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Progress in Primary Aldosteronism: Present Challenges and Perspectives

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Abstract

Primary Aldosteronism (PA) is a disorder of the adrenal zona glomerulosa (ZG) in which aldosterone secretion is increased and is relatively autonomous of normal regulatory mechanisms. A recent conference in Munich organized by Prof. Reincke addressed advances and challenges related to the screening, diagnosis, and identification of uni- and bilateral involvement of the diseased adrenal of PA. Some infrequently addressed issues are described herein. We postulate that most cases of PA are due to the activation by unknown mechanisms of subset of cells resulting in the formation of a multiple foci or nodules of hyperactive zona glomerulosa cells. This implies that one or several yet unidentified stimuli can drive aldosterone overproduction, as well as the proliferation of aldosterone-producing cells. Current diagnostic procedures allow to determine whether inappropriate aldosterone production is driven by one or both adrenal glands and thus to establish optimal treatment.

Keywords

adrenal adenoma; adrenal cortex; aldosterone; mineralocorticoid; adrenal tumor; steroidogenesis

Preamble

Primary Aldosteronism (PA) is a disorder of the adrenal zona glomerulosa (ZG) in which aldosterone secretion is increased and relatively autonomous of normal regulatory mechanisms. A recent conference in Munich organized by Prof. Martin Reincke of the Klinikum der Ludwig-Maximilians-Universität addressed advances and challenges related to the various aspects of Primary Aldosteronism. The main topics included the prevalence, confirmatory testing, adrenal vein catheterization, animal models, and therapy. This is a discussion of some of the challenges identified and some not considered.

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What is Primary Aldosteronism?

PA is a disorder originally described by Jerome Conn from the University of Michigan [1] and reported by him in the 60's to be common [2, 3]. The initial definition was that of an aldosterone-producing adenoma (APA) causing a syndrome of hypertension and hypokalemic alkalosis associated with high urinary excretion of aldosterone and suppression of plasma renin activity [3]. PA is now recognized to entail a spectrum of disorders ranging from a solitary APA at one hand to bilateral nodular hyperplasia at the other, with several intermediate phenotypes. While differing in terms of pathology, pathophysiology and treatment, the different subtypes of PA fit similar diagnostic criteria. Even though Dr. Conn described PA to be relatively common, subsequent authors believed that the early studies of PA done at the University of Michigan likely overestimated the prevalence of PA because of a referral bias, as at that time very few centers throughout the world were able to measure aldosterone in urine or plasma, and that PA was a quite rare disorder [4, 5]. A problem compounding the difficulty in diagnosing APA in those early years was that generally only patients that presented with hypertension and "spontaneous" hypokalemia were screened for inappropriately high aldosterone production. Advances in screening procedures indicate that PA is present in 5–15% of patients with hypertension [6–15] and that most PA patients are not hypokalemic when blood samples are collected in the usual way with a tourniquet [16].

Diagnosis of Primary Aldosteronism

The renin-angiotensin system is believed to be the primary stimulatory factor in aldosterone secretion. Hence, the diagnosis of PA is based on the demonstration of a nonsuppressible aldosterone secretion and a suppressed level of renin. Earlier studies involved time-consuming maneuvers to demonstrate the failure of plasma renin to increase when stimulated, most often by sodium depletion with or without a diuretic [17], and the lack of aldosterone suppression in response to excess oral or intravenous sodium administration, with or without the additional administration of an exogenous mineralocorticoid (DOC or fludrocortisone [6,17–19]). Alternatively, the secretory rate of aldosterone was inferred by the measurement of surrogate metabolites in the urine, including the renal metabolite 18-oxoglucuronide (acid-labile metabolite commonly called urinary aldosterone), which corresponds to 5–10% of secreted aldosterone [20] or the liver metabolite 3α,5β-tetrahydroaldosterone-3-glucuronide (corresponding to 30–45% of secreted aldosterone) [16,20].

The diagnosis of PA advanced greatly with the recognition by Hiramatsu et al. [21] that expression of the measurements of plasma (or serum) aldosterone and plasma renin activity as a ratio [Aldosterone Renin Ratio (ARR)] from random samples, but preferably those obtained under standardized conditions was a good screening test for PA. Use of the ARR followed by additional confirmatory testing demonstrated that PA is a common disorder among patients with "essential hypertension" [13–15].

