Primary Aldosteronism
Novel Approaches and Future Outlooks

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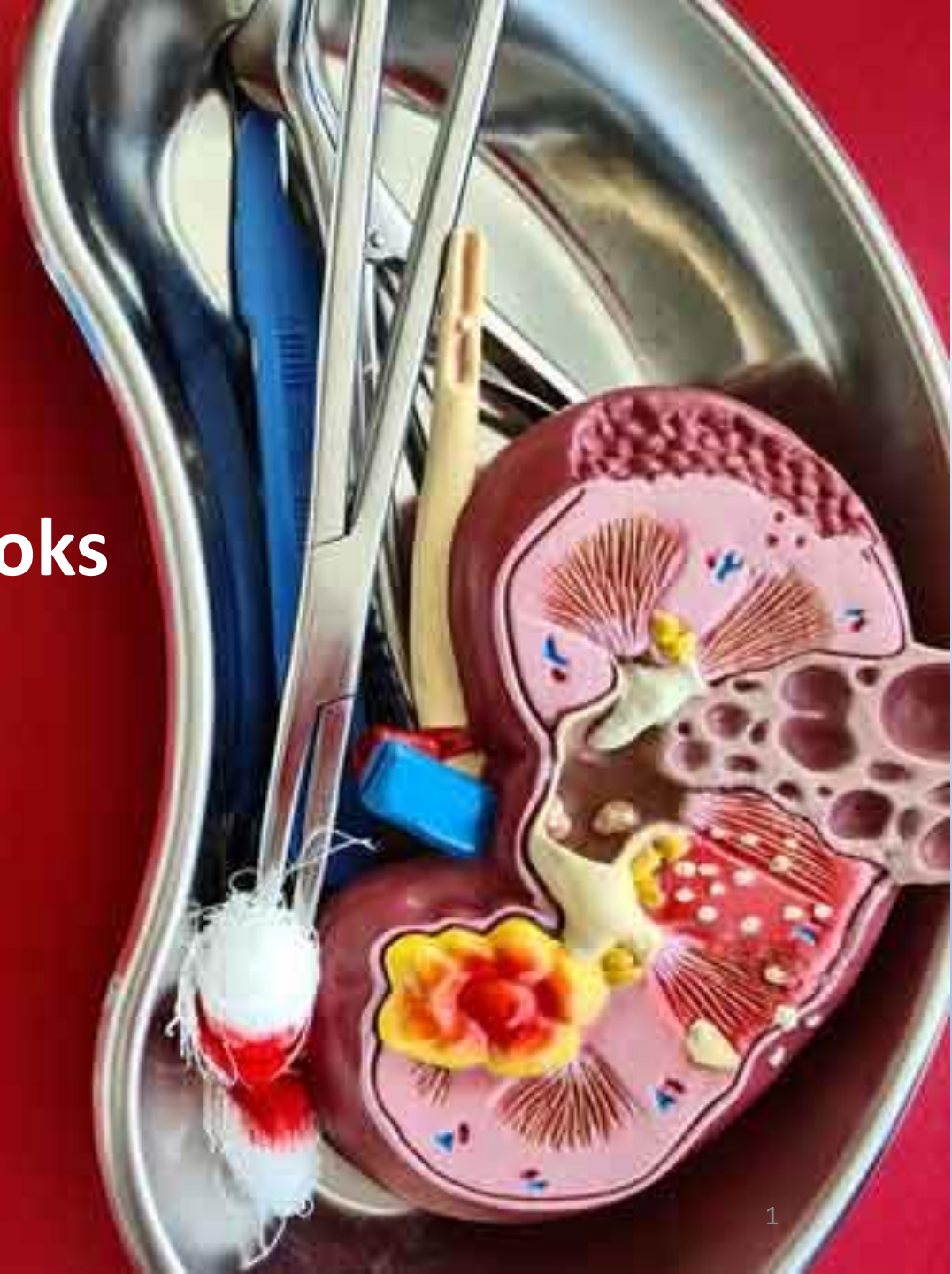


Primary Aldosteronism: A Common but Under-recognized Cause of Hypertension

- **Primary aldosteronism:**
  - **The commonest secondary cause of hypertension**
  - **Estimated prevalence: 3.2 - 14% among primary care populations**

- **Significant challenges exist in screening and diagnosing PA and therefore current estimates of prevalence may be modest in the overall context of disease.**

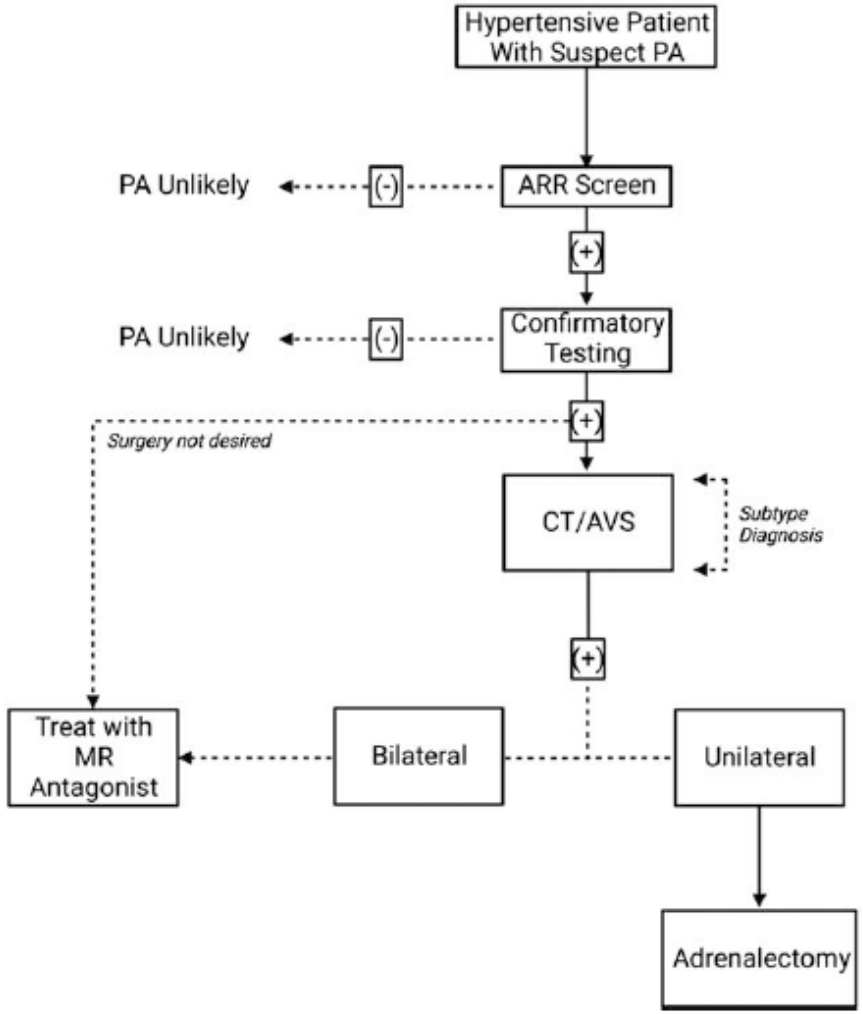


Figure 1. The traditional approach to the diagnosis and management of patients with PA: Initial diagnosis is determined by a positive aldosterone–renin ratio (ARR) screen with at least 1 positive confirmatory test (discussed in "Screening, Diagnosis, and the Spectrum of Disease"). Following diagnosis, subtype diagnosis (ie, lateralization) is sought through use of adrenal imaging/adrenal vein sampling (AVS) (discussed in "Current Approach to Lateralization"). Unilateral disease is commonly treated with adrenalectomy of the diseased adrenal whereas in cases of bilateral disease, mineralocorticoid receptor (MR) antagonists are commonly prescribed (discussed in "Advances in Pharmacotherapy").

