

## SPECIAL SITUATIONS

# Clinical and Laboratory Assessment of Patients with Suspected Primary Aldosteronism

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## ABSTRACT

Primary aldosteronism (PA) was described over 60 years ago, but the relevance of PA to the burden of hypertension has never been greater. Best estimates from studies in a variety of settings indicate that PA is present in 5 to 8% of all patients with hypertension and up to 20% of patients with resistant hypertension. Progress in our understanding of the pathogenesis of PA helps to explain how PA can be so common and the genesis of bilateral hyperaldosteronism (BHA). Pitfalls in the evaluation of PA certainly exist, but these difficulties with the later stages of the evaluation should not impede liberal screening in groups of patients with a high prevalence of PA. In fact, the initial stages of the evaluation are utterly simple, and screening can make an enormous impact on the care of these patients. This article will provide a practical review of the approach to the patient suspected of having PA, which is by far the most common cause of secondary hypertension.

**Keywords:** Adrenal adenoma, Adrenal hyperplasia, Aldosterone, Hypertension, Hypokalemia, Ion channel, Primary aldosteronism, Renin.

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## INTRODUCTION

Throughout human history, the ability to conserve sodium and thus to maintain plasma volume has been critical for survival. Several defense mechanisms exist to defend against volume depletion from hemorrhage, environmental stress, and sepsis. Both neural and humoral mechanisms cooperate to conserve sodium when necessary. On the contrary, we are not well designed to excrete excess sodium, particularly if heart or kidney function is impaired. This bias for sodium conservation helps to explain the high prevalence of hypertension in developed

countries with diets high in sodium. Furthermore, even mild derangements in sodium conservation mechanisms can exacerbate the tendency for hypertension under conditions of sodium surfeit. One such mechanism is the group of conditions included under the diagnosis of PA.

## SODIUM HOMEOSTASIS AND ALDOSTERONE

Central to the sodium conservation mechanisms is the renin–angiotensin (Ang)–aldosterone system. Reduced sodium delivery to the renal macula densa stimulates renin synthesis, and renin cleaves angiotensinogen to AngI. The converting enzyme generates AngII from AngI, and AngII both acts as a vasoconstrictor and stimulates aldosterone synthesis from the adrenal zona glomerulosa. Aldosterone acts directly on the principal cells of the distal nephron to enhance resorption of the last 2% of filtered sodium. While this small fraction might not seem like much, it is this last bit of sodium that is critical for blood pressure regulation. Furthermore, aldosterone has direct actions on the brain to stimulate sympathetic nerve activity,<sup>1</sup> and thus exerts pressor activity via a second mechanism.<sup>2</sup>

For these reasons, the “normal range” of serum aldosterone must be defined in terms of volume status and sodium intake, reflecting the dynamic nature of aldosterone production to meet the need for sodium conservation. In healthy individuals, plasma renin activity (PRA; alternatively, renin concentration) inversely reflects plasma volume and sodium homeostasis; consequently, PRA and aldosterone normally rise and fall in parallel. The only other strong stimulus for aldosterone production is hyperkalemia, and adrenocorticotropin elicits a moderate but transient rise in aldosterone. In a salt-loaded society, most individuals have low PRA and therefore produce little aldosterone, with circulating concentrations <4 ng/dL (<0.1 nmol/L), among the lowest concentrations of any active steroid hormone in the body. Unfortunately, this system leaves little room for error. Aldosterone is <50% protein bound and thus mostly bioactive, and aldosterone has an affinity of ~1 nmol/L for the mineralocorticoid receptor (MR). Therefore, even mild aldosterone excess has the potential to drive MR activation, sodium retention, and hypertension. In turn, autonomous aldosterone excess will lower PRA via volume expansion, and low PRA is a hallmark of all mineralocorticoid excess syndromes.

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## APPROACH TO THE PATIENT WITH SUSPECTED PA

While the exact prevalence of PA in the hypertensive population is debated, in part due to subtleties in defining PA, the prevalence is at least 5% and up to four times higher among those with resistant hypertension. The joint American College of Cardiology/American Heart Association hypertension guidelines<sup>3</sup> list major criteria for PA screening (Table 1). The Endocrine Society clinical practice guidelines add additional criteria,<sup>4</sup> and the Japanese Society of Hypertension recommends screening all patients with hypertension for PA.<sup>5</sup> While the exact indications are debated, the concept is that patients with difficult-to-control hypertension, early-onset hypertension, and hypertension with excessive potassium wasting are prime suspects for PA. In addition, the prevalence of atrial fibrillation and congestive heart failure is much higher in patients with PA than in other forms of hypertension,<sup>6</sup> which should also raise suspicion. Because PA is by far the most common cause of secondary hypertension, any hypertensive patient with a clinical course suggestive of secondary hypertension should be screened for PA.