The rationale for undertaking the screening of hypertensive patients for PA depends on: i) the recognition that there are cardiovascular consequences of the elevation of the aldosterone in excess of those associated with the elevation of the blood pressure per se [22]; and ii) the

possibility that patients with APA and unilateral hyperplasia could be long-term cured surgically. Moreover, treating PA patients medically with a specific mineralocorticoid receptor (MR) antagonist have beneficial cardiovascular consequences, which appear to be incompletely related to lowering of the blood pressure [23–28].

While the ARR is now widely used for screening for PA, there is wide range of opinions on the conditions under which the blood sample should be drawn, the assay for aldosterone and renin to be used, or even the definition of a positive ARR cutoff value [14,15,29]. Most investigators recommend the elimination of all antihypertensive agents for at least 2–3 weeks and MR antagonists for at least 6 weeks [30]; others believe that patients can remain on less intrusive antihypertensive treatment such as a long-acting calcium channel antagonist and/or an α1 blocker [14], discontinuing only MR antagonists, sodium channel blockers, and beta blockers [15, 31]. Measurement of the ARR has also been used to detect patients whose BP might respond to administration of a MR antagonist, as well as those who may have PA [32]. However, the fact that also patients with essential hypertension do respond to the MR antagonist spironolactone has limited the usefulness of this approach as a diagnostic test [33].

Limitations of the ARR

The ARR is a crude bivariate analysis, which can account for the fact that there are problems relying solely on it for the diagnosis. Renin is frequently very low, in some cases undetectable, producing a high ARR, even in patients with aldosterone levels in the normal range, particularly in those patients who are (or were) taking beta blockers. Therefore, the ARR may be positive at whatever level the cutoff is set. Because aldosterone is secreted in bursts, which are of higher frequency and magnitude during the early morning [34–36], the ARR can vary widely with samples taken few minutes apart. Even considering all these caveats, the reproducibility of the ARR from the same patient under similar outpatient conditions is reasonable [37]. When the cutoff of the ARR is set at a low value to maximize sensitivity of the screening, further tests are done in patients with ARRs above a set value, usually between 26–50 (using aldosterone units of ng/dl and PRA as ng/ml/h), and often taking into consideration the absolute level of aldosterone in serum or plasma (at least greater than 12 ng/dl, but sometimes greater than 15 ng/dl) [10, 13]. In general medical practice, the ARR has been widely used not only for screening, but as a diagnostic tool of reasonable reliability when cutoffs are set very high and elevated ARRs are associated with clearly elevated plasma aldosterone levels. However, with such high cutoff values the more severely affected patients are usually identified [38], but the far more abundant milder cases of APA that can benefit from adrenalectomy can be missed [39].

Are Confirmatory Tests Necessary to Diagnose PA?

Most experts consider the ARR a screening method to be followed by confirmatory procedures [14,15]. The four confirmatory tests that are being used, which include oral salt loading, saline infusion, captopril challenge, and the fludrocortisone-salt test [15] are all based on the assumption that aldosterone secretion would be autonomous from the RAS in patients with PA. This contention was challenged by the evidence from several groups that

this is not the case in a substantial proportion of the PA patients. In the first report that described the lack of suppression of plasma aldosterone in patients with APA there were only 5 cases in whom this diagnosis was certain, and conversely there were many patients that were held not to have PA who also did not suppress aldosterone secretion [40]. Gordon et al. thereafter reported that 43 % of a series of 14 APA did respond to an angiotensin II infusion and also to posture with an overt increase of plasma aldosterone [41]. Likewise, Biglieri's laboratory found that 5 % of the 154 PA cases had adrenocortical nodular hyperplasia and 2.6 % had an APA that were responsive to stimulatory and suppressive maneuvers involving the RAS [42]. The existence of angiotensin II-responsive APA was further supported by findings by Phillips et al. who described an increase of PAC with ambulation in 71 % of their APA patients which, on that ground, were indistinguishable from the patients presumed to have idiopathic hyperaldosteronism (IHA) [43]. More recently, a low sensitivity (72.8%) and specificity (76.1%), leading to an overall accuracy that was only moderate, was observed with the saline infusion test in the PAPY Study [44]. This was due to the fact that there were false negative results among the patients with APA and false positive results among the patients without. The test accuracy was no higher when the captopril challenge was used instead of the saline infusion test. In fact, it was lower when sodium intake was lower than 133 mEq/day, indicating that an unrestricted salt intake is crucial for optimizing the diagnostic performance of the captopril challenge [45].