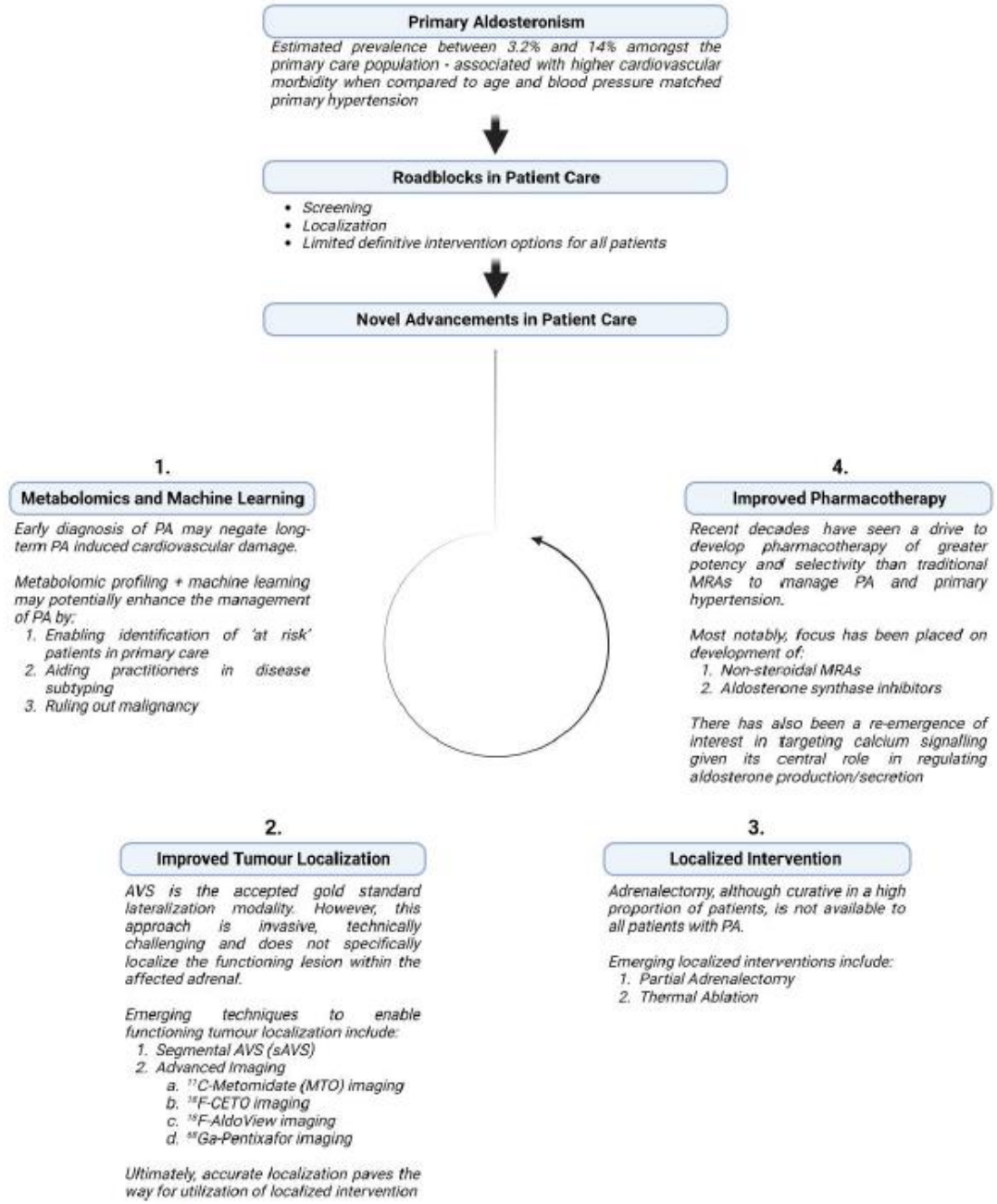


Figure 2. Outline of current "roadblocks" in primary aldosteronism (PA) care, with suggested approaches to addressing these, including: 1. Improved screening for, and diagnosis of PA through application of metabolomics and machine learning; 2. Utilization of advanced lateralization techniques including molecular (functional) imaging to permit precise tumor localization; 3. Use of focal adrenal-sparing interventions (eg, adrenal-sparing surgery or thermal ablation) where appropriate; 4. Continued development of more selective pharmacological agents. Figure created with *BioRender.com*.

Improving the Diagnosis of PA
Overcoming Challenges of the Current Diagnostic Approach

- **Early diagnosis of PA predicts response to therapy.**

- **Ideally screening should be undertaken in primary care or by generalists.**

- **Current screening for PA typically relies on determining the ARR. Measurement of plasma aldosterone and plasma renin, and interpretation of the ARR, is challenged by:**
  - **(1) assay availability**
  - **(2) stability of renin at room temperature following venesection**
  - **(3) requirement for specific sampling conditions (midmorning, seated for 15 minutes following 2 hours ambulation)**
  - **(4) assay interpretation in the face of interfering antihypertensive medications**
  - **(5) requirement for confirmatory testing to establish the diagnosis due to low specificity of the ARR (approx. 65%)**
  - **(6) the intraindividual variability in screening aldosterone concentrations, renin measurements (plasma renin concentration and plasma renin activity), and their corresponding ARRs.**

- **A more pragmatic and practical approach is therefore required to:**

  (1) improve recognition of patients who should be prioritized for PA screening within primary care

  (2) facilitate interpretation of screening tests in the face of potential medication interference

  (3) increase access to laboratory assays which do not require specialist sample handling

- **In this regard, the introduction of laboratory assays/methods that can be more easily performed on samples (blood or urine) collected in a nonspecialist setting should offer the prospect of getting many more patients over the first hurdle and onwards toward successful treatment.**

Metabolomics and Machine Learning

- **Metabolomics measures several steroids, their metabolites, fatty acids, monoamines, polyamines and other endocrine mediators from a single urine or blood sample.**

- **In general, *urine samples* are preferred because (1) analytes are typically collected over a *24-hour period* giving a more complete analysis rather than a single point in time analysis obtained from a blood sample; (2) urine and its metabolite content remain *stable at room temperature* and can be stored at temperatures between *–20 °C and +4 °C* for prolonged periods, therefore allowing sampling within environments which are remote to the analyzing laboratory.**

- **In recent years, metabolomic profiling, with analyses supported by machine-learning algorithms, has demonstrated potential utility in the diagnosis and management of Cushing syndrome and ACC.**

- **Emerging data in hypertension and PA also points to a possible role in establishing or excluding the diagnosis of PA and in subtype categorization.**

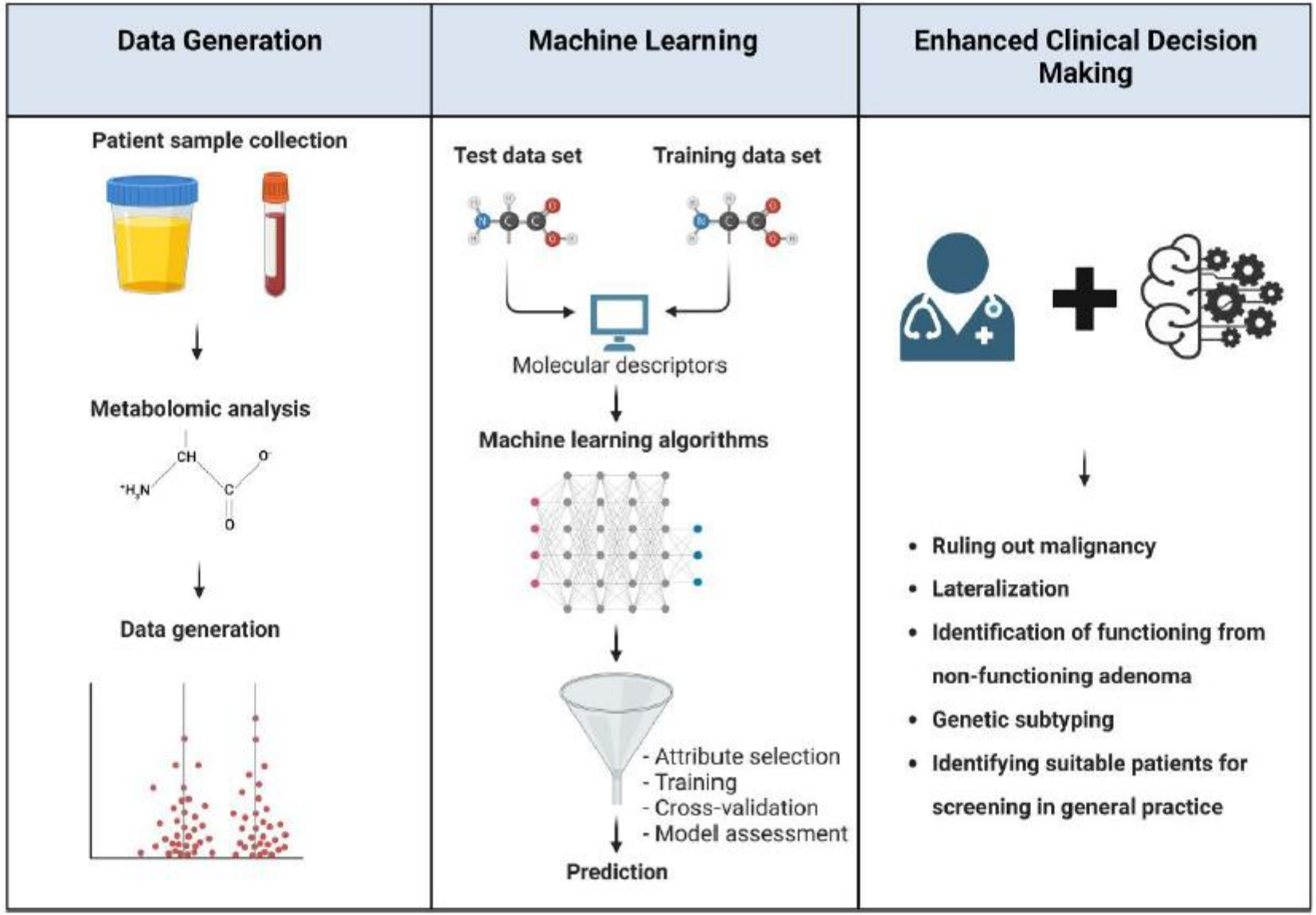


Figure 4. Outline of metabolomics/machine-learning workflow. Following patient sample collection, metabolomic analysis is usually carried out using liquid chromatography tandem mass spectrometry, yielding a large amount of data. Through combination with machine learning, a detailed metabolomic fingerprint can be generated of disease subtypes to streamline clinical decision making. Figure created with *BioRender.com*.

