable, as the dietary contribution to VMA estimation is small (17). Nevertheless, these foods cause marginal increases similar to what was seen in our study, and in these cases, at least a two-fold elevation is necessary to be considered diagnostic of a phaeochromocytoma (17).

Table 5: Estimated costs of various tests utilized during investigation for phaeochromocytoma

Test	Cost (USD)
Plasma metanephrines[+]	189
Urinary vanillylmandelic acid[+]	27
Abdominal ultrasound[*]	39
Abdominal CT Scan[*]	272
VMA tests x 2 and abdominal CT scan	326

Notes:
1. Quotes from a [+]private laboratory facility, Kingston, Jamaica and [*]Radiology Department, UHWI (April 2010).
2. Rates calculated using foreign currency exchange rate 89 JMD to 1 USD
3. CT = computed tomography

In conclusion, VMA testing has low positive predictive value, and special care must be taken in interpreting marginally elevated results. Increasing the upper reference limit for VMA testing or using a more specific biochemical assay may increase the PPV. The best testing strategy is not certain at this time; and the approach could differ depending on whether the patient has a high or low clinical probability of having a phaeochromocytoma.

ACKNOWLEDGEMENTS

We thank the staff of the Medical Records Department, University Hospital of the West Indies for assistance with patient record retrieval. We also thank Dr Georgiana Gordon-Strachan for statistical advice/assistance.

REFERENCES

1. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet, 2005; **366:** 665–75.
2. Beard CM, Sheps SG, Kurland LT, Carney JA, Lie JT. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc 1983; **58:** 802–4.
3. Eschen O, Frobert O, Jensen V, Hvitfeldt Poulsen S. Pheochromocytoma, a rare cause of acute cardiogenic shock. Clin Res Cardiol 2007; **96:** 232–5.
4. Bravo EL, Gifford RW Jr. Pheochromocytoma. Endocrinol Metab Clin North Am 1993; **22:** 329–41.
5. Bravo EL. Evolving concepts in the pathophysiology, diagnosis, and treatment of pheochromocytoma. Endocr Rev 1994; **15:** 356–68.
6. Boyle JG, Davidson DF, Perry CG, Connell JM. Comparison of diagnostic accuracy of urinary free metanephrines, vanillyl mandelic Acid,

and catecholamines and plasma catecholamines for diagnosis of pheochromocytoma. J Clin Endocrinol Metab 2007; **92:** 4602–8.
7. Bravo EL, Gifford RW Jr. Current concepts. Pheochromocytoma: diagnosis, localization and management. N Engl J Med 1984; **311:** 1298–1303.
8. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr *et al.* Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; **42:** 1206–52.
9. Eisenhofer G, Keiser H, Friberg P, Mezey E, Huynh TT, Hiremagalur B et al. Plasma metanephrines are markers of pheochromocytoma produced by catechol-O-methyltransferase within tumors. J Clin Endocrinol Metab 1998; **83**: 2175–85.
10. Eisenhofer G, Lenders JW, Pacak K. Choice of biochemical test for diagnosis of pheochromocytoma: validation of plasma metanephrines. Curr Hypertens Rep 2002; **4:** 250–5.
11. Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 2002; **287:** 1427–34.
12. Goldstein DS, Eisenhofer G, Flynn JA, Wand G, Pacak K. Diagnosis and localization of pheochromocytoma. Hypertension 2004; **43:** 907–10.
13. Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab 2003; **88:** 553–8.
14. Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. Endocr Rev 2003; **24:** 539–53.
15. Ram CV, Fierro-Carrion GA. Pheochromocytoma. Semin Nephrol 1995; **15:** 126–37.
16. Pisano JJ, Crout JR, Abraham D. Determination of 3-methoxy-4-hydroxymandelic acid in urine. Clin Chim Acta 1962; **7:** 285–91.
17. Karet FE, Brown MJ. Phaeochromocytoma: diagnosis and management. Postgrad Med J 1994; **70:** 326–8.