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Screening for Adrenal-Endocrine Hypertension: Overview of Accuracy and Cost Effectiveness

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Introduction

Hypertension is a highly prevalent disorder afflicting 29% of adults in the United States (1). It is a major risk factor for cardiovascular disease morbidity and mortality including myocardial infarction, congestive heart failure, stroke, renal disease and dementia (2-5). Multiple treatment trials have clearly demonstrated the effectiveness of blood pressure control in preventing cardiovascular disease events (6,7). Although control rates are improving, approximately 50% of adults with hypertension remain uncontrolled (1). Most adults with elevated blood pressure have primary or “essential” hypertension for which the cause(s) is unknown. Generally, lifelong treatment is required. The proportion of patients with secondary or identifiable causes of hypertension is uncertain. Older studies suggest that secondary forms account for less than 10% of hypertension (8). However, with the development of newer screening and diagnostic procedures, the frequency of some secondary forms of hypertension may be much higher than previously thought (9). Detection of secondary hypertension is important because, depending on the cause, it may be possible to cure the hypertension or tailor therapy to achieve control with fewer medications reducing cost and side-effects. In the case of endocrine causes of hypertension, identification is also important because undetected disorders can be fatal and confer adverse effects beyond those due to elevated blood pressure.

This presentation focuses on issues of accuracy and cost-effectiveness of screening strategies for two important endocrine causes of hypertension – primary aldosteronism - a relatively common secondary cause of hypertension and pheochromocytoma- a rare secondary cause of hypertension. Cost effectiveness of screening involves an understanding of the clinical contexts where the likelihood of these disorders is high enough to justify testing and where the potential adverse clinical consequences of missing the diagnosis justify the expense and risks associated with screening. It also requires an understanding of

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the diagnostic accuracy of current screening tests and strategies and the effect of positive and negative results on the probability of disease in order to limit further diagnostic investigations to those most likely to have one of these disorders.

Basics of cost-effectiveness of health interventions

Formal cost-effectiveness analysis is an analytic tool that assesses the costs and effects of an intervention designed to prevent, diagnose, or treat a disease compared to an alternative strategy designed to achieve the same goals (10,11). A ratio is constructed where the numerator is the net expenditure of health care resources (a monetary measure) and the denominator is the net improvement in health (a nonmonetary measure). In the context of the present discussion, for each of the endocrine causes of hypertension, the immediate costs are those associated with performing the relevant screening test(s) and any subsequent tests required to confirm the diagnosis and, where necessary, to identify subtypes of disease as well as costs related to any disease specific interventions. Additional costs considered are those due to patient time expended (lost wages), care giving (paid or unpaid), travel expenses, and economic costs to employers. The most common measure of net improvement in health used in the denominator is quality-adjusted life years (QALY's) gained. The final value of the cost-effectiveness ratio represents the marginal effects in both the numerator and the denominator of the intervention compared to the alternative strategy which in the context of this discussion represents the costs related to management of the blood pressure in the setting of an unrecognized endocrine cause and the estimated effect of missing the diagnosis on QALY's. No formal cost-effectiveness analyses have been carried out with regards to screening for the endocrine causes of hypertension considered here. The issue of the marginal effects on cost and health improvement arising from screening for endocrine causes of hypertension can only be discussed in general terms in this presentation.

Principles underlying accuracy of diagnostic testing

Use of a screening test to evaluate for the presence of a disease requires an understanding of the mathematical relationships between test characteristics (i.e., sensitivity and specificity) as well as some estimate of the likelihood that the disease is present (pre-test probability) in various clinical contexts (12). A simple way of illustrating the relationship of a screening test result and the presence or absence of a disease is shown in Figure 1. In this scheme, the screening test results are interpreted as either being positive or negative using a defined cut-point value (which is the case for most screening tests for endocrine hypertension). Sensitivity is defined as the proportion of people with the disease who have a positive test result. Specificity is the proportion of people without the disease who have a negative test result. As will be pointed out in more detail later, sensitivity and specificity have not been clearly determined for many of the screening tests used to evaluate for endocrine hypertension. In part this is due to the lack of an established "gold-standard" used across studies to define the presence of the disease. Use of different gold-standards for diagnosis will yield different estimates of sensitivity and specificity. In addition, negative results of screening tests are less well studied than positive results in the medical literature. This is because of a reluctance to perform confirmation testing in persons with a negative screening test result. Thus, the false-negative rates for screening tests are often underestimated.

