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Clinical Practice Guideline

Familial hyperaldosteronism: an European Reference Network on Rare Endocrine Conditions clinical practice guideline

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Abstract

We describe herein the European Reference Network on Rare Endocrine Conditions clinical practice guideline on diagnosis and management of familial forms of hyperaldosteronism. The guideline panel consisted of 10 experts in primary aldosteronism, endocrine hypertension, paediatric endocrinology, and cardiology as well as a methodologist. A systematic literature search was conducted, and because of the rarity of the condition, most recommendations were based on expert opinion and small patient series. The guideline includes a brief description of the genetics and molecular pathophysiology associated with each condition, the patients to be screened, and how to screen. Diagnostic and treatment approaches for patients with genetically determined diagnosis are presented. The recommendations apply to patients with genetically proven familial hyperaldosteronism and not to families with more than one case of primary aldosteronism without demonstration of a responsible pathogenic variant.

Keywords: adrenal cortex, diagnosis of endocrine disease, genetics in endocrinology

Significance

Familial hyperaldosteronism is a group of severe and often underdiagnosed hereditary conditions associated in most cases with florid clinical and biochemical phenotypes, which if left untreated are associated with a high risk of complications. Their early recognition is fundamental to establish correct therapies and reduce the incidence of events.

Introduction

Primary aldosteronism (PA) is a frequent and often unrecognized cause of secondary hypertension.[1,2] Primary aldosteronism is characterized by aldosterone secretion that is excessive for body sodium status and relatively autonomous of renin–angiotensin system activity,[3,4] which is suppressed. Aldosterone excess causes hypertension, may induce hypokalaemia, and is also associated with detrimental effects on non-epithelial tissues,[5] leading to an increased risk of cardiovascular and cerebrovascular events[6] and kidney damage.[7]

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Primary aldosteronism comprises sporadic subtypes, mainly unilateral aldosterone-producing adenoma (APA) and bilateral PA[1,8] and genetic forms, including familial hyperaldosteronism (FH) types I-IV and PA, seizures, and neurological abnormalities (PASNA) syndrome, a non-familial, genetic variant of PA.[9] The prevalence of FH in PA has not been systematically investigated but is reported to be between 1% and 5%.[10-12] However, the actual prevalence of genetically determined FH might be overestimated if diagnosed in the presence of 2 first-degree relatives with PA in the same family without genetic confirmation, since sporadic PA is not uncommon and therefore can occur by chance in more than one family member. Therefore, the true prevalence of FH is probably below 1%. Conversely, some FH cases can be missed because of incomplete penetrance of the PA phenotype or in cases with de novo pathogenic variants.

In this Endo-ERN clinical practice guideline, we discuss the available scientific evidence for the diagnosis and treatment of familial monogenic forms of FH and provide suggestions and recommendations for the management of this condition. Importantly, these recommendations apply to patients with genetically proven FH and not to families with more than 1 case of PA without the demonstration of a responsible pathogenic variant.

Genetics and pathophysiology of FH

To date, disease genes have been identified in 4 subtypes of FH and PASNA syndrome. Familial hyperaldosteronism is inherited in an autosomal-dominant fashion or caused by de novo pathogenic variants.

Familial hyperaldosteronism I

Familial hyperaldosteronism I, also known as glucocorticoid-remediable aldosteronism, was first described in 1966,[13] and its genetic basis was elucidated 26 years later.[14] Familial hyperaldosteronism I is caused by unequal crossing-over between the highly homologous *CYP11B1* (11β-hydroxylase, involved in cortisol production, regulated by ACTH) and *CYP11B2* (aldosterone synthase) genes. The breakpoint is located within the first 2-4 introns, resulting in a chimeric gene. Because the hybrid gene carries the promoter region of *CYP11B1*, it is expressed within the adrenal zona fasciculata and regulated by ACTH. Due to the presence of *CYP11B2* coding sequence, the encoded enzyme has aldosterone synthase activity.[15] Intracellular co-expression of aldosterone synthase and 11β-hydroxylase activity results in aldosterone and 18-oxocortisol synthesis within the zona fasciculata of affected patients[16] (Figure 1). Dexamethasone suppression of ACTH normalizes aldosterone concentrations and ameliorates hypertension.

