ESE Research Roadmap/EndoCompass Chapter by Adrenal and Cardiovascular Working Group

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Introduction

The adrenal glands are a pair of remarkably dynamic endocrine organs. Their intricate structure and multifaceted functions make the adrenal glands a vital player in the orchestration of physiological responses to stress, salt and water balance, and metabolism. The mesenchymal derived adrenal cortex consists of three zones each producing a specific class of steroid hormones: mineralocorticoids (aldosterone) regulating blood pressure, water and electrolyte balance, glucocorticoids (cortisol) regulating stress, immune responses and intermediary metabolism, as well as androgen precursors and adrenal-specific androgens. The main regulator of cortisol secretion is adrenocorticotropic hormone (ACTH) secreted from the pituitary creating a pulsatile feedback loop. Aldosterone is mainly regulated by the renin-angiotensin system (RAS) and potassium levels. The neural crest-derived adrenal medulla consists of chromaffin cells, modified secondary sympathetic neurons, that produce catecholamines, noradrenalin and mainly adrenalin.

Endocrine disorders of the adrenal cortex can be broadly divided into deficient hormone production (adrenal insufficiency), overproduction of hormones, and combinations of these such as in congenital adrenal hyperplasia. Many of these conditions are rare, but overproduction of aldosterone (primary aldosteronism) and cortisol (mild autonomous cortisol secretion) affects millions of individuals living in Europe and are major causes of hypertension, type 2 diabetes, obesity and osteoporosis. There are still major knowledge gaps in our understanding of the basic mechanisms underlying these diseases. Efficient diagnostic and therapeutic strategies for adrenal disorders are fundamental for the public health in Europe, and in many areas, there is a high unmet medical need that require increased research efforts.

Subtopic 1: Adrenal insufficiency

Adrenal insufficiency is defined by the failure to produce cortisol and/or aldosterone from the adrenal cortex. This may be caused by a condition affecting the function of the adrenal cortex (primary adrenal insufficiency, PAI) or by a condition affecting the regulatory system (secondary/tertiary adrenal insufficiency). Acquired PAI is most commonly caused by destruction of the adrenal either by an autoimmune attack, infection, tumour or

haemorrhage. Another common cause is inherited enzyme defects of steroidogenesis called congenital adrenal hyperplasia (CAH). Similar to PAI there is a deficiency of cortisol; however, depending on the specific enzyme deficiency this is accompanied with either deficiency or excess of mineralocorticoids and sex steroids, respectively. Individuals with secondary and tertiary adrenal insufficiency lack ACTH which causes deficiency of cortisol and androgen production, leaving aldosterone production intact. The symptoms of adrenal insufficiency depend on the cause, but most patients experience fatigue, nausea, reduced stress tolerance, and weight loss. Skin pigmentation depends on ACTH concentrations; typically, PAI patients are hyperpigmented while those with secondary and tertiary causes are not.

Subtopic 1a: Primary adrenal insufficiency, including congenital adrenal hyperplasia (CAH)

1. Epidemiology, societal impact, research state of the art: The prevalence of PAI varies in different age groups. Genetic conditions commonly present during infancy and childhood; however, increasing evidence suggests delayed onset of milder forms. 2 The prevalence of acquired autoimmune PAI, also known as Addison's disease, is about 150 per million (about 100,000 cases in Europe) and the incidence about 5 per million per year. This is a condition where the immune system attacks the adrenal cortex (PMID:33484633). The most common cause of inherited PAI is CAH due to 21-hydroxylase deficiency occurring in its severe classic form in about 1 in 15,000 life-births (about 45,000-60,000 affected individuals in the whole of Europe).