There are several reasons to screen patients with hypertension for PA. First, if the diagnosis is established and the patient has an aldosterone-producing adenoma (APA), localization and surgery can either cure the hypertension or significantly improve blood pressure control often with less medications. This objective assumes that screening will be followed with the specialized subsequent evaluation steps necessary to assure proper management. Second, making a diagnosis of PA then should remain in the patient's medical record to remind subsequent providers that, if surgery is not an option, the patient should receive MR antagonist therapy at a minimum.

Contrary to widely held misconceptions, screening for PA is simple and can be performed in patients taking any hypertensive medications, as long as the principles of screening are well understood. Primary aldosteronism screening involves simultaneous measurement of PRA

and serum aldosterone in a simple blood test, and it is best to obtain a serum potassium as well. Based on the preceding discussion, renin and aldosterone normally rise and fall in parallel. Fundamentally, screening asks if aldosterone production persists when renin is low. For convenience, this assessment traditionally employs the calculation of the aldosterone/renin ratio (ARR = aldosterone in ng/dL divided by PRA in ng/mL/h). In normotensive individuals, the ARR is typically 2 to 7 using these units.<sup>7</sup> Rather than using a strict single ARR cut-off value to diagnose PA, the screening results should be viewed as a continuum reflecting probability of the diagnosis. Furthermore, the individual values should be assessed systematically as described below.<sup>8</sup>

### Plasma Renin Activity

Is it low (<1), medium (1–5), or high (>5)? If the PRA is low, the screen can be interpreted, regardless of any medications the patient might be taking. If the PRA is medium, PA cannot be diagnosed, but if the patient is taking blood pressure medications, the result can be a false-negative. Most blood pressure medications are either vasodilators or diuretics, which will tend to raise PRA and thus can obscure a low PRA in the absence of these medications—particularly MR antagonists. While official recommendations are to wait up to 6 weeks after stopping MR antagonists to screen for PA, most patients with PA will still have low PRA despite typical doses of MR antagonists or require only 1 to 2 weeks for the PRA to fall. Patients with PA rarely have high PRA despite any medications in the absence of other concomitant illness. Beta-blockers tend to lower PRA but lower aldosterone proportionately do not interfere with PA screening. Finally, many laboratories are converting from PRA to renin mass or “direct renin” immunoassays. As a rule of thumb, the direct renin values in pg/mL are a factor of 10 higher than PRA in ng/mL/h,<sup>7</sup> and <10 pg/mL should be considered low and consistent with PA.

### Serum Aldosterone

If a normal serum aldosterone in a patient with low PRA is <4 ng/dL, how much is too much? One should consider the answer as a continuum from low-renin hypertension to overt PA with intermediate results likely reflecting PA in evolution. As with all hormone excess syndromes, patients often progress through an early, mild, or “sub-clinical” stage before developing overt disease.<sup>9</sup> With a low PRA, aldosterone values >20 ng/dL are essentially diagnostic, values 10 to 20 ng/dL are likely PA but require further evaluation, and values 5 to 10 ng/dL are not strictly normal but generally not high enough to pursue

**Table 1:** Indications for PA screening

Hypertension resistant to three conventional drugs including a diuretic
Hypertension with spontaneous or diuretic-induced hypokalemia
Hypertension with a family history of early-onset hypertension or stroke at age <40 years
Hypertension in a patient known to have an adrenal mass
Controlled hypertension requiring four or more drugs
Sustained blood pressure >150/100
Hypertension with sleep apnea
Hypertensive first-degree relatives of patients with PA
Patients under evaluation for secondary hypertension

the workup further, because these patients might have early PA in evolution but not likely to have an APA with dominant aldosterone production from one adrenal gland. As will be discussed below, all other should be treated with MR antagonists if the blood pressure is not controlled in the absence of contraindications.

### Serum Potassium

Low potassium inhibits and high potassium stimulates aldosterone production. An aldosterone >10 ng/dL in the face of hypokalemia is almost certainly indicative of aldosterone excess, because the aldosterone would be higher if the potassium was normal. Conversely, hyperkalemia can raise aldosterone and cause a rare false-positive screen, but hyperkalemic patients are not usually evaluated for PA.