The ideal screening test would be characterized by having both a high sensitivity and specificity, however, for most screening tests there is a trade-off between sensitivity and specificity which is required when test results have a range of potential values. This is certainly the case for endocrine-hypertension screening tests which measure laboratory values that vary across a continuum (plasma renin activity, serum aldosterone concentration, plasma or urine catecholamines or their metabolites, plasma, urine or salivary cortisol).

Under these circumstances, the location of a cut-point that distinguishes normal from abnormal is somewhat arbitrary. Receiver-operator characteristic curves are used to obtain the cut-point value that optimizes sensitivity and specificity for a given screening test (Figure 2).

Knowledge of test characteristics of sensitivity and specificity are important considerations when choosing a specific test to screen for a given disease. For example, the most sensitive test available should be used to screen for a dangerous but treatable disease such as pheochromocytoma. Highly sensitive screening tests are also useful when the probability of disease is low and the purpose of the test is to discover a disease. This is because a highly sensitive test is rarely negative in the presence of disease (few false negative results). A highly sensitive test is most helpful when negative as it “rules-out” the disease. In contrast a highly specific test is best suited to confirm a diagnosis that is suggested by other data. This is because a highly specific test is rarely positive in the absence of disease (few false positives). A highly specific test is most helpful when the result is positive as it “rules-in” disease.

It is important to point out that sensitivity and specificity of diagnostic tests are often determined using samples of persons with known disease (cases) and persons known not to have the disease (controls). Under these extremes, the test may perform very well. However, sensitivity/specificity may change when the test is applied to patients in clinical practice where the severity of disease may differ from the extremes used in case-control studies or when patients without the disease differ from the controls by frequently having other conditions that cause a false positive result.

The predictive value of a test is defined as the probability of the disease given the test results (post-test probability, Figure 2). Positive predictive value is the probability of having the disease in a patient with a positive test result, whereas, negative predictive value is the probability of not having the disease in a patient with a negative test result. Predictive value is determined from the sensitivity and specificity of the test and an estimate of the prevalence of the disease in the population being tested (pre-test probability). For endocrine hypertension, there is variable information available regarding prevalence of disease in various clinical contexts which influences the ability to estimate the predictive value of screening tests under all circumstances. The importance of pre-test probability in test interpretation is illustrated by the fact that a positive result even for a test with high specificity will likely be a false positive if the pre-test probability of disease is low. Similarly, a negative result even for a test with high sensitivity will likely be a false negative if the pre-test probability of disease is high.

An alternative way of describing the performance of a diagnostic test is the use of likelihood ratios. The likelihood ratio for a particular value of a diagnostic test is defined as the probability of the test result in the presence of disease divided by the probability of the result in the absence of disease. It simply expresses how many times more or less likely a test result is present in persons with the disease compared to those without the disease. A major advantage of using likelihood ratios is that it is possible to summarize the information contained in a test result for any value of the test across the entire range of possible values rather than limiting interpretation at a single cut-off point. The potential value of using likelihood ratios across values of screening test results rather than a single cut-point will be discussed.

Finally, because screening tests for endocrine hypertension are imperfect and characterized by intermediate sensitivities and specificities, use of multiple tests are sometimes suggested as a screening strategy. Generally, multiple tests are carried out in two ways They can be

performed in parallel (all at the same time) in which case a positive result from any single test is interpreted as evidence for disease or they can be performed serially (consecutively) with subsequent tests performed based on positive results of a previous test. When performed serially, all tests must be positive to make the diagnosis.

In general, multiple tests performed in parallel increase the sensitivity and, therefore the negative predictive value for a given pre-test probability (prevalence) above that of any of the single tests at the expense of a lower specificity and positive predictive value. Parallel testing is useful when a sensitive screening strategy is desired but only two or more relatively insensitive tests are available. This strategy misses fewer persons with the disease but increases the number without the disease who may undergo additional tests or interventions.

In general, multiple tests performed serially increases the specificity and, therefore, the positive predictive value for a given pre-test probability (prevalence) above that of any of the single tests at the expense of a lower sensitivity and negative predictive value. Serial testing is useful when none of the available individual tests are highly specific. This strategy makes one more certain that a positive result represents disease but at an increased risk that some with disease will be missed. When using two tests in series, use of the test with the higher specificity (and usually lower sensitivity) first is more cost effective as it usually leads to the same number of cases identified with fewer patients subjected to both tests.