Autoimmune PAI commonly affects individuals between 30-50 years of age, and is more common in females than males, with a female-to-male ratio of about 1.5 to 2.5 (PMID: 19858318). The risk of developing autoimmune PAI is increased in patients with other autoimmune diseases, such as type 1 diabetes, autoimmune thyroid disease, pernicious anaemia, or vitiligo and many develop several of these disorders, called autoimmune polyglandular syndromes (APS) (PMID: 29562162). The pathogenesis of autoimmune PAI is incompletely known. Almost all patients develop autoantibodies against 21-hydroxylase (PMID:1351548), which can be used as a diagnostic biomarker (PMID:34665570), but autoreactive T cells are thought to be the main mediators of the adrenocortical destruction (PMID:34711410). The key associated genes were recently mapped in a GWAS explaining 40% of the heritability across 9 loci (PMID:33574239), and a polygenic risk score has been developed (PMID: 37151110). The aetiology of PAI in the elderly population is quite different, dominated by infections, haemorrhage and malignant diseases affecting the adrenals (for example metastasis or primary tumours). Diagnosis of monogenic forms of PAI are more common in children and adolescents but may also manifest in adults. CAH is a group of monogenic disorders leading to cortisol deficiency due to deficiency of steroidogenic enzymes. The most common is 21-hydroxylase deficiency (>95% of cases) causing cortisol deficiency and androgen excess, and in two-thirds of cases clinical apparent aldosterone deficiency. Adrenal insufficiency develops in severe forms in the neonatal period. Females display different degrees of hyperandrogenism, but males have no distinct phenotype. Individuals with CAH have increased long-term comorbidities affecting most organ systems and an increased early mortality has been suggested. Other monogenic forms are X-linked including adrenoleukodystrophy caused by mutations in the *ABCD1* gene affecting peroxisomal beta-oxidation leading to accumulation of very long-chain fatty acids. Adrenal hypoplasia congenita is caused by mutations in *DAX1*, a nuclear receptor protein involved in the regulation of steroidogenesis. Several other rare genetic causes are known (PMID: 33484633).

Current treatment relies on replacement of lacking hormones. In addition, forms of CAH associated with androgen excess require normalization of adrenal androgen concentrations. Standard replacement treatment is twice, or thrice daily hydrocortisone tablets in adults and thrice or four-times daily in children and young people combined with once daily fludrocortisone. Children, young people and physically active adults frequently require additional oral sodium replacement. The role for adrenal androgen replacement is poorly defined, although women with autoimmune PAI are generally deficient. CAH associated with hyperandrogenism often requires higher glucocorticoid doses than in

PAI and secondary adrenal insufficiency to 3normalize adrenal androgen production. Recently extended-release and modified-release glucocorticoid formulations have become available (PMID: 19383806; 25494662). Experimental pump treatment, both circadian and ultradian (pulsed) replacement therapy is now also feasible. Several novel additional therapy modalities are currently under development to treat hyperandrogenism in CAH, including corticotropin releasing hormone antagonists (PMID 38828955, PMID: 38828945); however, their clinical usefulness in wider clinical practice needs to be established. There is an association between corticosteroid replacement and cardiovascular disease, especially in women (PMID 30608542). Thus, treatment mimicking the physiological situation is required but not yet feasible in clinical practice.

2. F**uture research priorities:**

1. Pathogenesis of adrenal insufficiency

The development of more targeted interventions requires a better understanding of the the pathogenesis of autoimmune PAI, and the genetic and the environmental factors that drives autoimmunity. Therefore, we advocate the development of mouse and other in vivo models to explore genotype-phenotype associations and disease modulators/compensators. Furthermore, this will support the development of novel immune modulatory treatment aimed at stopping, reversing, or ideally preventing autoimmune PAI. Such treatment modalities include gene therapy, stem cells, and chimeric antigen receptor T cell therapy.

Application of rapid clinical genetic testing to diagnose rare forms of adrenal insufficiency is in demand and their health benefit needs to be defined (health economic models).

2. Natural course of adrenal insufficiency

The natural history of adrenal insufficiency remains not fully understood. Therefore, it will be vital to establish patient registries and biobanks to map the natural course and long-term outcome including growth, sexual function, fertility, pregnancy, cardiovascular risk, bone health and adrenal crisis.

3. *Treatment of adrenal insufficiency*

We need to develop novel replacement modalities to normalise cortisol and mineralocorticoid rhythms and normalise adrenal androgen production in CAH. In addition, better tools to tackle adrenal crises, including strategies for prevention and early treatment of adrenal crisis (e.g. a hydrocortisone-penject device) will be needed to decrease hospitalisation, comorbidities and mortality.