### Aldosterone/Renin Ratio

Whereas a normal ARR is 2 to 7, we typically use a cut-off of 20 for a positive screen, which is three times higher than normal. An important caveat is that as PRA falls, the values approach zero, and since PRA is the denominator of the ARR, the ARR approaches infinity.<sup>10</sup> In other words, if a PRA of 0.1 is used to calculate the ARR, then patients with serum aldosterone as low as 2 ng/dL would have an ARR >20—but they do not have PA since the aldosterone is suppressed. Thus, PRA values not lower than 0.5 ng/mL/h should be used for calculating the ARR, even if the laboratory reports the values lower.<sup>8</sup>

To summarize PA screening, medications can cause false-negatives by raising the PRA, and for patients in whom the index of suspicion for PA is high, removal of medications and rescreening is appropriate. The clue will be that these patients still have a high ARR and very high aldosterone (>20 ng/dL). Few false-positives are encountered when screening for PA, primarily hyperkalemia and the use of values PRA <0.5 for calculating ARR. Thus, one should be more concerned about false-negatives than false-positives when screening for PA (Table 2).

**Table 2:** Pitfalls of screening

Serum potassium
Hyperkalemia stimulates aldosterone production, yields rare false-positives
Hypokalemia impairs aldosterone production, yields false-negatives
MR antagonists
Raise renin and can cause false-negatives
PRA reporting
Values <0.5 ng/mL/h artificially inflate ARR to higher values and cause false-positives

### CONFIRMATORY TESTING AND SUBTYPING STEPS

In a patient with hypokalemia, suppressed PRA, and serum aldosterone >20 ng/dL, a diagnosis of PA is made from screening alone.<sup>4</sup> In patients without hypokalemia and/or a serum aldosterone 10 to 20 ng/dL, confirmatory testing is required to establish the diagnosis. Table 3 lists common confirmatory tests and cut-off values to diagnose PA. In particular, the criterion of serum aldosterone >6 ng/dL for the fludrocortisone suppression test emphasizes what a fine line exists between normal aldosterone dynamics and PA. Whereas all providers who care for patients with hypertension should screen for PA, confirmatory testing and later stages of the evaluation are usually performed after referral to an endocrinologist or hypertension specialist with experience in conducting and interpreting these tests.

Conceptually, PA has been dichotomized into unilateral PA (due to an APA) and BHA. This dichotomy is a slight oversimplification for two reasons. First, not all patients with unilateral PA have a single adenoma. Some have no identifiable neoplasm, and other might have more than one adenoma, though often one of these accounts for most of the aldosterone production, based on staining for the aldosterone synthase (CYP11B2) enzyme.<sup>11</sup> Conversely, patients with BHA were assumed to have hyperplasia of the zona glomerulosa, but in fact they might have different pathologies discussed below. Second, cases with an APA and unilateral dominance but significant aldosterone production from the nondominant adrenal are being increasingly recognized. Nevertheless, the evaluation subsequent to confirmatory testing endeavors to determine as completely as possible the subtype of disease causing the PA and the contribution of each adrenal gland to the aldosterone production.

In general, a computed tomography (CT) scan with and without contrast of the adrenal glands is the imaging procedure of choice for PA.<sup>4</sup> A third set of images is also obtained to measure contrast washout. Computed tomography has higher resolution than magnetic resonance imaging and so can detect small tumors <1 cm

**Table 3:** Confirmatory testing options

Test	Method	Criteria for PA
24 h urine Na, aldo	24 h urine on third day high-salt diet	Aldo >12 µg/24 h Na >200 mEq
Saline infusion	Infuse 2 L normal saline over 4 h	Serum aldo >10 ng/dL
Fludrocortisone suppression	Fludrocortisone 0.1 mg q6h × 4 d	Serum aldo >6 ng/dL
Captopril challenge	Captopril 25–50 mg; basal and 1–2 h	No fall in serum aldo

Na: Sodium; aldo: Aldosterone

capable of causing PA; however, incidental nonfunctional adrenal tumors are increasingly common with age and cannot be distinguished from APA by imaging criteria alone. The major purpose of CT scanning is to screen for abnormal adrenal anatomy and to assess for large tumors. Adrenocortical carcinomas rarely cause PA but are easily identified as large heterogeneous masses on CT scan. More importantly, APAs often cosecrete cortisol,<sup>12</sup> and in tumors >3 cm, this mixed hormone production can interfere with subsequent testing.<sup>13</sup> Unlike aldosterone production in APAs, which correlates poorly with tumor size, cortisol production generally tracks with tumor size. Thus, a dexamethasone suppression test is often employed in the evaluation of PA to screen for cortisol cosecretion, particularly in patients with a >2.5 cm tumor identified on CT scan.