Steroid metabolomic profiling

- **has been used clinically for many years to aid in the diagnosis of *disorders of adrenal biosynthesis and metabolism*.**

- **It has also gained widespread clinical use in the analysis and detection of patterns of steroid metabolite excretion which reveal the *use of performance-enhancing drugs in sport.***

- **The more mainstream options for steroid metabolomic assays are GC-MS/MS or LC-MS/MS. The former is a labor-intensive and expensive technique, requiring significant expertise and set-up, and which is limited to a handful of international centers. In contrast, LC-MS/MS, a high-throughput technique which is more widely available, provides precise, well-validated, clinical laboratory–based assays for large steroid metabolite panels in both urine and blood.**

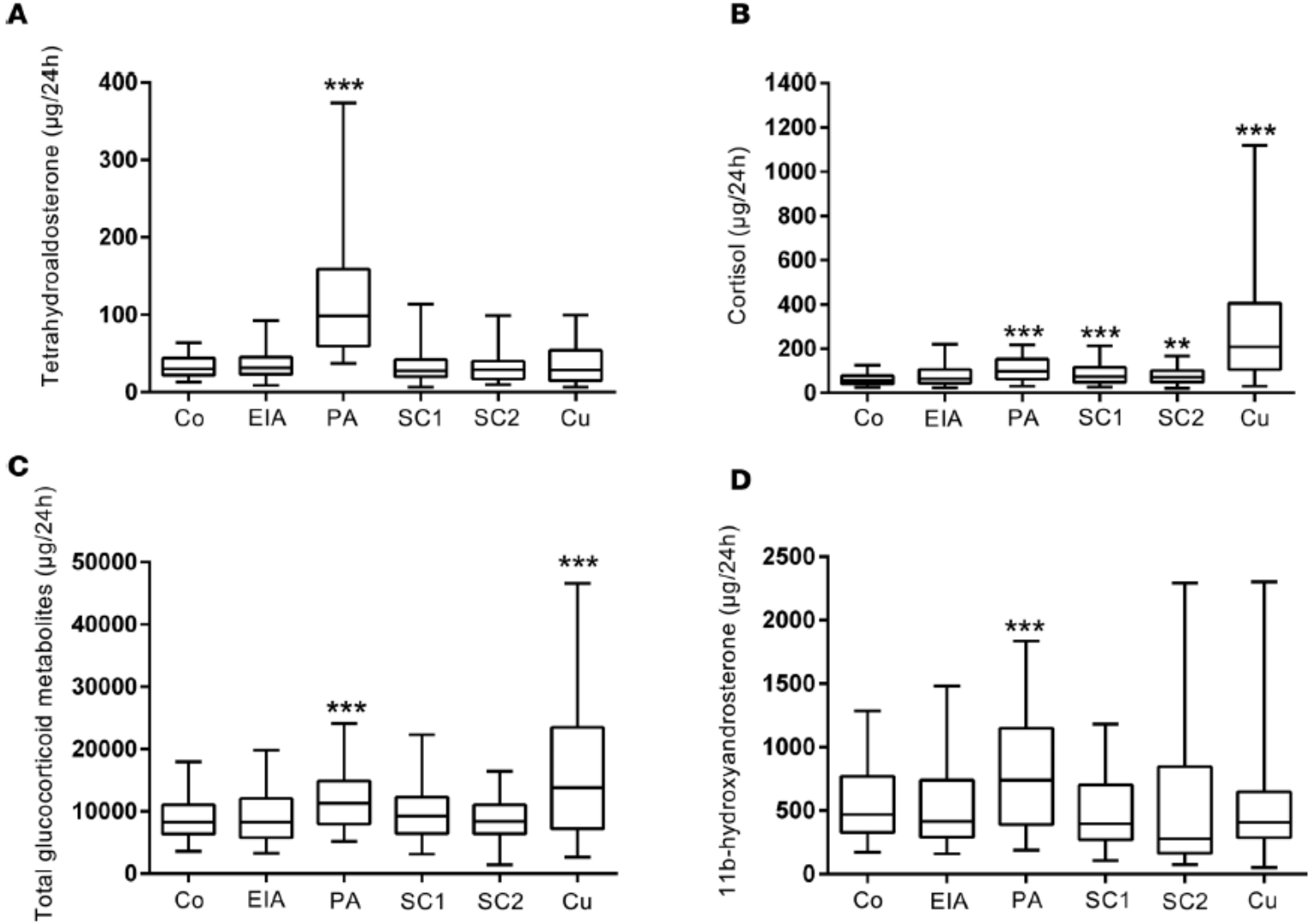


Figure 3. Steroid metabolite excretion in primary aldosteronism in comparison to healthy controls and patients with endocrine-inactive and cortisol-producing adrenal adenomas. The panels show the 24-hour urinary excretion of tetrahydroaldosterone (**A**), cortisol (**B**), total glucocorticoid metabolites (**C**), and the major adrenal androgen metabolite 11β-hydroxyandrosterone (**D**) in primary aldosteronism patients (PA; *n* = 174) in comparison to healthy controls (Co; *n* = 162), patients with endocrine-inactive adrenal adenoma (EIA; *n* = 56), patients with subclinical Cushing's (differentiated into 2 groups: SC1 (*n* = 55), morning cortisol after 1 mg dexamethasone overnight > 50 and < 138 nmol/l; SC2 (*n* = 49), morning cortisol >138 nmol/l), and overt adrenal Cushing's syndrome patients (Cu; *n* = 47). Boxes represent median and interquartile range, whiskers represent 5th and 95th centiles. $^{**}P < 0.01$ versus controls, $^{***}P < 0.001$ versus controls. Comparisons between groups were made with linear regression models to adjust for age and sex in comparisons between all 6 groups.

Arlt W *et al.* Steroid metabolome analysis reveals prevalent glucocorticoid excess in primary aldosteronism. *JCI Insight.* 2017;2(8): e93136.

- **The authors coined the term “Connshing’s syndrome” in order to describe this phenomenon.**

- ***“Connshing’s syndrome”*** **was not associated with overt hypercortisolism/features of overt Cushing syndrome and patients demonstrating this metabolomic profile** *neither failed screening for Cushing* **syndrome with the ODST,** *nor did they demonstrate the typically suppressed ACTH* **level associated with adrenal Cushing syndrome.**

- **Higher glucocorticoid metabolite levels in the urine of patients with PA was associated with** *higher CYP11B1 expression on IHC* **and higher overall urinary cortisol and glucocorticoid metabolite levels than those seen in patients with subclinical Cushing.**

- ***Higher glucocorticoid metabolites*** **in the urine in PA was also accompanied by production of** ***higher*** **rather than lower** ***androgen metabolites*****, in contrast to the typical androgen suppression associated with benign adrenal Cushing syndrome or mild autonomous cortisol secretion.**

- **Post hoc correlation analysis across the total cohort identified an** ***association between high glucocorticoid metabolite excretion and several markers of an adverse metabolic profile*****. The authors suggested that** ***MRA alone*** **within this subgroup of PA patients were** ***sufficient to control hypertension*** **and desuppress renin, but** ***may not be sufficient*** **to control a disease phenotype driven by aldosterone and cortisol.**

- **Resolution of the metabolomic abnormality for mineralocorticoid and glucocorticoid metabolites was demonstrated following adrenalectomy in patients with UPA.**

- **the name Connshing syndrome may be premature until further prospective studies are carried out to add clarity to the true clinical significance of what is, in essence, a biochemical entity.**

- **Urine analysis:**
  - **noninvasive, sample stability, provides measurements reflective of a longer period of time.**
  - **However, it requires adherence to a sampling procedure over 24h and is not always convenient for, or properly collected by patients.**

- **In this regard, a more detailed steroid analysis of a *single blood sample* collected at the time of ARR screening offers the potential to conveniently and accurately diagnose PA.**

- **Eisenhofer et al, demonstrated the utility of a multianalyte steroid profile drawn at the time of ARR measurement:**

(1) to distinguish between primary hypertension and PA with greater sensitivity and specificity than the ARR alone and

(2) to identify patients with unilateral adenomas, driven by *KCNJ5* mutations vs *KCNJ5* wildtype.

- **A score derived from a *total combination of 7 steroids* was useful in *stratifying PA subtypes*. The top 3 ranking steroids were consistently identified as *aldosterone, 18-oxocortisol*, and *18-hydroxycortisol*. Patients with *KCNJ5 mutations* demonstrated considerably *higher levels of all 3 steroids* than other PA subtypes.**