A better understanding of adrenal stem cell physiology would form the foundation to develop new treatment modalities to replace missing adrenocortical cells (PAI). In addition, other approaches to correct altered gene function (e.g. by viral vectors in CAH, other monogenic diseases) or by transplantation of tissue/cells would revolutionise treatment of adrenal insufficiency.

4. Biomarkers for corticosteroid action

The current lack of biomarkers of corticosteroid action complicates the design of clinical outcome studies. Thus, defining biomarkers for cortisol and mineralocorticoid effects and their use could support the individualisation and optimisation of corticosteroid replacement across the life span including puberty, pregnancy and stress. Furthermore, biomarkers would be useful to identify and prevent systemic consequences of corticosteroid excess and deficiency. Furthermore, they could be used as hard endpoints in future clinical studies.

5. Clinical management:

To develop education and information programmes and assess their ability to promote health in patients.

3. Anticipated impact of future research: Improved quality of life and ability of patients with adrenal insufficiency to work, reduction of complications (fertility, mortality, overtreatment with its metabolic side effects), adrenal crisis reduction (decreased mortality).

Novel diagnostic, treatment and monitoring tools will improve early diagnosis, outcomes of adrenal insufficiency, improve quality of life and ability to work, reduce mortality and complications and enable more patient participation in their own disease.

Subtopic 1b: Secondary and Tertiary adrenal insufficiency

1. Epidemiology, societal impact, research state of the art: Secondary adrenal insufficiency is due to deficient stimulation of the adrenal cortex by adrenocorticotropic hormone (ACTH, see chapter on Pituitary diseases). When the suppression of ACTH production is caused by exogenous glucocorticoid treatment it is called tertiary adrenal insufficiency. Glucocorticoids are a cornerstone in treating a wide range of medical conditions, such as autoimmune diseases, inflammatory disorders, severe allergic reactions, prevention of transplant rejection and cancer. Their use is very common. Continuous (> 3 months) oral glucocorticoids were prescribed for 0.5% of the total population and 1.4% of patients aged 55 years or older (PMID: 8760745). In a population-based study from Denmark, the annual prevalence of systemic glucocorticoid prescription in primary care was 3% of the population and up to 10% among elderly (PMID: 28554927). Systematic studies of side effects are few both after short- and long-term use. The prevalence of adrenal insufficiency and adrenal crises require systematic studies. There is also little evidence on how to taper and stop glucocorticoid treatment.

2. F**uture research priorities:**

1. Define biomarkers for pharmacologically glucocorticoid treatment.

We need to develop biomarkers enabling us to individualise glucocorticoid treatment to optimize treatment outcome and minimize side-effects. The sensitivity to glucocorticoids shows wide interindividual variation, but usually patients are given a standard dose, putting many at risk inferior treatment outcome, side-effects and complications.

2. Standardized tapering regimens

Evidence-based tapering regimes are lacking, and clinical trials are needed to define optimal and safe tapering og glucocorticoids, including reliable and efficient ways to screen for adrenal insufficiency.

3. Drug development

In order to reduce the side-effects and complications of pharmacological glucocorticoid treatment, we need to develop novel glucocorticoids with fewer side-effects.

4. Research of hypothalamus-pituitary-adrenal axis regulation

A number of patients experience permanent adrenal insufficiency after glucocorticoid treatment. We need research to understand why the hypothalamus-pituitary-adrenal axis “shuts down” in certain individuals and develop ways to “reawake” the axis, including cure of genetic disorders.

6. Patient education

We have to improve patient education to facilitate tapering and understand the difference between disease flare, glucocorticoid withdrawal and adrenal insufficiency.

3. Anticipated impact of future research:

Future research should allow improving diagnosis and outcome of secondary and tertiary adrenal insufficiency. This includes ways to individualise treatment and tapering of glucocorticoids and reduce the risk of short term (adrenal crisis) and long-term complications (e.g. cardiovascular disease and osteoporosis)

Translational research questions:

- What is the differential impact of adrenal insufficiency on females and males as consequence of altered steroid hormone levels; linking into different health problems (e.g fertility issues)
- What model systems including animal models are required to understand pathophysiology and systemic dysregulation due to hormone deficiency and excess?
- What is the effect of adrenocortical dysfunction on adrenal medullary function and catecholamine physiology?
- How can sex differences in adrenal diseases be explained?