Familial hyperaldosteronism II

Familial hyperaldosteronism II was described for the first time in 2018 and is caused by germline pathogenic variants of the *CLCN2* gene. *CLCN2* encodes ClC-2, a voltage-gated chloride channel expressed in many tissues, including the zona glomerulosa of the adrenal gland. Both de novo pathogenic variants and those affecting several generations have been reported.[17,18] These pathogenic variants cause gain of chloride channel function, leading to increased chloride efflux and depolarization of glomerulosa cells, followed by increased voltage-gated calcium influx. Elevated intracellular calcium is the major signal for aldosterone production, leading to aldosterone overproduction[17-20] (Figure 1).

Familial hyperaldosteronism III

In 2011, FH-III was reported to be caused by heterozygous germline pathogenic variants of an inwardly rectifying potassium channel gene, *KCNJ5* (Kir3.4).[21] *KCNJ5* is expressed, among other tissues, in the zona glomerulosa. Pathogenic variants in FH-III cause abnormal permeability of the channel for sodium ions. Sodium influx leads to depolarization and voltage-gated calcium influx, thereby increasing aldosterone concentrations, as in FH-II[21,22] (Figure 1).

Familial hyperaldosteronism IV

Familial hyperaldosteronism IV was described for the first time in 2015 and is caused by heterozygous germline pathogenic variants of a voltage-gated calcium channel ($Ca_V3.2$) encoded by the *CACNA1H* gene.[23] These pathogenic variants confer a gain of function, with impaired channel inactivation and, in some cases, a shift of activation to more negative (hyperpolarized) potentials.[23,24] $Ca_V3.2$ is a major calcium influx pathway in zona glomerulosa cells. Mutant channels directly cause elevated calcium influx and increased glomerulosa calcium levels, leading to increased aldosterone production[25,26] (Figure 1).

PASNA syndrome

De novo pathogenic variants in *CACNA1D*, encoding the voltage-gated calcium channel $Ca_V1.3$, are found in a complex syndrome of PA associated with seizures and neurological abnormalities (PASNA), first described in 2013.[27,28] Similar to *CACNA1H*, *CACNA1D* pathogenic variants cause a gain of function, directly raising calcium influx and aldosterone production[27] (Figure 1).

Other forms

Variants in the *ARMC5* gene have been linked to PA in one study[29] but not in a subsequent one.[30] Therefore, the role of this gene in familial PA remains to be determined.

Families with 2 or more patients with PA have been observed, without pathogenic variants in genes causing FH.[11,31] A recent study identified new *loci* associated with bilateral PA.[32] However, at present, most of these cases should be considered due to sporadic PA in the same family.

Genotype/phenotype correlation in patients with FH

Patients with FH present with variable degrees of hypertension, hypokalaemia, metabolic alkalosis, suppressed renin, and elevated aldosterone production, typically with onset early in life.

The clinical phenotype of FH-I varies widely in terms of age of onset, severity, and penetrance[33-41] (Table 1). A history of early cardiovascular and cerebrovascular events is common but not universal,[41] and the clinical phenotypes of genetically affected individuals within the same family may differ greatly; some patients harbouring the pathogenic variant have early, severe hypertension, and marked increases in aldosterone and 18-oxocortisol production, while others are normotensive and normokalaemic.[33-35] While no correlation between the crossing-over point of the 2 genes *CYP11B1* and *CYP11B2* and severity of the syndrome was found, maternal inheritance