For these reasons, considering the low accuracy of the confirmatory tests and also taking into account the decent reproducibility of the ARR when performed under controlled conditions [37] some experts currently base their decision on whether to proceed or not to adrenal vein sampling (AVS) on repeating the ARR under baseline conditions rather than on performing a "confirmatory" test [46]. Whether this is the best strategy or not requires further prospective studies using the presence or absence of APA as reference, which is feasible only with systematic use of AVS.

Are Functional Tests Useful for Discriminating Between PA Subtypes?

The use of the ARR and confirmatory test for the diagnosis of primary aldosteronism has attempted to differentiate between inappropriate aldosterone secretion in relation to the levels of the primary stimuli for aldosterone secretion, angiotensin II (as estimated by the measurement of renin), and autonomous and excessive secretion of aldosterone as determined by suppressive test, all of which involve sodium overload in different ways. When first described, PA was equated to an APA that could be surgically cured [47, 48]. IHA, due to bilateral ZG hyperplasia, was thought to be a variant of "low renin hypertension" and while many cases of IHA were biochemically similar to an APA, they were considered an entity distinct from "Conn Syndrome" [49, 50]. IHA was described as not responding to surgery, including bilateral adrenalectomy, and having a variable response to MR antagonists like spironolactone [49,51,52]. The screening and confirmatory tests for the diagnosis of IHA suggest that this form of primary aldosteronism is a quantitative trait like hypertension rather than a qualitative trait like pheochromocytoma [12,53] or APA. The difference in opinion in the definition of PA due to IHA as a variant of low renin hypertension is largely a semantic concern [48].

Studies in normotensive individuals in the Framingham community study demonstrate that subjects in the top quartile of ARR ratio are at an increased risk of progressive increase in BP and incidence of hypertension and that the ARR is a heritable trait influenced by clinical and genetic factors [54, 55]. There is a continuous gradient of increasing risk of BP progression across ARR levels in these nonhypertensive individuals [55]. This is in line with the concept that was proposed more than 30 years ago [50] that patients with IHA represent an extreme of the continuum of low renin hypertension.

Suppression of aldosterone excretion in the urine by a high salt intake was found to be abnormal in many patients with hypertension, both in those with normal or with low renin hypertension [56, 57]. Patients with essential hypertension could be divided into those who suppressed urinary aldosterone normally, for example, to <6μg/24 h, and those who could not, but the latter were not deemed to have PA unless their salt-suppressed aldosterone secretion was >12μg/24h [56]. Patients with abnormal suppression of urinary aldosterone to salt loading were found to exhibit similar BP elevations as those with normal suppression of urinary aldosterone to salt loading, but showed increased plasma aldosterone responsiveness to the infusion of angiotensin II [58]. There is a continuum of responsiveness to angiotensin II infusion in patients with low renin hypertension and those with idiopathic hyperaldosteronism [58–61]. The set point for the diagnosis of PA is an arbitrary cut-off, for example, a relative point where there is a higher likelihood that the patient has PA. However, as in most tests, there is overlap with patients that have essential or idiopathic hypertension and even between patients with APA and IHA as shown by many studies [16]. Hence, in our view these functional tests are of no value for distinguishing between APA and IHA on an individual basis.

Are Most Cases of Primary Aldosteronism Due to an Aldosterone-producing Adenoma, and Idiopathic Hyperaldosteronism Due to Hypersecreting and Relatively Autonomous Nodule(s) Analogous to a Multinodular Goiter?