Primary Aldosteronism

Primary aldosteronism (PA) is the syndrome resulting from the autonomous over production of aldosterone. In general, it is due to a unilateral aldosterone producing adenoma (APA) or bilateral adrenal hyperplasia (idiopathic PA [IPA]). Other rare variants also occur. Morbidity arises from both elevated blood pressure and non-blood pressure effects of aldosterone acting through the mineralocorticoid receptor inducing vascular injury and fibrosis in the heart and kidneys (13-15). Thus, at the same level of blood pressure, patients with PA have higher morbidity and mortality than those with essential hypertension (16). However, it is not certain if under the conditions of blood pressure control, morbidity or mortality outcomes differ between these groups. Distinction of the two major subtypes is important because removal of an APA may lead to cure of hypertension with attendant reduction in health risks and improvement in quality of life, whereas patients with IHA require lifelong treatment with antihypertensive drugs; However, targeted therapy using a mineralocorticoid receptor blocker may lead to improved blood pressure control with the need for fewer medications in some patients.

Screening for PA- considerations related to cost effectiveness

Although anecdotal clinical experience suggests detection of PA to be associated with improved blood pressure control and patient satisfaction, there are no data from clinical trials that directly link screening for PA to reduced morbidity, mortality, or improvements in quality-of-life. Given this limitation of evidence, screening should be restricted to patient subgroups where the alternative treatment strategy, assuming a diagnosis of essential hypertension, could be reasonably considered to be inferior. Moreover, given the limitations of the currently recommended screening test (reviewed below), a decision regarding the relative harm of missing the diagnosis versus the potential costs and harms related to subjecting patients with false positive screening results to further diagnostic studies also needs to be considered.

Screening for PA -Pre-test probability of disease in hypertensive subsets

Current clinical guidelines from the Endocrine Society advises clinicians to limit screening for PA to patient subgroups with a relatively high prevalence of the disease (pre-test probability), (17). This is reasonable as screening restricted to hypertensive subgroups with a moderate prevalence of disease limits the number of false positive screening results.

Estimates of the prevalence of PA vary across studies related in part to whether primary or referral populations are assessed (referral bias) and to variation in the reference standard used to confirm the diagnosis (verification bias), (18). However, PA appears to be the most common, potentially curable secondary form of hypertension. In a study by Schwartz et al using a community-based sample of adults with presumed essential hypertension (no referral bias) in which all participants (regardless of screening test results) underwent confirmatory testing for PA with dietary sodium loading, the prevalence was 13% (95% CI 7% to 20%) (19). In a study by Mosso et al, assessing patients from primary care clinics (no referral bias) who underwent confirmatory testing with a fludrocortisone suppression test only if screening test results were positive, the prevalence of PA increased with the severity of hypertension (mild HTN 2%, moderate HTN 8%, severe HTN 13%), (20). Multiple studies have shown a high prevalence of PA ranging from 17% to 23% in patients referred with resistant or difficult to control hypertension (21-24). The Primary Aldosteronism Prevalence in Hypertensives (PAPY) study screened 1125 newly diagnosed hypertensive adults for PA (9). Screen positive patients had the diagnosis confirmed with captopril suppression testing or with application of a validated logistic function. Importantly, in this study PA subtype (APA versus IHA) was determined in all diagnosed patients. The overall prevalence of PA was 11.2% with 43% due to APA and 57% due to IHA. Thus, in the overall sample <5% of patients had an APA which is the potentially curable form of PA.

Table 1 includes a complete listing of subgroups of the hypertensive population suggested for PA screening by the Endocrine Society (17) with estimates of the prevalence of PA associated with each subgroup (17,25). It should be noted that this list includes subsets with a moderate pre-test probability of disease, and other subsets where the pre-test probability is presumed to be elevated but remains uncertain. This uncertainty impairs determination of the predictive value of the screening test. In addition, this list includes subsets where the pre-test probability may be quite low such as persons with hypertension and an adrenal incidentaloma. Motivation for screening such patients is derived from the possibility of finding surgically curable disease. This motivation must be tempered by the clinical context. The cost-effectiveness of screening a person with an adrenal mass but without hypokalemia and with easily controlled hypertension may not be justifiable. This is especially true given that only 33% of patients with APA are cured with surgical removal of the tumor (26). Also, if the pre-test probability of disease is low (1% to 2%), a higher-rate of false positive screening results will follow and in the context of a known adrenal mass the likelihood of carrying out further invasive diagnostic studies with their associated costs and risks will be high.