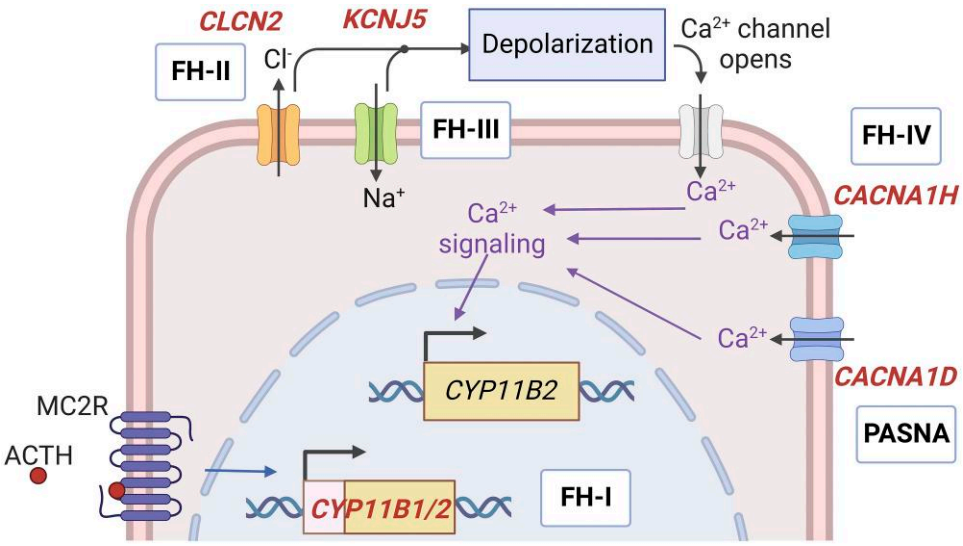

Figure 1. Pathophysiology of FH. In FH-I, a hybrid gene (*CYP11B1*/*CYP11B2*) causes aberrant expression of an enzyme with aldosterone synthase activity in the zona fasciculata under the control of ACTH. In FH-II, pathogenic variants in *CLCN2* lead to increased chloride efflux, and in FH-III, pathogenic variants in *KCNJ5* render the encoded potassium channel permeable to sodium ions. In both FH-II and FH-III, the resulting membrane depolarization causes voltage-gated calcium influx. *CACNA1H* pathogenic variants in FH-IV and *CACNA1D* pathogenic variants in PASNA syndrome directly increase calcium influx. Calcium is the main signal for aldosterone production in the zona glomerulosa.[9] Created with BioRender.com. FH, familial hyperaldosteronism.

was associated with higher blood pressure (BP).[36] In another study, hypertension was more severe in males and related to the degree of aldosterone and 18-oxocortisol overproduction.[42]

Familial hyperaldosteronism II typically presents as classical bilateral hyperaldosteronism at an early age; however, incomplete penetrance with normotension in adulthood has been reported[17,18] (Table 1).

The first described FH-III family comprised a father and 2 daughters with severe hyperaldosteronism presenting at a young age who required bilateral adrenalectomy for effective treatment.[21,43] The site and type of *KCNJ5* pathogenic variants correlate with the FH-III phenotypes. Pathogenic variants at T158A, G151R, I157S, and E145Q usually present with severe, resistant, or refractory hypertension at an early age and, in most but not all cases, massively enlarged adrenals.[21,43-48] The G151E pathogenic variant causes significant cell lethality in vitro and is associated with a mild phenotype and no adrenal hyperplasia.[48,49] The Y152C pathogenic variant was associated with a milder and late onset phenotype and resulted in a smaller disturbance of the intracellular calcium homeostasis.[47] Elevated 18-oxocortisol levels were reported in patients with FH-III[43] (Table 1).

Familial hyperaldosteronism IV is associated with a variable onset of the hyperaldosteronism phenotype.[23,24] The *CACNA1H* pathogenic variants M1549V[23] and p.M1549I[24] were associated with early onset hyperaldosteronism;[23,24] p.S196L, p.P2083L, and p.V1951E were identified in adults,[24] although the pathogenicity of p.V1951E is doubtful given that it was found in the germline of an individual with APA, who was cured by adrenalectomy (Table 1).

The clinical presentation of individuals with gain-of-function variants in the *CACNA1D* gene is highly variable. Hyperinsulinaemia with hypoglycaemia and heart defects are found in some cases with PASNA syndrome.[27,28] Of note, not all cases with *CACNA1D* gain-of-function pathogenic variants manifest PA. Some lack endocrine abnormalities and display autism as the main feature.[50] The severe neurological abnormalities presumably preclude inheritance in most cases. However, in a family with a milder presentation without PA, inheritance from a father to 2 children was reported[51] (Table 1).

Methodology

These guidelines were developed on behalf of the European Reference Network on Rare Endocrine Conditions (Endo-ERN). All guideline participants completed conflict of interest forms. A draft of the guideline was reviewed by 4 experts in the field (see "Acknowledgments" section) and has been distributed to all Endo-ERN members for comments.

Target audience and aims

This guideline was developed for healthcare providers who may see patients with FH. In general, these patients should preferably be treated by a multidisciplinary team of experts. General practitioners, internists, and patients might also find the guideline useful. Additionally, the guideline can serve as a source document for patient information leaflets and educational materials.

In clinical practice, when making treatment decisions, both the recommendations and the clinical judgement of the treating physician should be taken into account in a patient-centred, shared-decision process. Recommendations are not meant to replace clinical acumen. Certain recommendations may not be feasible in individual countries and must be interpreted in the context of available resources.

Summary of methods used

The Endo-ERN guidelines in general use Grading of Recommendations, Assessment, Development, and Evaluation as a methodological base.[52] The first step was to define clinical questions (see further); the second was to perform a systematic literature search. After including all relevant articles for each clinical question, we rated the quality of the evidence. The quality of the evidence behind the recommendations is classified as

Table 1. Genotype/phenotype correlation in FH type I-IV and PASNA syndrome.