In a <40-year-old patient with hypokalemia, an age range in which adrenal adenomas are not common, a >1 cm adenoma with a clearly normal contralateral adrenal gland is sufficient to offer the patient adrenalectomy for the gland bearing the adenoma without further evaluation.<sup>4,14</sup> Otherwise, the only way to definitively identify the source(s) of aldosterone is adrenal vein sampling (AVS). Adrenal vein sampling is a technically challenging procedure, due to the anatomy of the right adrenal vein (RAV), which is a short vessel connecting the right adrenal gland with the posterior wall of the inferior vena cava (IVC). The left adrenal vein (LAV) meets with the superior wall of the left renal vein near the entry of the left inferior phrenic vein. The radiologist obtains samples from the IVC, RAV, and LAV; cortisol and aldosterone are measured for these samples. Various procedures have been developed and adopted at centers around the world, with the major variables being the use of basal samples or under cosyntropin infusion or bolus; simultaneous *vs* sequential sampling of the RAV and LAV, and use of superselective microcatheters to sample regions within each adrenal.<sup>15</sup>

The interpretation of AVS data consists of three steps.<sup>15</sup> Because adrenal blood flow is so small relative to the volume of the samples obtained, AV samples always contain a variable amount of mixed venous blood. Consequently, the first step is evaluation of the cortisol concentrations as a marker of AV blood. Cortisol concentrations in the AV samples should be at least four times higher than the mixed venous blood in the IVC when cosyntropin is used and at least two times without cosyntropin. These criteria are called the selectivity index, which assures that the AVs were successfully accessed and corrects for the variable dilution with mixed venous blood. Next, one calculates the aldosterone/cortisol (A/C) ratios (cortisol-corrected aldosterone values), which corrects the aldosterone for the dilution of the AV sample with mixed venous blood. Finally, the higher A/C ratio

(dominant side) is divided by the lower A/C ratio (nondominant side), which yields the lateralization index (LI). With cosyntropin stimulation, LI values >4 confidently lateralize aldosterone production to one adrenal gland, and these patients are offered adrenalectomy of the dominant side. LI values <2 indicate bilateral disease, and these patients are treated with MR antagonist. LI values of 2 to 4 are indeterminate but are uncommon. While not required to interpret an AVS study as lateralized when the LI is >4, the contralateral index (CI), which is the nondominant A/C ratio divided by the IVC A/C ratio, is helpful when the LI is 2 to 4. A CI value <1, which is called "contralateral suppression," confidently indicates that the nondominant side is minor contributor to the total aldosterone production, and these patients are also offered adrenalectomy. Without cosyntropin stimulation, LI values >2 are consistent with lateralized aldosterone production.

## THErapy FOR PA

As discussed above, patients who lateralization on AVS are offered surgery, and those with bilateral disease are treated with MR antagonists. Patients with lateralized AVS might also be managed with MR antagonists, particularly if they are poor surgical candidates. Conversely, patients with BHA and inadequate control and/or side effects with MR antagonist might be offered unilateral adrenalectomy of the dominant side; however, the expectations for improvement are modest.<sup>16</sup>

How should patients be counseled about the effectiveness of surgery? The Primary Aldosteronism Surgical Outcome (PASO) consortium sought to standardize the definition of complete or partial (and absent) biochemical and clinical successes using the Delphi process.<sup>17</sup> The group then analyzed data from over 700 patients with PA treated with surgery after lateralized AVS. Complete biochemical success, meaning normal ARR and serum potassium, occurred in 94% of patients, which attests to the accuracy of AVS in guiding surgery. Complete clinical success, meaning normal blood pressure without any antihypertensive drugs, was achieved in only 37%. Partial clinical success, meaning lower blood pressure with the same drugs and/or similar blood pressure using fewer drugs, was achieved in 47%. Women and younger patients were most likely to experience complete or partial clinical success, whereas higher preoperative use of antihypertensive medications was predictive of lower likelihood complete clinical success.<sup>17</sup>

Despite reduction or discontinuation of antihypertensive medications postoperatively, two complications are seen following adrenalectomy. Because PA is in a hyperfiltration state, a small rise in serum creatinine is often seen after surgery. Age, male sex, hypokalemia, large tumors,

and high serum aldosterone concentrations are all risk factors for impaired renal function and for a creatinine rise after surgery.<sup>18,19</sup> A second complication following surgery is prolonged hyperkalemia due to suppression of the contralateral zona glomerulosa, which occurs in 5% of cases.<sup>20</sup> Impaired renal function preoperatively, a rise in creatinine and/or microalbuminuria postoperatively, and contralateral suppression on AVS<sup>21</sup> are all predictors of hyperkalemia, which can persist up to 6 months and might require fludrocortisone and/or dietary potassium restriction.