For the most part, the other subsets recommended for screening (Table 1) are those in which the alternative treatment strategy (assuming a diagnosis of essential hypertension) is often unsuccessful or is associated with the need for intensive treatment with its associated high costs and negative effects on quality of life. In these settings, screening has a higher likelihood of being cost-effective. Screening of all persons for PA at the time of the diagnosis of hypertension cannot be supported on the basis of current knowledge.

Screening for PA- Plasma Aldosterone-Renin Ratio (ARR)

The recommended screening test of choice for PA is the ARR which represents the ratio of values of simultaneously measured plasma aldosterone concentration divided by plasma renin activity (17). The rationale for the ARR as a screening test is based on the assumption that the usual dependency of aldosterone on renin is lost in PA and aldosterone becomes disproportionately elevated relative to the concomitant renin. Moreover, as aldosterone causes extracellular volume expansion, renin becomes secondarily suppressed, resulting in a further increase in the ratio value. A single cut-point value of the ratio is used to distinguish positive from negative results. Values of the ratio differ by methods and units used to report measures of renin and aldosterone. Most often plasma aldosterone is expressed in conventional units of ng/dL and PRA in conventional units of ng/mL/hour. Sometimes PRA and PAC are expressed in SI units and more recently direct renin concentration (DRC) is measured in some laboratories and expressed as mU/liter. To convert conventional units of PRA to SI units of ng/L-s, one multiplies by 0.2778; to convert conventional units of aldosterone to SI units of pmol/L one multiplies by 27.74. In some laboratories, the ratio is calculated using aldosterone expressed in SI units and PRA expressed in conventional units. Dividing such ratio values by 27.4 gives the corresponding value determined by using conventional units for both PRA and aldosterone. Finally, a PRA of 1 ng/mL/hour is equivalent to a DRC of 8.2 mU/liter. For this discussion, values of the ratio using conventional units for both PRA and aldosterone will be used.

Diagnostic Accuracy of the ARR

Unfortunately, few studies have determined the test characteristics of the ARR (sensitivity, specificity, predictive value and likelihood ratios) at different cut-point values. In 2002, Montori et al reviewed 16 prospective studies (>3000 participants) of the ARR as a screening test for PA (27). They observed that none of these studies evaluated the ARR and reference standard independent of each other; only two studies evaluated screen negative patients with the reference standard; and only 16.7% of the participants had both the ARR and the reference standard performed. Moreover, the origin of the study samples (primary care versus referral clinics), the conditions of measurement (on or off antihypertensive drug therapy), the details of measurement (time of day, body position) and the specific laboratory methods of measuring PRA and aldosterone varied among studies. They concluded that there were no published valid estimates of the test characteristics of the ARR when used to screen for primary aldosteronism in patients with presumed essential hypertension. Schwartz and Turner conducted a study to determine the diagnostic accuracy of the ARR and to assess the effects of antihypertensive drug therapy with hydrochlorothiazide and variations in dietary sodium balance on test characteristics (19). This study overcame most of the deficiencies noted in the review by Montori et al (27). Referral bias was avoided by using a community-based sample of adults with presumed essential hypertension. All participants were subjected to confirmatory testing for PA regardless of the ARR results. The reference standard used for diagnosis of PA was 24-hour urine aldosterone excretion $\geq 12 \mu\text{g}$ following 4 days of dietary sodium loading with $>200 \text{ mEq}$ sodium in the 24-hour urine collection. Study personnel were blinded to the results of the screening test and reference standard until the time of data analysis. The overall prevalence of biochemical PA in the study sample was 13%. Receiver operator characteristic curves were constructed for the ARR under each of the four clinical conditions studied and the optimum cut-off values for the ARR were determined (Figure 2). Table 2 summarizes the optimum cut-points of the ARR and their associated test characteristics under each of the clinical conditions assessed. This study demonstrated that the optimum cut-off value of the ARR varied with clinical conditions, ranging from 8.9 when assessed under conditions of acute sodium diuresis to 14.9 with usual sodium intake and off antihypertensive drugs. Depending on clinical conditions of testing,

sensitivity varied from 73% to 93% and specificity varied from 71% to 84%. Predictive value of a positive test was relatively poor ($\leq 41\%$), suggesting the diagnosis should not be based on the ARR alone. However, the predictive value of a negative test was quite high ($\geq 95\%$) under all clinical conditions assessed. The study demonstrated that the ARR had only fair diagnostic accuracy in screening for PA.