Subforms	Gene	Phenotype	Therapy
FH-I (OMIM #103900)	*CYP11B1/CYP11B2* (cytogenetic location 8q24.3)	Primary aldosteronism, dexamethasone-responsive; high levels of hybrid steroids (18-hydroxycortisol, 18-oxocortisol); increased prevalence of intracranial aneurysms and haemorrhagic stroke	Dexamethasone (first choice in adults), MRA (second choice in adults, first choice in children)
FH-II (OMIM #605635)	*CLCN2* (cytogenetic location 3q27.1)	Primary aldosteronism	MRA
FH-III (OMIM #613677)	*KCNJ5* (cytogenetic location 11q24.3)	Severe to mild primary aldosteronism; hybrid steroids (18-hydroxycortisol, 18-oxocortisol), in some cases massive adrenal hyperplasia	MRA (first choice), bilateral adrenalectomy (second choice in MRAs not effective)
FH-IV (OMIM #617027)	*CACNA1H* (cytogenetic location 16p13.3)	Primary aldosteronism	MRA
PASNA syndrome (OMIM #615474)	*CACNA1D* (cytogenetic location 3p21.1)	Primary aldosteronism variably associated with seizures, neurological abnormalities, heart defects, hypoglycaemia, and hyperinsulinaemia	MRA, calcium channel blockers

FH, familial hyperaldosteronism; MRA, mineralocorticoid receptor antagonist; PASNA, primary aldosteronism, seizures and neurological abnormalities.

very low (+OOO), low (++OO), moderate (+++O), or strong (++++) per outcome.[53] Only recommendations regarding therapy were formally graded.

For the recommendations, we considered the quality of the evidence, the balance of desirable and undesirable outcomes, and individual values and preferences (goals for health, costs, management inconvenience, feasibility of implementation, etc.).[54] The recommendations are worded as "recommend" (strong recommendation) or "suggest" (weak recommendation). The meaning of a strong recommendation is that all reasonably informed persons (clinicians, politicians, and patients) would manage the patients in accordance with the recommendation. For a weak recommendation, most persons would still act in accordance with the guideline, but a substantial number may not.[55] Importantly, one cannot abstain from making recommendations when there is scarce evidence, as treatment decisions will have to be made anyway. This applies especially to those instances in which the scientific literature on FH is based on accumulated descriptions of single cases or 1 or 2 families. Recommendations are accompanied by an explanation as to why the recommendation was made.

Systematic review of therapy in FH

The clinical question for the systematic review was as follows:

What is the efficacy, effectiveness, and safety of the different therapeutic options (surgery and drug therapy) in FH-I to IV and PASNA syndrome?

All types of studies were considered, although it is acknowledged upfront that only case reports and small uncontrolled cohort studies were available. Endpoints considered were BP, potassium, renin and aldosterone levels, weight, quality of life, cardiovascular events, and mortality. We considered full-text English publications only.

The search retrieved 979 articles. Following the screening of titles and abstracts, 17 studies were included: 10 in FH-I and 7 in FH-III. The largest series comprised 11 patients with FH-I.[56] It should be emphasized that most studies mainly focussed on the genetic aspects of the patients. Treatment history was often not described in all details, follow-up was not standardized, and treatment effects were reported at variable time points during follow-up. Detailed biochemical analyses were not always performed and different treatment protocols were used. No study systematically evaluated long-term treatment effects on quality of life or cardiovascular events. Details of included studies are described in the Appendix.

For treatment, the quality of evidence from the review was considered very low, mainly given the small number of patients, the non-standardized follow-up and evaluation, and the lack of formal comparisons between different treatments (either type of drug or dose).

For FH-I, most described patients received dexamethasone (0.125-0.75 mg/day), and both BP and potassium concentrations were generally well controlled with this treatment. The use of spironolactone or eplerenone was also reported and resulted in good BP control (Appendix). The studies do not allow any conclusion regarding the optimal treatment or optimal dose. In addition, the effects on long-term cardiovascular outcomes are not well defined.

In FH-III, some patients were well controlled with spironolactone only,[48] whereas in many patients, despite aggressive medical treatment, BP remained elevated[43] requiring bilateral adrenalectomy. The studies do not allow any conclusion regarding the optimal treatment or the optimal timing of adrenalectomy. Effects on long-term cardiovascular outcomes are not well defined.