The concept that PA is due only to APA is attractive as it hypothesizes a single etiology, a benign neoplastic transformation of cells of the adrenal ZG producing aldosterone, regardless of the molecular mechanism. However, the histological characteristics of most cases classified as an APA are heterogeneous when one considers the surrounding adrenal cortex [62, 63]. APAs have varying proportions of four different types of cells: clear cells with large vacuolated lipid-laden cytoplasm and central round nuclear similar to cells from the zona fasciculata; lipid-poor ZG-like cells; compact eosinophilic cells indistinguishable from those of the zona reticularis, and some cells with cytological features of both zona fasciculata and ZG cells showing variable contents of clear lipid microvacuoles and granular eosinophilic cytoplasm, which are designated “hybrid” or “intermediate” cells [62–64]. Very few of the adenomas have a single cell type [62]. The lipid-rich clear cells usually predominate in these tumors, giving them a characteristic golden yellow color [64]. Some tumors have predominantly glomerulosa-like cells. Neville and O’Hare [62, 63] found that all patients with the diagnosis of an adrenal tumor-producing aldosterone had either

hyperplasia of the ZG in the rest of the adrenal (40 %) or hyperplasia of the ZG with nodules (56 %).

The tissue surrounding the APA and in the contralateral adrenal often contains multiple nodules ranging from microscopic to macroscopic comprised of clear-cells. Paradoxically, the gland with the APA often has hyperplasia of the "normal" ZG [62]. Overall the findings indicate that patients with APA have extensive microscopic changes suggestive of nodular hyperplasia in the rest of the adrenal and in the few cases studied, similar changes were found in the contralateral adrenal. Therefore, it could be contended that one or more unknown stimuli can trigger the development of multiple nodules throughout the adrenal cortex, among which one can become the dominant APA. These considerations, along with a high recurrence rate of PA when adrenocortical sparing surgery was performed, led the surgeons to put forward the paradigm that the whole adrenal gland should be removed. In most cases, surgical excision of the adrenal with the adenoma results in cure or improvement of the hyperaldosteronism [65]. In situ hybridization for the steroidogenic enzymes has been employed to assess the functional significance of the adenoma and surrounding tissues. Unfortunately, the homology at the protein level of the aldosterone synthase and 11β-hydroxylase is very high (94 %) and no specific antibodies have been reported to date that can differentiate them by immunohistochemistry or Western blot in the human. Enberg et al. [65] showed aldosterone synthase expression by in situ hybridization in the dominant nodule of the resected adrenal in 22 out of 27 patients with the histopathological diagnosis of an adenoma. Fourteen of these patients also had expression in the ZG and adrenalectomy resulted in a "cure". However, in one patient who had high aldosterone synthase expression in the ZG surrounding the adenoma, the syndrome recurred. In two patients the aldosterone synthase expression by in situ was in the small nodules, rather than the dominant one and these patients were not cured by the adrenalectomy. Similar results were found by Shigematsu et al. [66, 67]. Most of the hyperplastic ZG and hyperplastic nodules of the adrenal cortices adhering to an APA had decreased steroidogenic activity. They classified the adrenal cortices adhering to the APA in 6 patterns: 1) minute nodules expressing all the steroidogenic enzyme mRNAs except for the 17α-hydroxylase and expected to produce aldosterone only, 2) nodules and 3) diffuse hyperplasia with cells expressing all of the steroidogenic enzymes including weak expression of the 17α-hydroxylase, 4) nodules expressing all steroidogenic enzyme mRNAs including high expression of the 17α-hydroxylase, and 5) nodules and 6) diffuse hyperplasia exhibiting low expression of the steroidogenic enzymes mRNAs. A microarray study of removed adenomas demonstrated low expression of the aldosterone synthase in the adenoma of some patients diagnosed with APA [68]. It is highly likely that the excessive production of aldosterone occurred in micronodules surrounding the "adenoma" in these patients, as adrenalectomy resulted in cure or improvement of the hypertension [68]. Alternatively, it could be that the increased aldosterone secretion is simply due to a much increased number of aldosterone producing cells, as compared to the normal ZG, even despite no overt CYP11B2 overexpression [68].

Adrenal adenomas have been classified as one of two types according to their response to ACTH and angiotensin II. The most common have an exaggerated response to ACTH stimulation [36,42,69–71] and appear to have predominantly fasciculata-type cells [72]. These tumors appear to not only secrete excessive amounts of aldosterone, but also excessive

amounts of 18-oxocortisol, a hybrid steroid that requires the presence, as in fasciculata cells, of the 17α-hydroxylase [71–74]. Angiotensin II-responsive adenomas occur in 10–50% of patients [42,70,72,75]. These patients excrete normal levels of the hybrid steroid 18-oxocortisol [72], reflecting a low expression of the 17α-hydroxylase in these tumors. The correlation between the predominant cell type and the responsiveness of the APA to ACTH or angiotensin II is not found consistently [76]. The response to the secretagogues in bilateral adrenal hyperplasia is also not uniform. Most are very sensitive to angiotensin II [59] and not to ACTH [36], while some are responsive to ACTH, but insensitive to angiotensin II [42].