The modest sensitivities observed in the study by Schwartz and Turner was not unexpected as it is known that the ARR can vary greatly in individuals with known PA. In one study of repeated determinations of the ratio under random and standardized conditions in 71 patients with confirmed PA due to aldosterone-producing adenomas, normal ARR values were observed in 31% of patients on at least one occasion and in only 37% of patients were the ARRs increased on all occasions of measurement (28). These observations support the recommendation of Gordon to obtain repeated measures of the ARR (31). This is a form of parallel testing which as previously noted will increase sensitivity (fewer false negatives) at the expense of lower specificity (more false positives). The cost-effectiveness of such a strategy has not been formally assessed.

The modest specificities observed in the study by Schwartz and Turner was also not unexpected given the known high frequency of low PRA among patients with essential hypertension (29). In a previous study, Schwartz et al measured aldosterone and PRA in a large sample of 505 black and white adults with presumed essential hypertension 4 weeks off of antihypertensive drug therapy (30). Using a cut-point value of 20, they determined the sensitivity, specificity and predictive value of the ARR to identify combinations of PRA and aldosterone compatible with PA (low PRA defined as a value within the lowest quartile of the sample distribution and elevated aldosterone for level of PRA defined as a value in the highest quartile predicted by linear regression on renin). Overall, the sensitivity of an increased ARR to identify combinations of PRA and aldosterone compatible with PA was 66% (80% in blacks versus 56% in whites). Overall specificity was 67% (46% in blacks and 84% in whites). Positive predictive value was only 34% (49% in whites and 27% in blacks). In 36% of instances, an elevated ARR was solely a measure of low PRA without increased aldosterone for renin. The renin dependency of the ARR was also noted in a study by Montori et al, who measured PRA and aldosterone in a sample of 497 black and white adults with presumed essential hypertension under several conditions (in the supine position and in the seated position after 30 minutes of ambulation off of antihypertensive drugs for 4 weeks and in the seated position after 30 minutes of ambulation following 4 weeks of treatment with hydrochlorothiazide) (31). They observed that variation in the ARR was strongly and inversely dependent on variation in PRA and predominately an indicator of low PRA rather than an indicator of renin-independent aldosterone levels suitable to assess for PA. To improve the specificity of the ARR some have advocated the addition of a minimum threshold value of aldosterone as part of the screening criteria (32). This represents a serial test strategy. As previously noted, such a strategy will increase specificity (fewer false positives) but at the expense of further reductions in sensitivity (more false negatives).

Finally, a practical problem facing clinicians in clinical practice is to decide on which cut-point value of the ARR to use for a positive result. Suggested cut-point values for the ARR range from 15-100 (17,19). The most commonly used cut-point values for a positive ARR are 20-30 (17). The use of a single cut-point value to determine whether the test is considered “positive” or “negative” excludes useful information available from any single value obtained during screening. Reporting of likelihood ratios associated with ranges of values of the ARR could be used by the clinician to determine the impact of any measured value of the ARR on the probability of PA. As can be seen by inspection of the ROC curves (Figure 2), very high values of the ARR have high specificity for PA. In certain clinical settings (e.g., hypertension with spontaneous hypokalemia associated with renal potassium

wasting), a very high value of the ARR by itself could be considered diagnostic for PA without the need for further confirmatory testing.

Pheochromocytoma

A pheochromocytoma is defined as a tumor arising from catecholamine-producing chromaffin cells in the adrenal medulla (intra-adrenal paraganglioma) or in extra-adrenal sympathetic and parasympathetic paraganglia (extra-adrenal paraganglioma). As will be detailed below, pheochromocytomas are a rare cause of hypertension. Motivation for screening and case detection is the recognition that pheochromocytoma can be fatal if unrecognized.

Screening for pheochromocytoma – considerations related to cost effectiveness

Although, a formal assessment of the cost-effectiveness of pheochromocytoma screening has not been performed, there are several issues that can be expected to influence this calculation. The first issue is the knowledge that pheochromocytoma can be a fatal disorder. Therefore, the potential health benefit (denominator) in the cost-effectiveness ratio is very high. The second issue is the recognition that pheochromocytoma is rare in the population but clinical presentations raising the possibility of pheochromocytoma are common. In one reported series, only 1 of 300 patients evaluated for pheochromocytoma had the disorder (33). A third issue relates to the diagnostic characteristics of the multiple available screening tests and how to use these most efficiently for case detection. A fourth issue relates to interpretation and clinical decision making for marginally elevated screening test results. Further testing involving expensive imaging modalities can add significantly to the cost of case detection.