Subtopic 2: Adrenal tumours

Adrenal tumour types are highly diverse in terms of prevalence, malignancy, secretion level, and molecular mechanisms. Research is active at the European level, with collective actions such as the European Network for the Study of Adrenal Tumours (ENSAT) boosting collaboration and federation, especially for rare tumour entities

Subtopic 2a: Malignant adrenal tumours (Adrenocortical carcinoma, ACC) and Pheochromocytoma and paraganglioma, PPGL)

1. Epidemiology, societal impact, research state of the art: ACC are rare tumours (0.5-2 per million). Their clinical outcome is heterogeneous with a 5-year survival ranging from 15 to 90%, mainly depending on initial tumour grade (Fassnacht et al. EJE 2018). Firstline treatment for patients with localized disease is surgical removal of the tumour. However, after a complete tumour resection, using current standard clinical and pathological features, it is not possible to properly predict whether the patient is going to remain free of disease or whether the disease will recur. Molecular studies have identified different molecular subtypes with different outcomes, but proposed prognostic biomarkers have not been implemented in clinical practice so far (REF Assié et al Nature Genetics 2014, Zheng et al Cancer Cell 2016). For patients with localized ACC, adjuvant treatment by mitotane may be proposed (REF Terzolo et al NEJM 2007 and Terzolo et al 2023).

For patients with advanced ACC – either recurring or metastatic, effective treatments are darely missed. Responses to routinely used mitotane and platin-based chemotherapies do not exceed 20% (Fassnacht et al. EJE 2018). New therapies - such as immunotherapy or IGF1 receptor antagonists as well as other tyrosine kinase inhibitors- have been tested with limited and unpredictable efficiency (REF: PMID: 32622829). The lacking infiltration by cytotoxic T cells has spurred studies to investigate the importance of the tumour immune microenvironment (Ref Landwehr et al J Immunother Cancer 2020). Specifically, the immunosuppressive role of intra-tumour cortisol secretion in a subset of ACC might negatively impact on the efficacy of immunotherapies and other targeted treatments. To which extent

prior treatment with mitotane and/or cytotoxic chemotherapy further impairs responsiveness to immunotherapy is currently unknown.

Pheochromocytomas and paragangliomas (PPGLs) are tumours derived from the adrenal medulla or other sympathetic ganglia. PPGLs have an estimated prevalence of 1:6,500 to 1:2,500. Approximately 15% of pheochromocytomas and paragangliomas are metastatic, with a heterogenous 5-year survival rate varying from 40-80% (REF DOI 10.1530/EJE-16-0189).

The majority of PPGLs are driven by a single inherited or acquired genetic variant, being estimated that about 40% of patients carry a germline mutation in one of the 20 susceptibility genes and a further 30-40% of tumours are driven by somatic driver variants (REF DOI: 10.1210/endrev/bnab019). Genotype-phenotype correlations have facilitated personalised surveillance strategies, but management remains challenging due to the heterogenous clinical behaviour of PPGLs, limited predictive markers of metastatic risk and inefficient therapeutic strategies for metastatic disease. After complete resection of PPGL, the risk of recurrence is difficult to predict. Germline *SDHB* variant status and tumour size greater than 5cm have been identified as the most sensitive predictors of local or metastatic recurrence (REF DOI:10.3389/fendo.2023.1279828). International guidelines also define a category of high-risk patients (young patients and those with a hereditary predisposition a large tumour and/or an extra-adrenal paraganglioma) for whom a lifelong annual follow-up is required. Recently, specific molecular alterations have been identified as sensitive predictors of metastatic potential, namely somatic *ATRX* variants, microsatellite instability, high CDK1 expression and *MAML3* fusions (REF 10.1038/s41467-023-36769-6). In this regards, metastatic PPGLs could benefit from precision medicine based on mutation status.