Demonstration that some APA and adrenal hyperplastic tissue express aberrant hormone receptors and respond to the administration of hormones not normally involved in adrenal physiology suggests that some, or many, of tumors responsible for APA may express aberrant receptors that are responsible for the increased aldosterone secretion in response to hormones not driving aldosterone secretion under physiological conditions [77–80]. In addition to the classical stimulators of aldosterone secretion (angiotensin, potassium, and ACTH), there are other stimuli including neuropeptides, catecholamines, prostaglandins, and still unidentified endothelial and adipocytes secreted factors [81, 82]. It is unknown whether these unidentified factors play a role in producing adrenocortical hyperplasia.

The situation is reminiscent of the toxic multinodular goiter of patients with long term multinodular goiters who develop adenomas that produce thyroid hormone autonomously due to activating mutations of the TSH receptor or G-protein α-subunit [83, 84]. The possibility of activating mutations of the angiotensin II receptor (AT1) in APA has been explored, however, no mutations have been found so far [85, 86]. Studies of other possible mutations in the signal transduction pathway have not been reported.

In summary, the multinodular nature of adrenocortical pathology in PA would suggest that one or, more likely, several unidentified stimuli can drive aldosterone overproduction and the expansion of an aldosterone-producing cell phenotype. Future research should therefore, aimed at developing better cell models for dissecting the molecular mechanisms underlying these changes.

Adrenal Vein Catheterization for Identification of Patients with Unilateral Production of Aldosterone (APA or Unilateral Hyperplasia) and the Pathogenic Challenges they Present

Because of the fallacies of imaging tests, including CT and MR, the consensus report from the American Endocrine Society [15] strongly advocates the use of adrenal vein catheterization for the diagnosis of unilateral production of aldosterone for patients to have a high likelihood of cure after adrenalectomy. After the adrenal veins are catheterized and samples collected, measurements of aldosterone and cortisol (to confirm placement of the catheter and correct for dilutions that might occur during sampling) are done. A ratio of aldosterone/cortisol from both sides is compared to assess if the aldosterone is coming from the site of the “adenoma” or from both sites in the case of IHA. The criteria of the ratio used

for lateralization by different groups vary. The most common ratio to differentiate unilateral production is 3 [15, 30, 39], but some have used a ratio as low as 1.1 with strong documentation of success [87].

The variation in the criteria and ratios has caused frustration among some groups [88]. The most likely cause of the variation in the ratios is the difficulty in catheterization of the right adrenal vein, resulting in the mixing of blood from renal capsular veins or hepatic veins, diluting the aldosterone from the adrenal. Catheterization of the hepatic vein or sampling where the hepatic vein opens into the adrenal vein cause more dilution of aldosterone, in fact the values of steroids might be lower than peripheral values, as they represent liver metabolism of steroids [89]. The problem has been addressed by using super-selective catheterization after identifying the hepatic vein and advancing the catheter until it is secure into the adrenal vein [89] or by rapid measurement of adrenal vein cortisol to confirm the localization of the catheter and making the adjustments as needed [90, 91]. However, expressing the results as a ratio, while very useful to predict response to surgical removal of the affected side, ignores the widely recognized but seldom reported finding that the contralateral adrenal gland, whatever criteria for lateralization is used, is seldom suppressed to levels similar to peripheral values and are most often higher, especially when stimulated with ACTH [92]. We have been unable to find reports of adrenal vein aldosterone and cortisol levels in normal individuals, most likely because this would be hardly feasible due to ethical considerations. Plasma and urinary aldosterone is suppressed to very low levels by the administration of DOC to normal humans [93], but there is no information about the adrenal production or the responsiveness to stimulation in this setting. Future research to obtain such measurements, especially in persons whose adrenal production of aldosterone is suppressed by an exogenous mineralocorticoid, would be very valuable in determining “normal” level of aldosterone production and establish normal range and thereby for choosing the cutoff for ascertaining lateralization. The prevalence of adrenocortical adenomas and hyperplasia was reported to be higher [94–96] or similar in patients with hypertension [97] than in normotensive subjects, but was described to vary between 1.4–20 % of patients at autopsy [94–97]. In a study of cell kinetics and clonality of patients with adrenal cortical adenomas and adrenal cortical nodular hyperplasia of mixed functional status, a high proportion of adenomas were found to be monoclonal and most hyperplasias were found to be of polyclonal origin [98]. Simultaneous downregulated apoptosis and high proliferation result in selective kinetic advantage with dominant clone expansion. Decreased apoptosis would enhance the chance of accumulation of mutations, some of which might have functional consequences and might result in hyperfunction in a small proportion of cells. This is a potential mechanism that should be explored in APA and IHA. Potential models could be studied using animal models of aldosteronism.