A rise in serum creatinine and/or potassium is also commonly observed with MR antagonist therapy, particularly in patients with impaired renal function. To avoid these complications, spironolactone should be started at a low dose of 12.5 to 25 mg/d with close monitoring of electrolytes and creatinine. The onset of blood pressure reduction from spironolactone is much slower than most other antihypertensive drugs, so dosage adjustment should not be made more frequently than every 4 to 6 weeks. Side effects of spironolactone, which are dose-dependent and rarely occur in the first 6 weeks or on doses <50 mg/d, include gynecomastia and sexual dysfunction in men or breast tenderness and vaginal spotting in women. When these side effects limit spironolactone use, eplerenone might be substituted as a selective MR antagonists that lacks these limitations but is less potent than spironolactone. Eplerenone should be started at twice the spironolactone dose and divided twice daily (50 mg/d spironolactone = 50 mg BID eplerenone). The same principles of subsequent dose titration for spironolactone also apply for eplerenone. The most common error in the use of spironolactone is advancing the dose too quickly. The most common error in the use of eplerenone is underdosing and not dosing twice daily.

The target of medical therapy for PA is not known, but normalization of blood pressure and serum potassium is a minimal indication of adequate MR antagonist dosing. Monitoring of PRA is helpful for two reasons. The first is that a rise in PRA to >1 indicates significant physiologic evidence of MR blockade, at least in the kidney. The second reason is that when the blood pressure remains elevated despite a dose of MR antagonist sufficient to raise the PRA to the normal range, higher doses of MR antagonist are not likely to lower the blood pressure further. In these cases, calcium channel blockers, beta-blockers, and even loop diuretics might be added to normalize blood pressure and serum potassium.

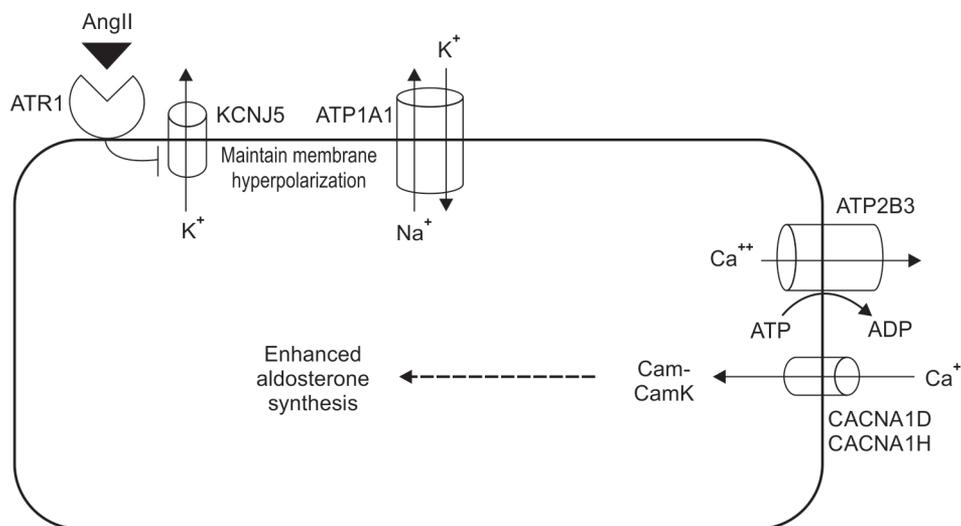
## PATHOGENESIS OF PA

Clues to the pathogenesis of PA have derived from rare genetic forms of PA, the familial hyperaldosteronism (FHA) syndromes types 1 to 3. The FHA1 is also