2. F**uture research priorities:**

A. To better **stratify** patients with malignant adrenal tumours at diagnosis, after surgery and during follow-up, combining clinical, morphological and molecular markers.

-For ACC after complete surgery, additional markers are needed to predict the risk of recurrence to personalize surveillance modalities and potential adjuvant treatments. In case of advanced ACC, markers predicting response to existing treatments (mitotane, chemotherapy, immunotherapy, tyrosine kinase inhibitors) are needed to identify for each treatment the small subset of patients for whom a response is expected – thus sparing precious time when disease is growing fast and heavy side effects for a majority of unresponsive treatments.

-For PPGL, the known relevance of genetic status should be further exploited and combined with clinical, morphological, biochemical and molecular imaging features to personalize treatment options, stratify long-term surveillance and better identify those patients at highest risk of metastatic or aggressive disease. The penetrance of susceptibility genes should be investigated, as well as the potential modifying factors (environmental factors, family history, polygenic risk scores), to identify the factors leading to recurrence or to the development of new tumours for the patients and their relatives carrying the mutation.

B. To **develop** efficient **treatments** for **advanced** adrenal malignant tumours.

-Screening for targetable molecular alterations should be generalized for all advanced ACC and PPGL, in a time frame compatible with the potentially rapid evolution of the disease. Any targetable molecular alteration should direct the role for for new treatments, with a systematic collection of the effect –whether positive or negative.

- The elucidation of mechanisms of resistance to immunotherapy is a priority. The identification of targetable factors that impair responsiveness to immunotherapy is urgently required. One prime example that requires further mechanistic understanding is the specific immunosuppressive action of

secreted hormones and metabolites in metastatic adrenal tumours – cortisol for ACC and catecholamines and oncometabolites in PPGL. The impact on tumour immune microenvironment should be explored in humans and in preclinical models, with the perspective of developing specific anti-tumour strategies, targeting intra-tumour blockade of hormone and metabolite secretions. In PPGL, the genotype influence on tumour immune environment should also be specifically explored.

C. To pursue the effort of **federated research** at the European level, owing to the **rarity** of these cancers.

-Convenient clinical data sharing solutions should be created, targeting the inclusion of all patients with malignant adrenal tumours, and aiming at extensively reporting the drugs tested and their efficiency. These shared data should incorporate translational research arms, addressing the need for novel biomarkers of treatment response, e.g. tumour/serum/urine metabolomics, genomics, radiomics.

-A European infrastructure promoting multicentric clinical trials should be created, testing the efficacy of innovative pharmacological and local treatments, aiming at reaching sufficient statistical power to conclude whether the treatment is efficient or not.

3. anticipated impact of future research:

- Patients with advanced ACC and PPGL are left with limited therapeutic options, the therapeutic need for them is major.

- Discoveries related to the specificity of hormones and immune modulating metabolites secreted by adrenal tumours may impact cancer management in general, beyond the rare and specific adrenal tumours

Subtopic 2b: Benign adrenocortical tumours

1. Epidemiology, societal impact, research state of the art: Benign adrenal tumours are common, being observed most often incidentally with a prevalence of 1 to 8% on imaging and autopsy series. Among these common tumours, up to 40% present hormone hypersecretion, consisting most often of a mild autonomous cortisol secretion (MACS)(REF 10.1016/S2213-8587(22)00100-0, DOI: 10.1093/ejendo/lvad066). Despite the absence of obvious clinical signs of Cushing Syndrome, MACS is associated with an increased prevalence of type 2 diabetes, obesity, hypertension and dyslipidemia, as well as osteoporosis and psychiatric symptoms (15%-40% higher), with significant impact on morbidity and mortality (REF PMID: 35533704). Adrenal surgery may improve this outcome (DOI: 10.1093/ejendo/lvad066; PMID: 35721734). However, it is currently not possible to establish the precise impact of MACS at an individual scale, nor the benefit of correcting MACS on blood pressure, weight and metabolism at the individual level. Finally, a subset of incidentally discovered tumours present intermediate morphological features (DOI: 10.1093/ejendo/lvad066). For these patients, the evaluation of the malignancy risk is challenging

Less common are benign tumours and benign adrenal cortex alterations (e.g. bilateral adrenal nodular hyperplasia) responsible for overt Cushing Syndrome, associated to severe comorbidities and increased mortality (PMID: 35979717). In most cases, these diseases are sporadic, but occasionally can be associated with familiar syndromes, especially in those patients with bilateral macronodular and micronodular adrenal hyperplasia. Patients with adrenal Cushing syndrome require specific treatments targeting cortisol excess and may benefit from genetic counselling to exclude germline genetic

alterations occurring in one of the few causative genes recently discovered (REF doi: 10.1210/endrev/bnac034.).