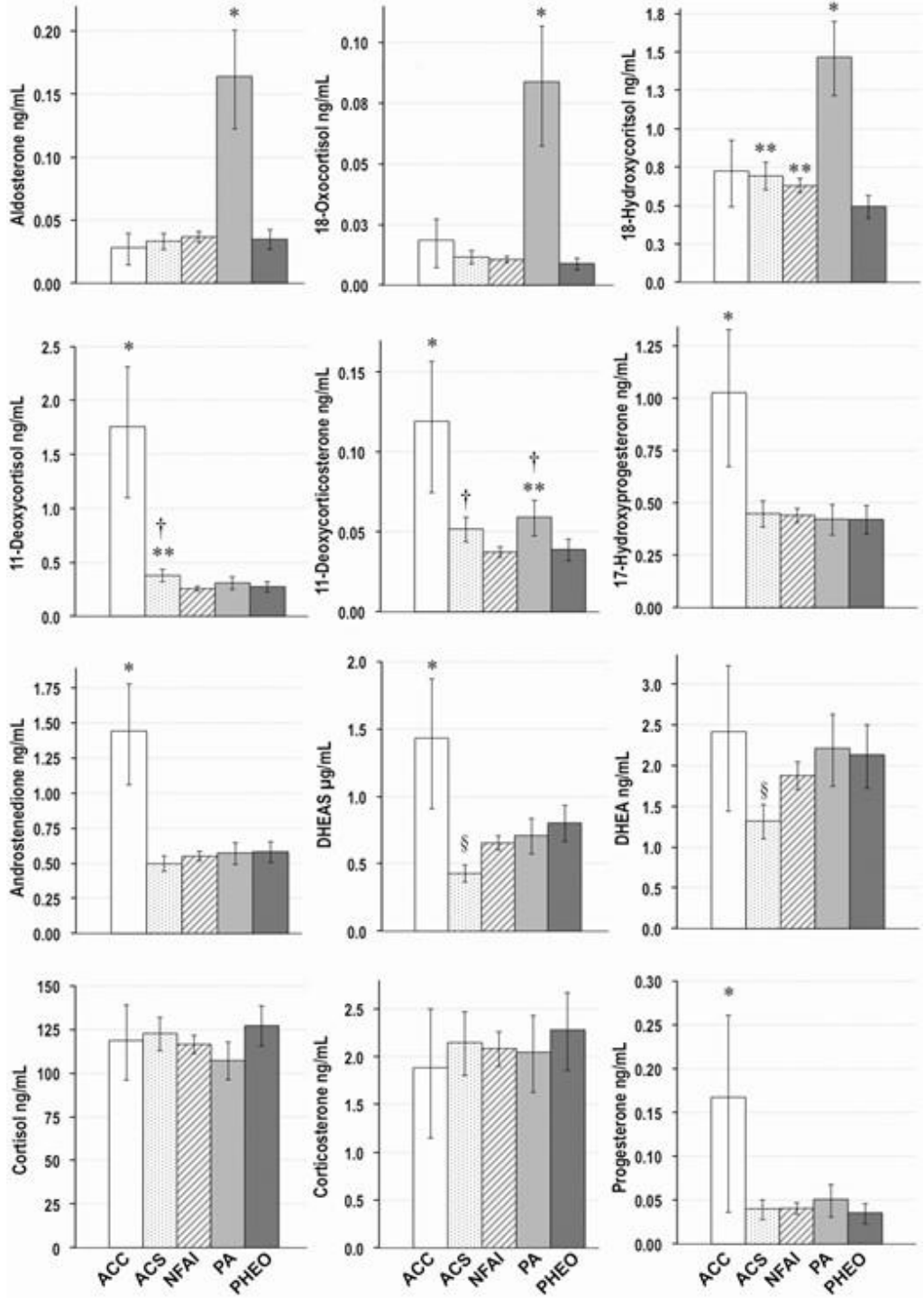
- **While this steroid combination had previously been identified as distinguishing between PA and primary hypertension, this study differed from others in using *machine learning* (random forest model) to interpret the results of the plasma steroid profile combined with the ARR.**

- **The AUC of the receiver operated was higher using the machine-learning analysis than ARR alone for distinguishing PA from primary hypertension (0.92 [0.899-0.946] vs 0.89 [0.856-0.916]) and considerably higher for identifying UPA driven by *KCNJ5* mutations vs primary hypertension and all other PA (area under the curve: 0.95 [0.922-0.969] vs 0.817 [0.758-0.863]).**

- **The authors concluded that their findings highlight the potential for the metabolomic model, supported by machine learning, to identify patients who would benefit most from surgical intervention.**

- **They also contended that biochemical distinction between unilateral and bilateral forms of PA, particularly in identifying *KCNJ5* mutations may facilitate improved confidence in the interpretation of adrenal CT as a lateralization modality.**

Plasma concentrations of 12 selected steroids in patients with adrenocortical carcinoma (ACC), autonomous cortisol secretion (ACS), nonfunctional adrenal incidentaloma (NFAI), primary aldosteronism (PA), and pheochromocytoma (PHEO). Results are shown as least square geometric means corrected for age and sex with 95% CIs. *P less than .05 higher than all 4 other groups; **P less than .05, higher than PHEO; †P less than .05, higher than NFAI; §P less than.05 lower than all 4 other groups; For conversion of ng/mL to nmol/mL or µg/mL to µmol/mL, divide by molecular weight (Supplementary Table 3).



Berke K, *et al.* Plasma steroid profiling in patients with adrenal incidentaloma. *J Clin Endocrinol Metab.* 2021;107(3): e1181-e1192.

- **Result of the study: plasma and/or urine steroid metabolomic panels offer *greater sensitivity and specificity* in diagnosing APA with a higher degree of accuracy than traditional approaches.**

- **It may also be argued that the current diagnostic pathway is sufficient for distinguishing between ACC, APA, and pheochromocytoma with a high degree of accuracy, using readily available and relatively cheap tests combined with clinical judgment.**

- **The challenge with the diagnosis of PA does not usually arise from distinguishing between it and other types of adrenal incidentalomas, but rather in differentiating between primary hypertension and PA.**

Study	Cohort	Reference standard for diagnosis	Findings	Notes
Erlic et al, 2021 (95) Retrospective Targeted metabolomics on plasma samples using LC-MS/MS. Analyzed with classical approach (using a series of univariate and multivariate analyses) or machine learning (random forest)	Primary hypertension: 282 Secondary hypertension: 223 total, 40 CS, 107 PA, and 76 PPGL	Not specifically defined: ("*The diagnosis (primary hypertension, CS, PA, PPGL) was made according to the current guidelines for screening and management of the specific diseases*" with reference to Funder et al, 2016)	[a]AUC • Classical approach: 0.86 • Machine learning: 0.83 [b]Sensitivity for secondary hypertension: Using metabolites: 80% Using metabolite ratios: 77% [b]Specificity for secondary hypertension: Using metabolites: 45% Using metabolite ratios: 37% [a]*Calculated based on the performance of the top 15 metabolites* [b]*Sensitivity/specificity was reported for differentiation of several forms of secondary hypertension (PA, PPGL, and CS) from primary hypertension*	Classical approach: When comparing primary hypertension and PA, 35 metabolites and 7 metabolite ratios had a significant association with the clinical diagnosis after controlling for sex and age group Machine-learning approach: When comparing primary hypertension and PA, 28 metabolites and 12 ratios were seen as key identifiers

- **However, there was *considerable overlap* between metabolites across the *various forms of endocrine hypertension* and distinction between different types of endocrine hypertension could not be made.**

- **While the study identified differences between the endocrine and primary hypertension groups, the *results are exploratory and preliminary*, and need to be prospectively validated.**

- **cumulative findings of the studies: a combined approach which employs metabolomics, tumor size, and character on CT, and analyzed using machine learning offers the prospect of improving diagnostic efficiency for PA and distinguishing primary and endocrine hypertension.**

- **This combination approach may also offer the prospect of better informing intervention or even personalizing therapy (medical or interventional) for PA.**

- **However, while encouraging, these studies must be interpreted with caution:**

  The majority are retrospective and exploratory.

  There is therefore a significant need to test these diagnostic approaches prospectively in large multicenter studies.

Machine learning to interpret traditional parameters

- **The use of machine learning to interpret clinical and laboratory parameters that are routinely collected during the initial assessment and diagnostic work-up of hypertension could help practitioners in primary and nonspecialist care to *identify patients who should be offered screening* for PA and referral for specialist care and/or confirmatory testing.**

- **This may *improve patient outcomes* and *direct resources more appropriately*.**

- **However, any use of machine learning must be prospectively analyzed and must show clear and consistent benefit over clinical decision-making alone.**

- **Additionally, any machine-learning approach must be clearly interpretable and designed to simplify the diagnostic pathway, rather than adding a layer of complexity.**

SToP-PA Score:
to distinguish primary HTN from PA, and to distinguish UPA from bilateral PA

The SToP-PA score ranges from 0 to 21.5 points:

cut-offs for prediction of a positive screening result for PA, or UPA diagnosis:
7.0 : 92% sensitivity
7.5 : 90.7% sensitivity
8.0 : 92.3%

cutoffs for achieving optimum specificity:
13.5: 91.8%
14.0: 96.4%
15.0: 98.1%

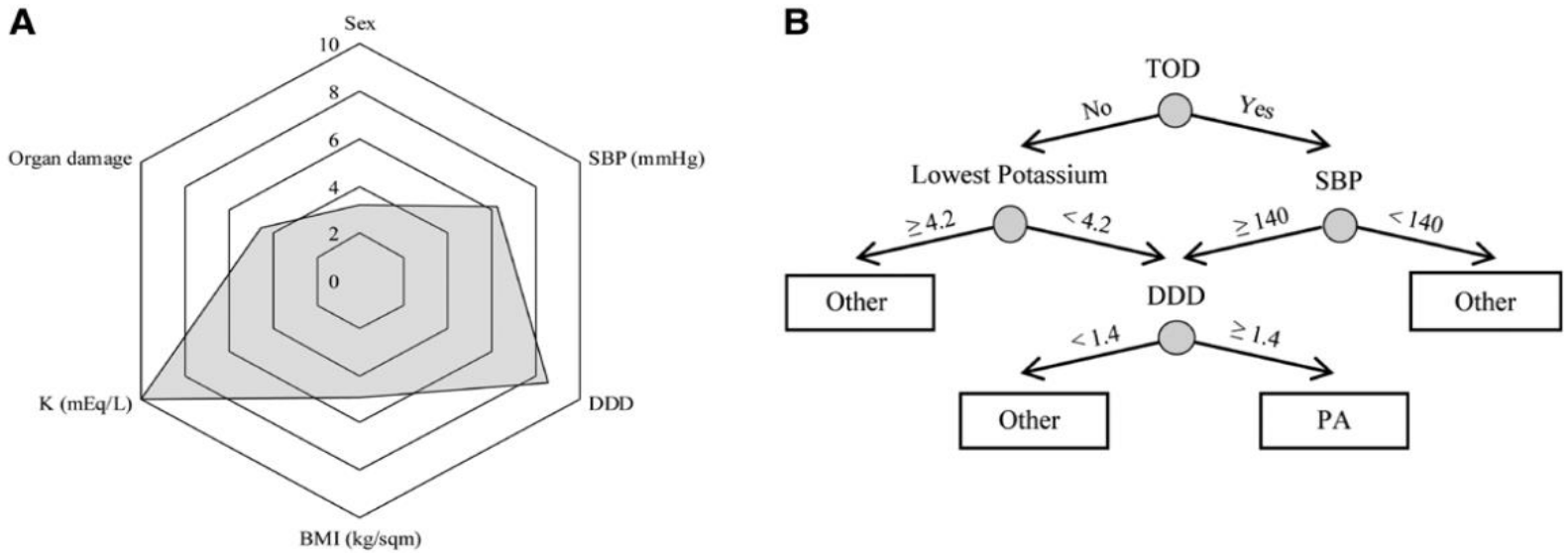


Figure 2. Development of the primary aldosteronism (PA) screening machine learning (ML) model.
The PA prediction ML model was built in the training cohort (n=3045) and tested in the validation cohort (n=1045). **A**, Radar charts reporting the 6 normalized predictors associated to the diagnosis of primary aldosteronism (PA). **B**, Representative classification tree from the random forest model. ROC (receiver operating characteristics) curve were used to assess the area under the curve (*Continued*)

Buffolo F, Burrello J, Burrello A, *et al.* Clinical score and machine learning-based model to predict diagnosis of primary aldosteronism in arterial hypertension. *Hypertension*. 2021;78(5):1595-1604.