An analysis by Sawka et al. illustrates how these issues can impact the cost of case detection. In this report, costs associated with 3 strategies of screening for pheochromocytoma (assuming diagnostic imaging for positive biochemical test results) in a population where disease prevalence was 0.5% ranged from \$60,000.00 to \$116,000.00 (34). Although, these costs appear high, they may be reasonable when expressed as cost per life saved. However, given these cost estimates it is obligatory that clinicians strive to identify the most effective and cost-efficient strategy for case identification.

Screening for pheochromocytoma-Pre-test probability of disease

Patients considered for pheochromocytoma screening include those with resistant hypertension, hyper-adrenergic spells, a family history of pheochromocytoma, a hypertensive response to anesthesia, early onset hypertension (<20 years old), hypertension and unexplained cardiomyopathy, an incidental adrenal mass identified on imaging tests, and those with genetic disorders known to be associated with pheochromocytoma. Estimates of the prevalence of pheochromocytoma in some of these clinical subsets are summarized in table 3 (35). For the vast majority of patients encountered in clinical practice, the clinical indications for screening are often resistant hypertension or hyper-adrenergic spells. The prevalence estimates of pheochromocytoma in such settings are low. As noted earlier, it is important to keep in mind that in settings where the prevalence of disease is low, a positive screening test result, even for a test with high specificity will likely be a false-positive. Therefore, clinical decision making is important when confronted with positive results from screening, especially if the results are only marginally positive. Considering test results in a binary fashion (positive or negative) is less informative than considerations related to the continuous nature of the results of screening tests for pheochromocytoma.

Screening tests for pheochromocytoma

Diagnosis of pheochromocytoma requires biochemical evidence of excessive catecholamine production by the tumor. A variety of screening tests are available and consist of measurements of catecholamines (epinephrine, norepinephrine) or their metabolites (metanephrine, normetanephrine or vanillylmandelic acid) in the blood or urine. The metabolites of epinephrine and norepinephrine can be reported as total metanephrines (sum of metanephrine +normetanephrine) or separately (fractionated metanephrines).

It is now clear that most of the metabolism of catecholamines occurs within the cells that produce them rather than after release into the circulation (36). Within catecholamine producing cells, vesicular stores of catecholamines are in a highly dynamic state of equilibrium with catecholamines in the cytoplasm. Active transport from cytoplasm to storage vesicles is countered by ongoing passive leakage of catecholamines from these vesicles. The small fractions of catecholamines that escape vesicular sequestration are subsequently metabolized by catechol-*O*-methyl transferase and the metabolites are released into the circulation. This process accounts for most of the measured catecholamine metabolites in the plasma and urine. Within a catecholamine-producing tumor, this process is occurring continuously and independent of catecholamine release which often occurs only intermittently. This provides a rationale for the observed higher diagnostic sensitivity of measures of plasma or urine catecholamine metabolites (metanephrines) than measures of plasma or urine catecholamines (37,38). Among the catecholamine metabolites, vanillylmandelic acid has been shown to have poor diagnostic sensitivity and, thus, measurement of the fractionated catecholamine metabolites-metanephrine and normetanephrine in the plasma or urine- are the preferred screening tests for pheochromocytoma (37,38,39).

Both plasma and urinary metanephrines are often measured by high pressure liquid chromatography with electrochemical detection (HPLC-EC). More recently methods using gas chromatography with mass spectrometry (GS-MS) or liquid chromatography with tandem mass spectrometry (LC-MS/MS) are being employed. These newer methods of analysis are preferred because they are less susceptible to medication interference and non-specific binding and, thus, are associated with higher diagnostic accuracy (40).

Plasma metanephrines circulate free in the plasma and are sulfated as they pass through the gastrointestinal circulation. The sulfated conjugates are excreted in the urine. Reported plasma metanephrines are usually measured in their free form, whereas, reported urine metanephrines are measured after being de-conjugated. Whether this results in differences in diagnostic performance between the tests is uncertain; however, plasma concentrations of free metanephrines are relatively independent of renal function which is not the case for urinary metanephrines. Thus, the plasma test is preferred in the presence of chronic kidney disease if glomerular filtration rate is <30 mL/min (41).