2. **future research priorities:**

A. To improve the management of patients with MACS:

-Patients should be better stratified: which are the best diagnostic criteria and best laboratory assays to recognise MACS in patients with adrenal tumours? Is autonomous cortisol secretion variable over the time? In general population, what is the prevalence of MACS in common diseases such as hypertension, diabetes, overweight, osteoporosis?

-Treatments (steroidogenesis inhibitors, adrenolitic compounds, glucocorticoid receptor antagonist, adrenal surgery) should be better evaluated: which are the benefits (on blood pressure, metabolism, weight, bone density as well as mortality)? On which patients?

B. Differential diagnosis of benign tumours focusing on masses with borderline features

For these tumours, large collections of clinical, morphologic (radiomic, nuclear medicine), molecular (metabolomic, genomic) data, are required to better predict the risk of malignancy, using multimodal machine learning approaches.

C. Understanding the biology and disease burden (cardiovascular and metabolic) of primary adrenal hyperplasia/dysplasia

Finding the predisposing genes of these rare diseases, finding the potentially associated diseases, understanding their role and exploring the penetrance in relatives are needed, to improve the management of these patients and their relatives.

3. anticipated impact of future research:

Identifying the glucocorticoid contribution to common health disorders such as hypertension, overweight, diabetes, osteoporosis, and dyslipidaemia could greatly improve the individual management of patients presenting these disorders.

Given the prevalence of adrenal incidentaloma on abdominal imaging, a standardized strategy for properly identifying tumours requiring extra work-up is needed.

Novel genes and mechanisms can lead to unpredictable development in other diseases, either rare or common.

Subtopic 3: Endocrine hypertension

Epidemiology, societal impact, research state of the art: Arterial hypertension (HT) is the most important cardiovascular risk factor, accounting for more than 10 million deaths per year due to myocardial infarction, heart failure, stroke, cognitive disorders, end-stage renal disease and premature death (PMID: **33069327)**. Within Europe, HT places increased strain on health care systems by negatively affecting economic development and impairing the health of many Europeans – particularly the elderly population. A significant proportion (5-20%) of patients with HT suffers from so-called secondary hypertension, due to a specific, identifiable, and curable underlying disease. Among them,

endocrine hypertension represents most cases and a major target for stratified intervention. Endocrine causes of hypertension are due to a group of adrenal disorders resulting in increased production of hormones that affect blood pressure**,** mainly aldosterone (primary aldosteronism, PA), catecholamines (pheochromocytoma/functional paraganglioma, PPGL) and cortisol (Cushing's syndrome, CS). Due to the diagnostic complexity for the work-up of these diseases, patients remain exposed to increased cardiovascular and metabolic risk and diminished quality of life due to delayed diagnosis and treatment and specific cardiovascular effects of hormone excess, which increase their risk beyond that of blood pressure matched hypertensive patients. While PPGL and CS is detailed in Subtopic 2, this section will focus on research priorities and future perspectives of PA.

PA is the most common form of secondary and curable HT, affecting 6% of the hypertensive population in primary care and up to 20% of patients with treatment resistant HT (PMID: **28385310;** PMID: **33742213)**. Given the diagnostic complexity, including invasive adrenal vein sampling, less than 2% of high-risk patients with treatment-resistant HT are tested for PA over their lifetime, and much less than 1% are ever diagnosed or appropriately treated with targeted therapy (PMID: **26934393;** PMID: **34657442**). In addition, recent clinical evidence suggests a continuum between dysregulated aldosterone production and PA in patients with HT, which parallels the severity of hypertension and may play a role in the development of high blood pressure in the general population (PMID: **32449886**).