- **Ultimately, these models *successfully identified all patients with UPA* and additionally *circumvented the necessity for screening in 32.7% of patients with non-PA hypertension*, while simultaneously *better selecting those who would benefit from screening.***

- **Both the SToP-PA score and machine-learning models have been made available as open-source software by the authors. However, they have not yet been validated in a large prospective study.**

- **Surprisingly, there are no data testing and validating these resources among retrospective cohorts in other centers where the work-up and diagnosis of patients with PA is routinely undertaken.**

Advances in Lateralization and Localization

Adrenal vein sampling

- **Following confirmation of a diagnosis of PA, cross-sectional imaging of the adrenal glands (CT or MRI) is typically undertaken to investigate for the presence of 1 or more nodules and exclude ACC.**

- **However, anatomical imaging alone is generally not considered sufficiently sensitive or specific to be the sole mode of lateralization in most patients**

- **Anatomical imaging alone may be sufficient to allow a patient to proceed direct to surgery without further lateralization when certain stringent conditions pertain:**

  (1) severe PA phenotype with clear-cut unilateral lesion >1.5 cm in diameter

  (2) young patients (<35 years) with spontaneous hypokalemia, marked aldosterone excess, and unilateral adrenal lesion with radiological features consistent with a cortical adenoma on adrenal CT scan.

- **Additionally, even in cases where CT and AVS appear “concordant” prior to surgery, the prominent CT identifiable nodule is not always the source of aldosterone secretion.**

- **As such, the use of AVS in tandem with CT imaging may not increase the lateralization power of CT to the degree that might be expected, and thereby question the validity of proceeding directly to adrenalectomy without assessing whether a CT identifiable nodule is functioning or not.**

- **AVS: gold standard lateralization modality for UPA for decades**

- **Challenges of AVS:**

  - is technically demanding, time consuming, associated with significant radiation exposure.

  - demonstrates considerable center to center and operator to operator variability in terms of success.

  - Successful cannulation of both adrenal veins is not achieved in up to 50% of patients and operator skill must be maintained with a critical number of procedures yearly.

  - Common methodological differences exist between centers.

  - This is resource heavy and availability of high quality AVS is limited to specialist centers.

  - Standard AVS lateralizes PA to 1 adrenal but cannot specifically localize the culprit lesion within the gland. Therefore, complete adrenalectomy, rather than adrenal-sparing surgery is preferred following standard AVS.

Advancing to localization using segmental AVS

- **Segmental adrenal vein sampling (sAVS) represents a more advanced technique that has emerged in some specialist centers.**

- **This highly skilled procedure can localize functioning adrenal tumors within and between glands. Under cosyntropin stimulation, multiple branches of the adrenal vein are typically cannulated to calculate the aldosterone:cortisol ratio, distinguishing between healthy tissue and a localized source of excess aldosterone.**

- **However, sensitivity and specificity for this procedure have not yet been reported within the currently available literature. While offering a modality for localization of aldosterone-secreting tumors within either adrenal gland, the feasibility of this procedure is offset by the requirement for a highly skilled operator and hence its limited availability.**

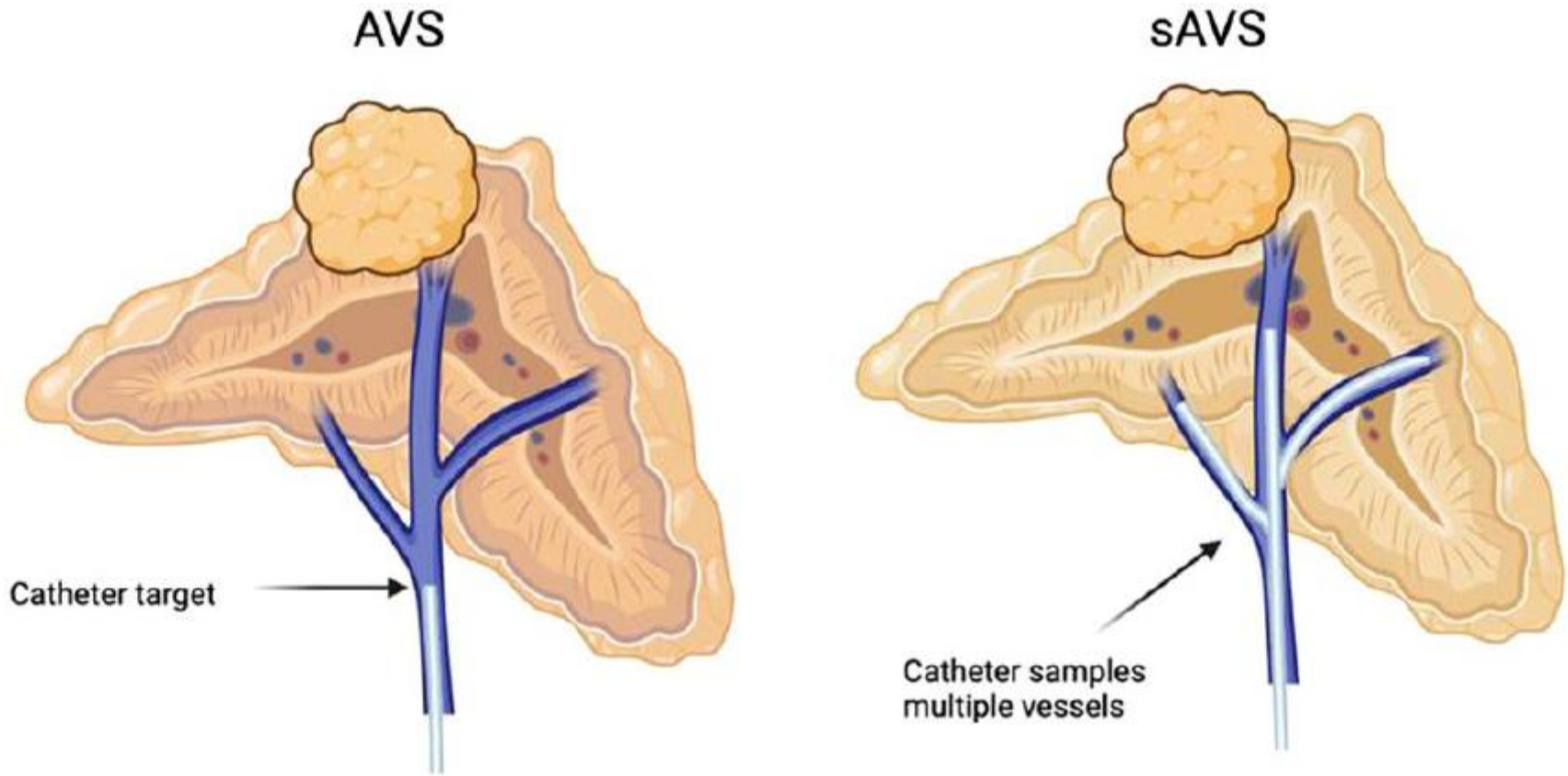


Figure 5. Schematic diagram outlining an AVS or segmental AVS (sAVS) procedure as described by Satani et al, 2016 (137). During a conventional AVS procedure, both central adrenal veins of the left and right adrenal are sampled to lateralize the affected adrenal. sAVS involves sampling from several adrenal tributaries to localize a section of adrenal as the source of aldosterone hypersecretion. Commonly, 3 main tributaries converge into 1 central vein. However, in some patients ≥3 tributaries may be present. Figure created with *BioRender.com*.

Noninvasive Lateralization

- **Recent advances in molecular (functional) imaging [especially positron emission tomography (PET)], now permit detection of small (even subcentimeter) functioning adrenal tumors.**

- **The use of hybrid imaging modalities (combining functional with anatomical imaging, eg, PET/CT or PET/MR) offers the potential to not only *lateralize* but also precisely *localize* the source of aldosterone excess in the affected adrenal. This is an attractive approach for the management of PA given that it is:**

  (1) noninvasive (2) offers an alternative for AVS (3) has potential to be more widely accessible than AVS.