Diagnostic accuracy of plasma free and urinary fractionated metanephrines

Several studies have assessed the test characteristics (sensitivity, specificity) of plasma free and urinary fractionated metanephrines (metanephrine and normetanephrine). Differences in results across studies can be influenced by a number of factors including the analytical method used for determination of results, the sample studied (proportion of patients with sporadic versus hereditary pheochromocytoma, inclusion of patients with renal dysfunction), and the upper value of the reference range used to distinguish a positive from a negative test result. Test characteristics from more recent studies are summarized in table 4 (38,40,42,43). In these studies, both sensitivity and specificity were slightly higher for plasma free metanephrines than for urinary fractionated metanephrines (for sensitivity - 96-100% versus

86-97%; for specificity – 89-98% versus 86-95%). However these differences are quite small and it is fair to conclude that the test characteristics of these tests are similar. Plasma free metanephrines avoid the inconvenience of a 24-hour urine collection (especially in children) and the concerns associated with a possible incomplete collection. Also, plasma free metanephrines are not influenced by renal dysfunction.

As noted earlier, consideration of the continuous distribution of values for these tests in clinical decision making rather than a binary positive or negative interpretation is important. For example, values of plasma metanephrines that are greater than 4-fold above the reference range are associated with an almost certainty of disease (44). Values that are marginally above the reference range must be interpreted carefully. Consideration of causes for false-positive results of either plasma or urine fractionated metanephrines should be made. These include concomitant use of drugs, especially phenoxybenzamine, tricyclic antidepressants, buspirone, and drugs containing catecholamines such as decongestants and weight loss aids. Other settings associated with false-positive results include sudden discontinuation of drugs such as clonidine, benzodiazepines, or ethanol and severe, untreated sleep apnea. For plasma free metanephrines, performance of the test in the supine, rather than sitting position may result in resolution of borderline elevations (39). Finally, diets rich in biogenic amines (i.e., fruits and nuts) can cause up to a 2-fold increase in de-conjugated normetanephrine levels (measured in the urine) but have no effect on plasma free metanephrines (45). Repeating the test after consideration of these issues would be appropriate. For marginally elevated plasma metanephrine or normetanephrine, values of the metanephrine/ epinephrine ratio <4.2 and the normetanephrine/norepinephrine ratio <0.52 are consistent with a false-positive elevation. Further, the response of normetanephrine to oral clonidine can help distinguish false from true positive results (44). Finally, measurement of plasma chromogranin A or urine fractionated metanephrines in patients with marginally elevated plasma metanephrines may improve diagnostic specificity (46).

Screening for pheochromocytoma - multiple testing strategies

It is common in practice to order multiple screening tests in patients who are considered to be at high-risk for pheochromocytoma. As noted previously, tests can be ordered in parallel or serially. It must be kept in mind that multiple tests ordered in parallel (all at the same time) increases the sensitivity of screening at the expense of lower specificity. This strategy is most often used when individual screening tests lack sensitivity but this is not the case for the recommended screening tests for pheochromocytoma and, thus, this practice is generally discouraged. In most patients encountered in clinical practice, the pre-test probability of disease is low, and a parallel screening strategy will most often lead to additional invasive testing in patients with false-positive results. However, in patients where the pre-test probability is high (Table 3) parallel testing may be justified.

As just discussed, several serial testing strategies have been suggested for further evaluation of marginally elevated plasma or urine fractionated metanephrines to improve specificity and reduce the number of false-positive patients undergoing further invasive diagnostic tests (44,46). In general, serial testing is useful when none of the available screening tests is highly-specific. As noted in table 4, both plasma and urine fractionated metanephrines have similar but only moderate specificity for pheochromocytoma. In general serial testing will increase specificity at the expense of lower sensitivity and this must be kept in mind when employing such strategies for identification of a potentially fatal disorder.

Summary

Formal studies have not been performed to assess the cost-effectiveness of screening strategies for endocrine causes of hypertension. However, an understanding of the diagnostic

accuracy of available screening tests and the clinical settings where disease identification will lead to improved health outcomes form the basis for a cost-effective strategy. Primary aldosteronism may be very common; however, screening should be selective and restricted to those settings where knowledge of the diagnosis has the greatest chance of improving health outcomes. Pheochromocytoma is very rare; however, because it is a potentially fatal disease, screening strategies should error on the side of not missing the diagnosis, especially in high-risk clinical settings.