called dexamethasone-suppressible or glucocorticoid-remediable aldosteronism. The FHA1 derives from a hybrid gene, which places the adrenocorticotropin-responsive promoter of the *CYP11B1* (11-hydroxylase) gene upstream of the *CYP11B2* (aldosterone synthase) gene.<sup>22</sup> This hybrid gene drives the adrenocorticotropin-dependent expression of an enzyme with aldosterone synthase activity in the zona glomerulosa. One feature of this disease is production of hybrid steroids, specifically 18-hydroxycortisol and 18-oxo-cortisol.<sup>23</sup> The FHA2 is probably a mixture of diseases without a known genetic defect. The molecular basis of FHA3 was elucidated in 2011<sup>24</sup> as autosomal dominant gain-of-function mutations in the *KCNJ5* gene encoding the Kir3.4 or GIRK4 potassium channel, which maintains the resting hyperpolarization of zona glomerulosa cells. The mutations modify the selectivity filter, allowing the channel to conduct sodium as well as potassium. This alteration leads to chronic depolarization, increased intracellular calcium, and autonomous aldosterone production. While only a few families with germline *KCNJ5* mutations have been identified, many studies have now shown that somatic *KCNJ5* mutations are commonly observed in APAs and are likely a major component of their pathogenesis.<sup>25</sup> Curiously, patients with FHA3 and APAs bearing *KCNJ5* mutations also produce excess 18-hydroxycortisol and 18-oxo-cortisol,<sup>26</sup> which illustrates that these diseases are not simply overgrowths of normal zona fasciculata cells.

Following the identification of *KCNJ5* mutations in APAs, mutations in other ion channels and pumps were also found in APAs, including the *ATP1A1* gene<sup>27</sup> encoding a sodium/potassium ATPase, the *ATP2B3* gene<sup>27</sup> encoding a calcium ATPase, and the *CACNA1D*<sup>28,29</sup> and *CACNA1H*<sup>30,31</sup> genes encoding L-type Cav1.3 and T-type Cav3.2 calcium channels respectively (Fig. 1). These mutations function via the final common pathway: Increased intracellular calcium, calmodulin activation, and increased expression of the enzymes and other proteins necessary for aldosterone production.

If ion channels and pumps are involved in the pathogenesis of APAs, what causes BHA? Recently, several groups have identified a clue from normal adrenal glands of adults. Using an antibody specific for aldosterone synthase, these investigators found not a continuous zona glomerulosa as found in adrenals from children and rodents but rather isolated small clusters of aldosterone synthase-positive cells scattered under the adrenal capsule.<sup>32</sup> Using laser-capture microdissection, they studied the molecular signatures of these aldosterone-producing cell clusters (APCCs) and found the mutations found in APAs, primarily *CACNA1D* but also *ATP1A1*



**Fig. 1:** Germline and somatic gene mutations implicated in primary aldosteronism. Gain-of-function mutations in the KCNJ5 (GIRK4, Kir3.4) potassium channel, which is normally inhibited upon AngII binding to its receptor (ATR1), are commonly found in APA. Mutations in the sodium/potassium ATPase ATP1A1 prevent the maintenance of hyperpolarization. Mutations in the calcium ATPase ATP2B3 or L-type CACNA1D and T-type CACNA1H calcium channels elevate intracellular calcium, which activates calmodulin and its kinase (Cam, CamK) to drive aldosterone production

and *ATP2B3*—yet not in *KCNJ5*. The prevalence and size of APCCs increase with age, such that most adrenals from adults age 50 or older contain one or more APCCs.<sup>32</sup> It is possible that accumulation of these APCCs over time causes BAH, and it is also possible that APCCs are precursors for at least some APAs following additional molecular alterations.

## CONCLUDING REMARKS

Primary aldosteronism is the most common cause of secondary hypertension, and screening for PA should be a routine part of hypertension practice. Screening is simple and can be performed without stopping any medications. The latter stages of the evaluation should be reserved for specialists and centers with experience in interpreting dynamic testing, performing AVS, and using minimally invasive adrenal surgery. The pathogenesis of PA is being unraveled, and the common occurrence of APCCs in adult adrenal glands might explain why PA is so common. We have much more to learn about the pathophysiology and management of PA. In the meantime, screening for PA is simple and routinely available but underutilized. Given the profound benefit a diagnosis of PA can make for an individual, screening should be considered routinely (Table 1). Even in those who cannot progress to the latter stages of the evaluation or who screen negative, MR antagonist therapy is likewise an underutilized tool in hypertension care and, as shown in the ASCOT<sup>33</sup> and PATHWAY-2<sup>34</sup> studies, extremely effective in patients with all forms of low-renin hypertension.

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