- **Importantly, however, this will be dependent on the availability of radiotracers which can be distributed to centers from a remote production site (in the same way that 18F-fluoro-deoxyglucose is used in routine clinical oncology practice).**

11C-metomidate imaging

- **Among the PET radiotracers which have been trialed for adrenocortical imaging in PA, 11C-metomidate (MTO) alone represents a *noninferior lateralization modality to AVS*.**

- **It is also a useful adjunct to CT and AVS in identifying the *causative lesion(s)* in PA.**

- **Metomidate, an imidazole-based methyl ester derivative of the anesthetic agent etomidate, binds with high affinity to the adrenal steroidogenic enzymes 11β-hydroxylase (encoded by *CYP11B1*) and aldosterone synthase (encoded by *CYP11B2*), which are rate limiting steps in the glucocorticoid and mineralocorticoid synthesis pathways.**

- **When radiolabeled with 11C, which releases a positron as it decays, it *can be used as a PET radiotracer* to visualize adrenocortical lesions.**

- **Importantly, when deployed to detect APAs/APNs in PA, *dexamethasone pretreatment* (for 72 hours) appears an essential prerequisite to achieve selectivity for CYP11B2-expressing lesions (through suppression of CYP11B1 expression).**

- **A key limitation of MTO-PET is the short half-life (T1/2 20 minutes) of the radiotracer such that scanning is only available at sites with an *on-site cyclotron facility*.**

- **However, development of *more stable isotopes*, such as *18F-CETO* (para-chloro-2-(18F)-fluoroethyl-etomidate) with a *longer half-life* (T1/2 110 minutes), is likely to significantly *increase accessibility* to molecular imaging using this family of radiotracers.**

18F-CETO imaging

- **18F-CETO : a specific adrenal tracer**

- **18F-CETO is likely to be a suitable alternative to MTO, with potential advantages in terms of *adrenal selectivity* and with respect to more widespread geographical *availability*.**

- **Two studies are currently examining the ability of 18F-CETO (including dexamethasone suppressed CETO-PET) to distinguish unilateral and bilateral causes of PA.**

18F-AldoView imaging

- **Sander and colleagues selected the benchmark benzimidazole derivative and labelled it with fluorine-18 to generate a *highly selective radiotracer* known as 18F-AldoView (CYP11B2 IC50 4.7 nM vs 435 nM for CYP11B1).**

- **In a study, there was a *high degree of concordance between IHC and 18F-AldoView binding patterns* in each case.**

- **The authors also demonstrated a favorable pharmacokinetic profile in studies in mice that included *rapid distribution and clearance of the tracer*. Clinical studies are awaited.**

CXCR4 imaging

- **As an alternative to targeting CYP11B2, based on the observation that *high levels of the CXC chemokine receptor type 4 (CXCR4) are expressed in APAs* (with strong correlation with sites of CYP11B2 expression), Heinze and colleagues explored the use of the *CXCR4 ligand 68Ga-pentixafor* in imaging 9 patients with APAs (150).**

- **at 100% specificity (SUVmax cut-off 7.3), the sensitivity was 77.8%**

- **at 100% sensitivity (SUVmax cut-off 4.7), specificity was 83.7%**

- **increased CXCR4 expression has been reported in *cortisol producing adenomas*, while increased 68Ga-pentixafor uptake is also observed in patients with Cushing syndrome**

- **In another study, 68Ga-pentixafor PET-CT *successfully diagnosed all AVS confirmed unilateral PA* cases when a nodule *of >10 mm* in diameter was present.**

- **However, *44.4%* of those who had *micronodular pathology* (4 of 9 patients) were *missed* by 68Ga pentixafor PET/CT, suggesting the sensitivity of this method might not be ideal for detecting smaller lesions.**

- **The *smallest nodule detected by PET/CT was 8 mm* in diameter.**

- **An upcoming 2-step randomized control trial (CASTUS) will assess:**

  (1) The *accuracy* of 68Ga-pentixafor PET/CT by determining the concordance between 68Ga-Pentixafor PET/CT and AVS. If found to meet the predefined concordance threshold, the study will progress:

  (2) assess the *clinical outcome* in a RCT of 68Ga-Pentixafor PET/CT vs AVS with the primary outcome being the daily defined doses of antihypertensive drugs for BP regulation after 1 year, and secondary outcomes being quality of life, biochemical, and clinical cure (according to the PASO criteria) and costs.

- **While current data highlight promising lateralization ability of 68Ga-Pentixafor PET/CT, this tracer *is not widely available* for routine clinical use for patients with PA at this time.**

Radiomics

- **Radiomics: a *quantitative approach* to medical imaging, assisted by *mathematical models* and *artificial intelligence*, which can *identify disease specific patterns* in biomedical images that may not be visible to the human eye.**

- **In the context of the adrenal, several studies have examined the ability of radiomics to differentiate adrenal tumor subtypes, including adenoma, metastases, pheochromocytoma, ACC, and cortisol-secreting adenomas.**

- **To date, however, *only a small number* have focused on the *differentiation of functioning and nonfunctioning* adenomas.**

- **In a study, the model was capable of differentiating nonfunctioning adrenal nodules, from APAs with sensitivity: 83.3%, specificity: 78.9%, and accuracy: 80.6% on unenhanced CT.**

  sensitivity: 81.2%, specificity: 100%, and accuracy: 87.5 on venous phase CT.

- **The model was also capable of *predicting biochemical and clinical success* following surgery.**

- **Although promising, it is important to bear in mind that the application of radiomics in clinical practice is still in its infancy and, as such, interstudy variability in methodology has highlighted significant problems with reproducibility.**

- **the quality of radiomic studies in adrenal disorders was unsatisfactory, for 3 potential reasons:**

  a lack of prospectively designed studies

  an absence of proper validation

  poor openness of data.

- **It requires future prospective studies to understand the true effectiveness of radiomics in aiding clinical decision making in the management of PA.**

Future perspective of PA lateralization

- **We envisage that with greater availability of molecular imaging, *PET CT may become the first line lateralizing procedure*—perhaps even performed as the *initial* radiological investigation (ie, without prior CT) because of its ability to provide both anatomical and functional information.**

- **AVS might then be reserved for the small number of cases where unilateral disease is strongly suspected but molecular imaging does not clearly localize a lesion. Such a scenario might occur when both adrenal glands appear morphologically normal on CT (ie, harbor lesions that are beyond the resolution of even modern PET CT).**

Novel Treatment Approaches
Partial Adrenalectomy: Targeted Tumor Resection

- **Complete unilateral adrenalectomy: treatment of choice for UPA**
  - **well-tolerated, safe, and effective.**

- **drawbacks of complete adrenalectomy:**

  - adrenalectomy has traditionally been considered in *lateralized cases* with an apparent APA, amounting to approximately *30% of PA patients*, with the remaining 70% of patients with bilateral disease reliant on pharmacological intervention.

  - Many patients with cardiorenal complications of PA: *poor operative candidates*.

  - Additionally, up to 30% of patients undergoing unilateral adrenalectomy for PA demonstrate *partial (often subclinical) or, less commonly, complete postprocedural glucocorticoid insufficiency*, albeit a temporary phenomenon in most instances. It is not clear whether this is due to loss of adrenal volume or the presence of co-secretion of glucocorticoids from APAs.

  - a small but important group of patients experience *mineralocorticoid insufficiency*.