PA is due to autonomous aldosterone production from the adrenal cortex, due in most cases to a unilateral aldosterone producing adenoma (APA), which is amenable to surgical cure, or bilateral adrenal hyperplasia (BAH), treated by mineralocorticoid receptor antagonists (MRA) and possibly aldosterone synthase inhibitors (ASI) currently under development (PMID: **32724183;** PMID: **37612380**). Four familial forms (familial hyperaldosteronism type I – IV) and one rare disease (PASNA, primary aldosteronism, seizures and neurological abnormalities) have been described. Familial forms account for ~6% of cases of PA, are transmitted as an autosomal dominant trait and are due to heterozygous germline mutations in different genes. Age of onset is variable, with most cases being diagnosed before age 20 years. Somatic mutations in the same genes, as well as additional ones, are found in more than 90% of APA. Mutations affect genes coding for ion channels (*KCNJ5, CLCN2, CACNA1D, CACNA1H, SLC30A1*) or ATPases (*ATP1A1, ATP2B3*) involved in the regulation of aldosterone biosynthesis, and genes regulating other cellular functions (*CTNNB1 and GNA11/GNAQ, CADM1*) (PMID: **36646167;** PMID: **37612380**). Somatic mutations have also been identified in so-called aldosterone producing micronodules (APM, also called aldosterone producing cell clusters) in adrenals with APA, in BAH and in normal adrenals. In addition, recent genome wide association studies have identified genetic loci that increase the susceptibility of developing PA, suggesting a continuum between APA and BAH (PMID: **36057693;** PMID: **36802911**). These risk loci are partially shared with genetic loci identified for blood pressure, providing a mechanistic basis to the continuum between dysregulated aldosterone production and PA observed in HT.

2. **Future research priorities:** Early detection of PA and instauration of targeted treatment have a major impact on clinical outcome and survival, given the important contribution of aldosterone excess to target organ damage. Since PA is one of the most underdiagnosed prevalent diseases world-wide, effective screening strategies represent a top priority and a major unmet need. Future research priorities include implementation of new stratification biomarkers directed at PA, new approaches for subtyping unilateral versus bilateral PA and identification of patients who would most benefit from surgery, stratification of patients for optimal treatment strategies, establishment of surrogate biomarkers for the underlying genetic causes and development of new targeted treatments.

Specific research priorities are the following:

1. To implement new biomarkers and artificial intelligence (including omics biomarkers, clinical scoring system, BNP, others) for improved diagnosis, subtype identification, treatment and prediction of outcome following specific surgical or medical therapy (MRA, ASI)
2. To investigate and optimize new imaging techniques, including ASI-based PET ligands for:

- diagnosis and subtype identification
- prediction of outcome after surgery (identification of patients with asymmetric PA, or latent foci of autonomous aldosterone production in the contralateral adrenal which might become activated after removal of the dominant adrenal) to identify patients who will benefit from unilateral adrenalectomy
- understanding the natural history of development of APM and to discover whether they are a maladaptive response to excess salt intake, and are preventable/reversible by reduction of salt intake

3. Implement new clinical trials:

- To assess new diagnostic and therapeutic procedures
- To assess whether screening for PA in all hypertensive patients improves morbidity, mortality, and quality of life
- To establish whether targeted treatment with ASI and MRI reduces the cardiovascular and metabolic risk for patients along the continuum of dysregulated aldosterone biosynthesis from low renin hypertension to florid PA

4. Investigate the genetic contribution to PA development and outcome:

- Investigate the relationship between dysregulated aldosterone production, PA susceptibility alleles and resistant hypertension
- Investigate whether different genotypes in APA reflect different pathogenesis and are associated with different prognosis and validate surrogate biomarkers for somatic mutations to select patients who will benefit from diagnostic/therapeutic interventions.

3. Anticipated impact of future research:

Future research should allow improving diagnosis and outcome of patients with PA, reducing cardiovascular risk and improving quality of life through earlier and better targeted treatment. This may extend to patients along the continuum of dysregulated aldosterone biosynthesis from low renin hypertension to florid PA.