Studies from Gomez-Sanchez’s laboratory have shown that ZG width and the expression of the aldosterone synthase is regulated as expected by sodium, increasing in both width of the ZG and cells expressing the aldosterone synthase in rats given a low sodium diet [99]. Administration of 1% sodium chloride solution as drinking fluid for 30 days decreases the width of the ZG and the number of cells that express the aldosterone synthase [99], but there is always a small proportion of cells that exhibit high expression of the aldosterone synthase even after 4 weeks of a very high salt diet in normal rats and aldosterone continues to be

produced, albeit at very low levels. It is not known if these represent different cell lines within the ZG; most that are highly regulated by the sodium status and others that are not. If a similar situation occurs in humans, the proliferation at an abnormally rapid rate or a lower rate of apoptosis resulting in the accumulation of cells not regulated by sodium, could cause PA. Asymmetric growth of such sodium-nonsuppressing cells might produce an adenoma, or unilateral hyperplasia. This hypothesis is supported by the in situ hybridization findings in patients with adenoma or unilateral hyperplasia [65–67,100].

The reported success of surgery for APA is highly variable and depends to a significant degree upon the definition of cure, but in most cases, when the diagnosis is based on AVS results and the hypertension is not long-standing and/or associated with vascular remodeling [101], unilateral adrenalectomy is associated with “cure” or “significant improvement” of the hypertension [12, 53]. However, over half to two thirds of patients with APA treated surgically continue to require antihypertensive medications, albeit with lower doses, or fewer drugs [12,53,65,102]. Very few studies have addressed the biochemical cure after adrenalectomy using functional studies. Rutherford [103] repeated the fludrocortisone suppression test 3 months after adrenalectomy and found that 53 % of patients were cured of hypertension and had normal fludrocortisone suppression test. In 47 % of patients, the hypertension improved, plasma renin activity became normal, but the fludrocortisone suppression tests were abnormal. The usual criteria of normalization of the ARR would have failed to identify the patients that remained relatively unresponsive to mineralocorticoid suppression. These findings require confirmation, but they suggest that almost half of the patients had bilateral, but asymmetric disease. The contribution of the predominant site was sufficiently large that its elimination resulted in improvement of hypertension and “normalization” of plasma and urinary aldosterone, however, the nonsuppressible tissue in the remaining adrenal continues to be kinetically abnormal, though at a lower level of production with less functional significance. A recent report found that in patients with bilateral PA subjected to unilateral adrenalectomy, 15% were “cured” and 20% improved [104], further indicating that relative normality can be attained by removal of an adrenal that was producing enough aldosterone to be above the physiological requirements. The contralateral adrenal in those patients that improved was obviously not producing enough aldosterone to cause the clinical syndrome of PA, even while abnormal.

Concluding Remarks

In summary, the Munich meeting primarily addressed the prevalence of hyperaldosteronism, differentiation between the various types of PA, animal models, and therapy. In this manuscript, we have addressed issues related to potential pathogenesis associated with patients with PA that require more attention in future research. In fact, despite the high prevalence of PA among the patients with hypertension, the molecular mechanisms by which a normal adrenal cortex develops into a disease featuring multinodular hyperplasia and/or a single APA, often surrounded by satellite nodules, are still largely unknown. Notwithstanding this, research on the past decade has contributed substantially to improve the screening for PA and the strategies for subtype differentiation. A more accurate diagnosis is likely to improve the outcome after surgical treatment as extensively discussed during this

Munich meeting. Nonetheless, more efforts should be devoted to elucidate the molecular mechanism of PA in order to identify novel target for treatment.

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