Partial adrenalectomy/adrenal sparing nodulectomy

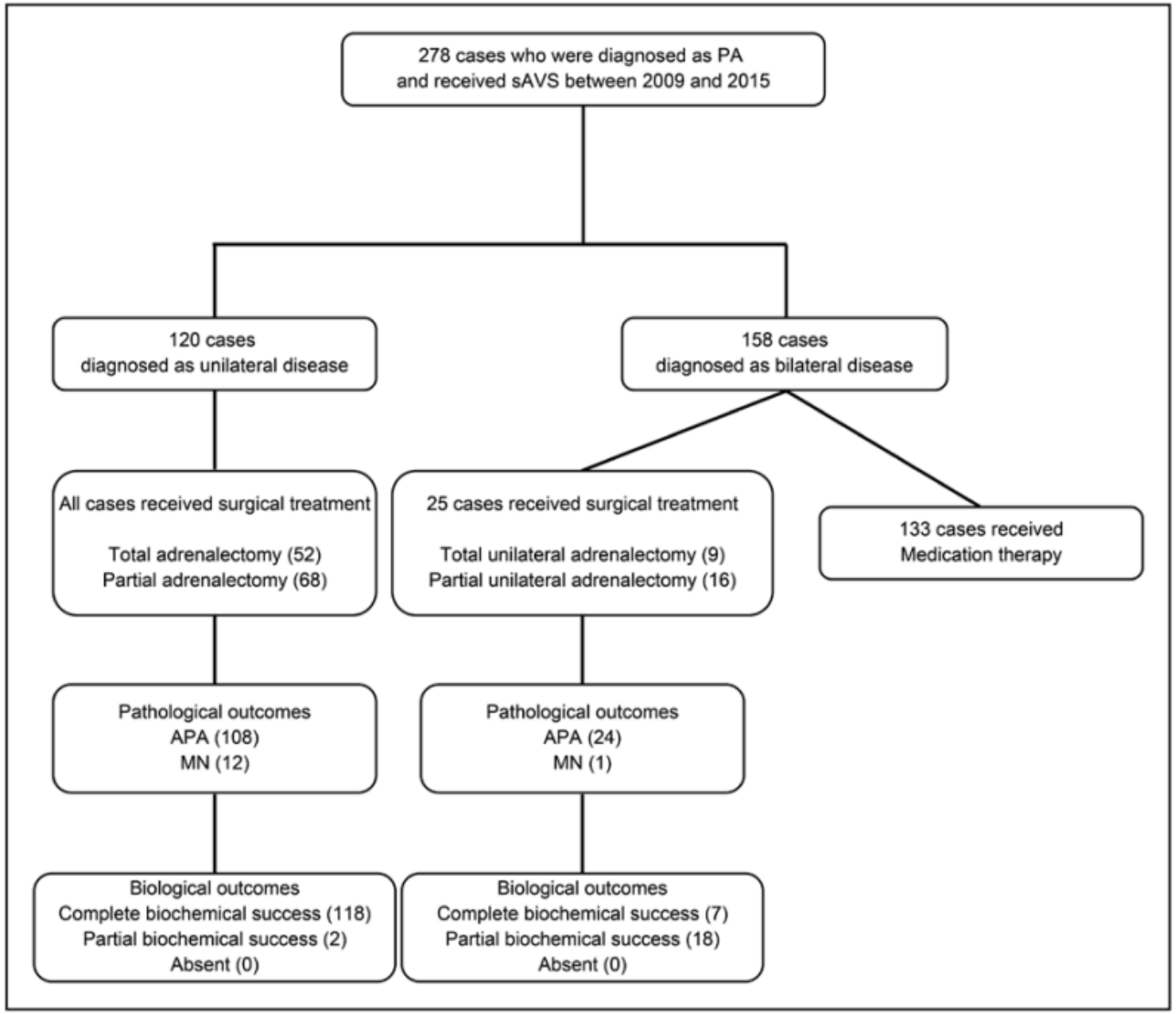


Figure 1. Flowchart of patient selection and diagnostic outcomes. Lateralization was determined by segmental selective adrenal venous sampling. The number of cases is mentioned in parentheses. APA indicates aldosterone-producing adenoma; MN, micronodule; PA, primary aldosteronism; and sAVS, segmental selective adrenal venous sampling.

Kitamoto T, Kitamoto KK, Omura M, *et al.* Precise mapping of intra-adrenal aldosterone activities provides a novel surgical strategy for primary aldosteronism. *Hypertension*. 2020;76(3):976-984.

Table 3. Surgical Outcomes of 120 Patients With Unilateral Primary Aldosteronism Treated With Total and Partial Adrenalectomy

Variables	Total Adrenalectomy (n=52)	Partial Adrenalectomy (n=68)	*P* Value
Preoperative data			
Sex (male/female)	22/30	29/39	1.000
Age, y	49.5±9.5	48.9±11.2	0.761
Plasma aldosterone, ng/dL	27.7 (19.6–49.7)	40.4 (26.7–55.2)	0.009*
Plasma renin activity, ng/mL per hour	0.3 (0.1–0.5)	0.2 (0.1–0.3)	0.014*
Tumor size, mm	9.5±7.3	15.3±5.3	<0.001*
Surgical side (right/left)	32/20	32/36	0.141
Max PAC in the tributary veins in the affected side, ng/dL	7655 (3170–22 425)	10 500 (6770–20 900)	0.100
Minimum PAC in the tributary veins in the affected side, ng/dL	1040 (473.75–3217.5)	385 (296–568)	<0.001*
Max PAC in the tributary veins in the unaffected side, ng/dL	571 (386.0–806.8)	466 (320.5–681.5)	0.078
Operative time	114.1±28.1	93.7±31.1	<0.001*
Pathological diagnosis	APA (30), mAPA (12), MN (10)	APA (64), mAPA (2), MN (2)	<0.001*
Postoperative data			
No. of antihypertensive medications	0 (0–1)	0 (0–1)	0.113
SBP, mm Hg	126 (114–138)	124 (116–134)	0.519
DBP, mm Hg	74 (68–84)	79 (69–86)	0.441
Plasma aldosterone, ng/dL	7.6 (6.2–9.7)	8.3 (5.9–10.2)	0.737
Plasma renin activity, ng/mL per hour	0.7 (0.4–1.7)	1.0 (0.5–2.0)	0.240
Plasma cortisol, μg/dL	7.5 (5.5–9.1)	6.6 (4.9–9.7)	0.568
Serum potassium, mEq/L†	4.2±0.3	4.1±0.3	0.166
Serum creatinine, mg/dL	0.8±0.2	0.9±0.3	0.392
eGFR, mL/min per 1.73 m^2	70.4±18.2	69.0±20.1	0.694
Urine albumin to creatinine ratio, mg/g	4.3 (3.2–8.9)	4.1 (2.7–8.8)	0.558
Biological outcome (complete/partial/absent) (complete [%])	50/2/0 (96.2%)	68/0/0 (100.0%)	0.186
Clinical outcome (complete/partial/absent) (complete [%])	25/25/2 (48.1%)	43/25/0 (63.2%)	0.095

- **The performance of partial adrenalectomy in bilateral disease was not as encouraging.**

- **Following partial adrenalectomy in the 25/158 bilateral cases:**
  - **the complete biochemical success rate: 28%**
  - **the partial biochemical success rate: 72%**
  - **the complete clinical success rate: 36%.**

- **Therefore, there was considerable residual disease in those undergoing partial adrenalectomy.**

- **Several studies have reported comparable levels of clinical and biochemical success for complete adrenalectomy and PAY.**

Limitations of partial adrenalectomy:

- PAY is *suitable only for a subgroup of patients*, although increased access to molecular imaging could mitigate its current dependence on sAVS which is available in only a handful of centers.

- It is associated with the *increased risk of hemorrhage* from residual, nonresected ipsilateral adrenal tissue

- *Preservation of adrenal blood supply* may be necessary for residual adrenal function, and therefore resection of an adrenal body tumor is likely to require complete rather than partial adrenalectomy.

- the most important limitation: the *potential presence of multiple nodules*, both contralateral and ipsilateral, which can render PAY futile if residual functioning tumors are left behind.

- Several histological studies have demonstrated that *MAPNs are found in as many as 21%* of complete adrenalectomy specimens. Given the nature of PAY and the likely formation of scar tissue following the procedure, it seems likely that any *future surgical intervention* following incomplete removal of abnormal functioning tissue would face added complexity.

Thermal Ablation: A Targeted Minimally Invasive Therapeutic Approach

- **Thermal ablation can potentially target the source of aldosterone hypersecretion using a minimally invasive percutaneous approach, with a short procedure time, without the need for overnight hospitalization and usually without the need for general anesthetic.**

- **Ablation involves localized delivery of nonionizing energy with a minimally invasive applicator placed under imaging guidance, typically CT or ultrasound, with the goal of delivering sufficient heating (>∼50 °C) to achieve coagulative necrosis.**

- **A variety of energy sources are available for thermal ablation, of these, radiofrequency ablation (RFA) and microwave ablation (MWA) have received the most attention for treatment of adrenal disease in recent decades, with demonstrated preclinical and clinical efficacy.**

- **Notably, use of *MWA* has potential for *treatment of localized bilateral adrenal nodules* with minimal risk of adrenocortical insufficiency.**

- **a recent meta-analysis reports that *RFA* offers *comparable efficacy to laparoscopic adrenalectomy*:**

  - shorter operative time, less intraoperative blood loss, and shorter hospital stay, while no significant differences in the complication rate.

- **However, the use of ablation for adrenal tumors is in its infancy and bespoke probe designs may be necessary with ablation patterns designed to minimize thermal damage to normal adrenal tissue.**

only 2 prospective studies using RFA in the treatment of PA have been published to date:

- **a pilot study involving 30 patients:**
    - **primary endpoint criterion: BP reduction to less than 135/85 mmHg without antihypertensive medications or a reduction of at least 20 mmHg for systolic or 10 mmHg for diastolic BP.**
    - **At 6-month follow-up, 47% of patients met the primary endpoint criterion.**