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TEST		DISEASE	
		Present	Absent
		True	False
Positive	Positive	a	b
	Negative	c	d
Negative		e	f

Sensitivity = a/(a+c)
Positive predictive value = a/(a+b)
Positive likelihood ratio = (a/b)/(c/d)

Specificity = d/(d+f)
Negative predictive value = d/(d+e)
Negative likelihood ratio = (c/d)/(a/b)

Figure 1.
Diagnostic test characteristics and definitions

Figure 2. ROC curves for the aldosterone/PRA ratio determined under four clinical conditions Drug Therapy = concurrent antihypertensive drug therapy; Drug Free = after a minimum 2-week antihypertensive drug-free interval; Sodium Loading = after 4 days of high sodium diet; Furosemide Diuresis = after acute furosemide diureis. Optimum cut-point in bold for each ROC curve is expressed using conventional units of ng/mL/hour for PRA and ng/dL for aldosterone. Data from reference 19: Schwartz GL, Turner ST. Screening for primary aldosteronism in essential hypertension: diagnostic accuracy of the ratio of plasma aldosterone concentration to plasma renin activity. *Clinical Chemistry* 2005;51(2):386-394 with permission of the publisher.

Table 1

Hypertensive subsets considered for primary aldosteronism screening

Hypertensive Subset	Prevalence (Pre-Test Probability)
Moderate/Severe HTN (BP >160/100 mm Hg)	8% to 13%
Resistant HTN Defined by BP $\geq$ 140/90 mm Hg despite full doses of three complimentary antihypertensive drugs including a diuretic appropriate for level of renal function.	17% to 23%
Hypertension with unprovoked hypokalemia associated with renal potassium wasting.(27)	50%
Hypertension and an adrenal incidentaloma	1% to 10% (1% to 2% in the absence of severe HTN or hypokalemia)
Hypertension and diuretic associated hypokalemia (especially if treatment resistant or in the presence of concomitant use of potassium-sparing diuretics or renin-angiotensin-system blocking drugs).	uncertain
Hypertensive first degree relatives of persons with PA.	uncertain
HTN and family history of early -onset HTN or stroke (especially cerebral hemorrhage at a young age (<40 yr).	uncertain

HTN, hypertension, BP, blood pressure; PA, primary aldosteronism Adopted with modifications from reference 17: Funder JW, Carey RM, Fardella C et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: An Endocrine Society Clinical Practice Guideline. *Endocrinol Metab* 2008;93:3266-3281.

Table 2

Test characteristics of the aldosterone/renin ratio (ARR) to screen for primary aldosteronism

	Drug therapy	Drug free	Sodium loading	Acute diuresis
Optimum-cut-point*	12.4	14.9	13.3	8.9
Sensitivity (%)	73	87	93	73
Specificity (%)	74	75	71	84
Likelihood ratio				
Positive test	2.8	3.4	3.2	4.4
Negative test	0.36	0.18	0.10	0.32
Predictive value (%)				
Positive test	29	33	32	41
Negative test	95	97	99	96

Drug therapy = concurrent antihypertensive drug therapy; Drug Free = after a minimum 2-week antihypertensive drug-free interval; Sodium loading = after 4 days of high sodium diet; Acute diuresis = after acute furosemide diureis.

* Optimum cut-point expressed using conventional units of ng/mL/hour for PRA and ng/dL for aldosterone. Data from reference 19: Schwartz GL, Turner ST. Screening for primary aldosteronism in essential hypertension: diagnostic accuracy of the ratio of plasma aldosterone concentration to plasma renin activity. *Clinical Chemistry* 2005;51(2):386-394.

Table 3

Patient subsets and prevalence of pheochromocytoma

Patient Subset	Prevalence (Pre-Test Probability)
Unselected hypertension population	0.2%
Hypertension and suggestive symptoms	0.5%
Adrenal incidentaloma	4%
Hereditary forms of pheochromocytoma	
Multiple endocrine neoplasia type II	30% - 50%
von Hippel-Lindau disease	15% - 20%
Neurofibromatosis type I	1% - 5%
Familial paraganglioma syndrome	20%

Table 4

Test Characteristics of plasma free and urinary fractionated metanephrines*

Study	Plasma free metanephrines		Urinary metanephrines	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Perry (ref. 42)			97.1	91.1
Hickman (ref. 38)	100	97.6	85.7	95.1
Grouzmann (ref. 43)	96	89	95	86
Peaston (ref. 40)	100	96		

Tests characteristics base on a positive test defined as either metanephrine or normetanephrine above the reference range and a negative test defined as both metanephrine and normetanephrine within the reference range.