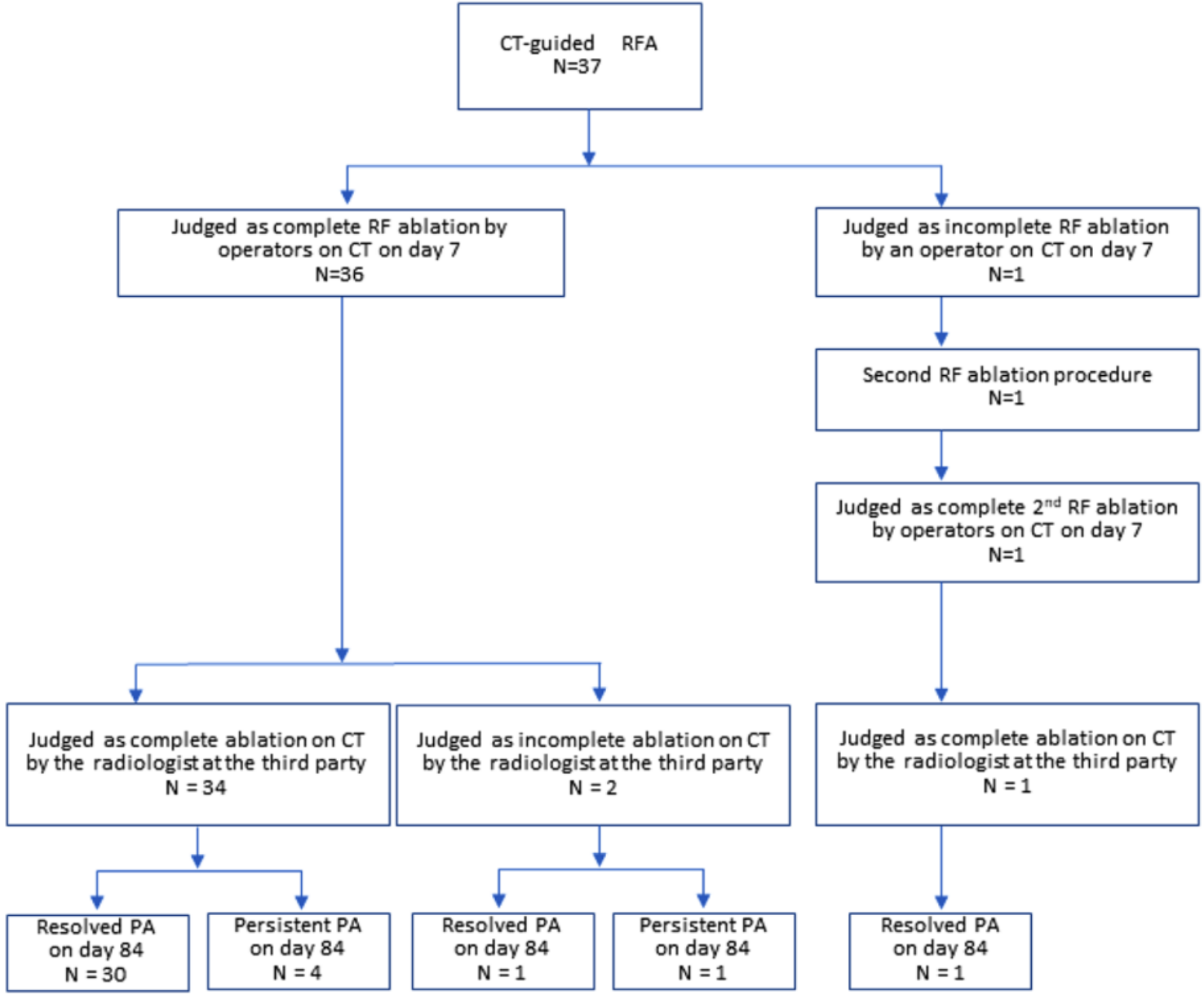


Figure 3. Flow charts results of RF procedure at 84 days.

Oguro S, Morimoto R, Seiji K, *et al.* Safety and feasibility of radiofrequency ablation using bipolar electrodes for aldosterone producing adenoma: a multicentric prospective clinical study. *Sci Rep*. 2022;12(1):1-9.

Drawbacks of thermal ablation

- Studies reporting an ***intraprocedural hypertensive crisis*** (presumed consequent to medullary degranulation), which suggests the requirement for preprocedural and periprocedural administration of pharmacological ***alpha-blockade***. However, the prevalence of this phenomenon is difficult to gauge and may be subject to reporting bias.

- ***Larger*** tumors can require ***multiple treatment cycles*** to achieve complete destruction of the tumor.

- Tumors that are located ***close to structures*** such as the inferior vena cava, lung, kidney, splenic artery, or liver are often not suited for ablation, given the difficulty in electrode placement and/or risk of organ injury, although this can be partially mitigated using hydrodissection.

- Tumors near blood vessels are also subject to a "**heat-sink**" effect where heat from the RF applicator dissipates through the circulating blood, reducing the effectiveness of the ablation procedure.

- ***Probe placement*** can also prove problematic and intercostal arterial injury may occur.

- **As an alternative to RFA, MWA may offer some benefits:**

  - **In general, MWA is *less susceptible to heat-sink*, while also being capable of producing *larger ablation zones* in a *shorter timeframe*, using continuous rather than pulsed energy application.**

Nanoparticle based approach

- **RFA and MWA do not discriminate between the targeted lesion and normal tissue.**

- **Nanoparticle-based approaches offer the opportunity for high precision therapy by coupling an energy source that has minimal effect on tissue in the absence of exogenous materials that absorb the delivered energy; precisely delivering nanoparticles to the target tissue offers a means for highly localized therapy.**

- ***Photothermal therapy with gold nanoparticles*** **or** ***carbon nanotubes*** **has been explored for treatment of disease in the prostate, liver, and other sites. Due to the limited penetration of light in the body, photothermal therapy would** ***require a minimally invasive applicator to target adrenal lesions.***

- **The use of** ***alternating magnetic fields*** ***to heat magnetic nanoparticles*** **offers the potential for noninvasive thermal therapy of adrenal nodules, though it is technically challenging to deliver adequate magnetic field strengths at depth while limiting off-target heating due to Eddy currents.**

Advances in Pharmacotherapy

- **The steroidal MRAs spironolactone and eplerenone: mainstay pharmacological management of PA**
- **Spironolactone is generally the first line MRA for PA. However due to off-target effects, gynecomastia, erectile dysfunction, and reduced libido in men, and mastodynia in women may complicate treatment.**
- **Eplerenone, is a more selective MRA approved for the management of heart failure and hypertension. It provides an alternative to spironolactone with fewer off-target side-effects but requires twice daily dosing and is metabolized by CYP3A4. It has approximately 50% the potency of spironolactone.**
- ***Second-line therapies*** **include** ***potassium-sparing diuretics (eg, amiloride and triamterene)*** **but the antihypertensive effect of these is counterbalanced by a compensatory but nonantagonized** ***increase in aldosterone*** **which may compromise endothelial function, although this has not been verified by clinical studies.**

- **As such, there has been a drive to develop pharmacotherapy of greater potency and selectivity than traditional MRAs to manage PA and primary hypertension:**

nonsteroidal MRAs

aldosterone synthase inhibitors

Nonsteroidal Mineralocorticoid Receptor Antagonists

- ***Esaxerenone (CS-3150)*** **is a nonsteroidal MRA which at low concentrations inhibits aldosterone-binding to the MR without glucocorticoid, androgen or progesterone activity.**
- **It gained first global approval for management of primary hypertension in Japan in 2019.**
- **It has high bioavailability and a longer half-life (t1/2) when compared with first-generation MRAs.**
- **Dosing at *2.5 mg/day* demonstrated *noninferiority to eplerenone* 50 mg/day in its antihypertensive effects, whereas a higher *5 mg/day* demonstrated *superiority.***
- ***Improvements in microalbuminuria*** **have also been demonstrated in patients with *type 2 diabetes*** **alone and in combination with other antihypertensives.**

- **The first in class dihydropyridine-based compound *finerenone* is a bulky passive antagonist that has a high selectivity for the MR.**

- **This agent received FDA approval in July 2021 for the management of CKD associated with DM2.**

- **There are currently *no human trials* registered with the primary outcome of investigating the *antihypertensive properties of finerenone in PA.***

Aldosterone Synthase Inhibitors

- Selective inhibition of CYP11B2 while leaving 11β-hydroxylase (CYP11B1) uninhibited is challenging given the homology between both enzymes" amino acidic sequences.

- Several CYP11B2 inhibitors have been investigated, with Osilodrostat (LCI699) being 1 of the first agents of its class to reach the early phase of clinical trials. This agent was effective at lowering BP in PA and in those with essential or resistant hypertension.

- However, 20.8% of patients exhibited an attenuated cortisol response on ACTH stimulation.

- This nonselectivity and consequent off-target effects at CYP11B1 (with inhibition of cortisol synthesis) meant that this agent has not progressed further for the treatment of PA, but instead has recently received approval by the FDA for treatment of Cushing syndrome.

- ***baxdrostat (RO6836191):*** **selective and potent inhibitor of CYP11B2, demonstrating a Ki value in human studies of 13 ± 2.2 nmol/L towards CYP11B2 vs 1310 ± 533 nmol/L for CYP11B1.**

- **In healthy subjects, single doses of baxdrostat reduced plasma and urine aldosterone levels, with the maximum effect seen at *10 mg*.**

- **Importantly, cortisol secretion following ACTH stimulation was unchanged.**

- **As already discussed, CYP11B2 inhibitors also offer the potential to be adapted for the development of radiotracer molecules (such as 18F-AldoView) to aid in the localization and subtyping of PA, which transforms not only the diagnostic approach, but which could also open the therapeutic options for selective and definitive management of PA.**

Potential Personalized Pharmacotherapy for PA: Calcium Signaling

- In a recent analysis, up to ***85% of APAs*** were found to ***harbor mutations*** in so-called “aldosterone driver genes”. Of these mutations, ***95% are sporadic*** with the remaining 5% comprising familial forms.

- Therefore, there exists the ***potential to target pharmacotherapy to mutations***. This approach is however challenged by the fact that most mutations driving PA are somatic and therefore not easily identifiable without ***tissue biopsy***.

- Sporadic somatic mutations most commonly occur in APAs and aldosterone-producing diffuse hyperplasia. A substantial proportion of these mutations affect genes encoding ion channels such as the potassium channel ***KCNJ5***, the calcium channels ***CACNA1D/CACNA1H***, the chloride channel ***CLCN1*** and ATPases ATP1A1 and ATP2B3.

- **Although the precise mechanism through which each mutation contributes to the pathogenesis of PA may differ, many mutations *ultimately increase intracellular calcium signaling* resulting in *amplification of CYP11B2 expression* and enhanced secretion of aldosterone.**
  - **In this regard, *calcium channel blockers* may demonstrate particular efficacy in the management of PA driven by *somatic mutations in channels like CACNA1D or CACNA1H*.**

- **GIRK4, a G protein-activated inward rectifier potassium channel, is a potential target for those with KCNJ5 mutations, given that mutations in this channel result in altered channel selectivity, causing cell membrane depolarization, increased calcium channel signaling, and increased aldosterone production. In vitro studies have shown that *macrolide antibiotics (eg, roxithromycin*) selectively inhibit mutated KCNJ5 channels.**

Novel Methods of Drug Delivery

- **Due to *nonadherence* and partial adherence of antihypertensive medication in patients with apparent treatment-resistant hypertension, including in those with PA who are pharmacologically managed, BP control remains poor.**

- **Adherence and resultant BP control could be improved by reducing pill burden and frequency. The use of a *subcutaneous PEGylated thermogeling system for spironolactone* in animal models has been studied, prolonging its release to nearly *2 months*.**