Recommendations

Screening and diagnostic workup

R.1.1. We recommend to test for PA in any patient with early onset (<40 years old) hypertension (in line with the ESH Consensus[2])

Rationale. Given that PA is highly prevalent (at least 5%-13%) in the adult hypertensive population,[1,57,58] it is prudent to assume that the prevalence of PA in the paediatric hypertensive population is not negligible. In a cohort of 130 hypertensive children,[59] serum aldosterone concentrations of >17.7 ng/dL (491.7 pmol/L) were observed in 9 (6.9%), plasma renin activity (PRA) levels of ≤0.5 ng/mL/h in 4 (3.1%), and aldosterone:renin ratio (ARR) levels of >10 (ng/dL/ng/mL/h) in 5 (3.9%) patients. Detection of PA at an early stage will facilitate timely treatment that may prevent or at least mitigate the development of cardiovascular and renal target organ damage owing to aldosterone excess. In adults with PA, the likelihood of cure of hypertension following removal of an APA is inversely

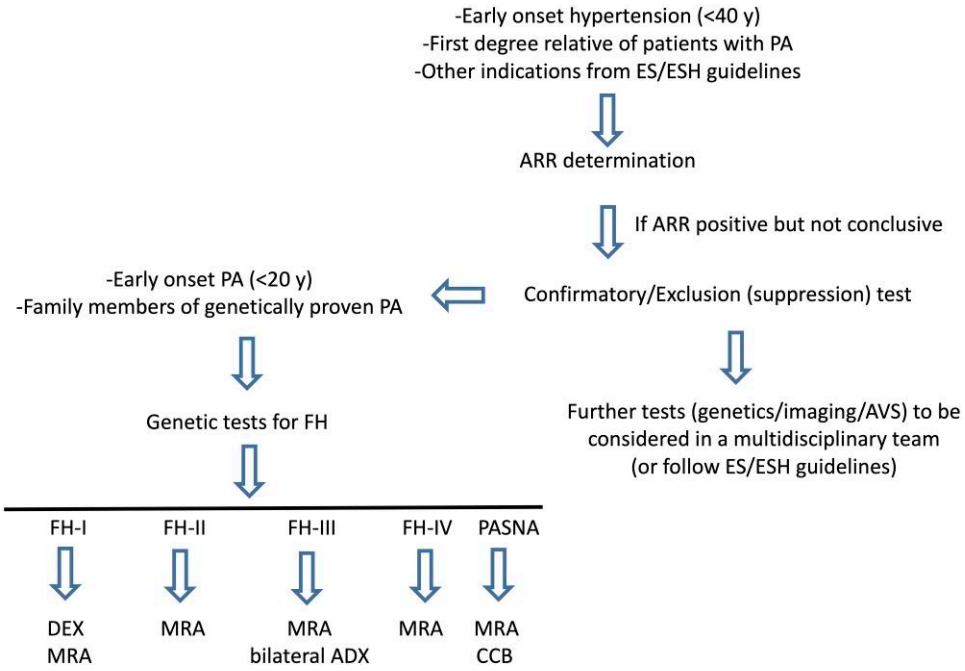

Figure 2. Proposed diagnostic flowchart for patients with suspected FH. ADX, adrenalectomy; ARR, aldosterone:renin ratio; AVS, adrenal vein sampling; CCB, calcium channel blockers; Dex, dexamethasone; ES, Endocrine Society; ESH, European Society of Hypertension; FH, familial hyperaldosteronism; MRA, mineralocorticoid receptor antagonist; PA: primary aldosteronism; PASNA, primary aldosteronism, seizures and neurological abnormalities.

correlated with age and duration of hypertension prior to surgery,[60] which further argues for early detection of PA (Figure 2). Furthermore, screening prior to initiation of antihypertensive agents, which affect plasma aldosterone and renin concentrations, renders the results easier to interpret.[61] Finally, in patients younger than 40 years and having stroke, the prevalence of PA is particularly high.[62]

In genetically inherited forms of PA, hypertension tends to be of early onset (<20 years of age).[9,63] Detection of those cases by biochemical screening followed by genetic testing enables genetic counselling of affected families (Figure 2).

R.1.2. We recommend the use of the plasma ARR as the initial screening test for FH

Rationale. The ARR is the preferred approach for screening for PA among hypertensive adults, being more sensitive than serum K^+ and aldosterone alone and more specific than renin alone[1-3,64] (Figure 2). In 130 hypertensive children tested for the hybrid *CYP11B1/CYP11B2* gene causing FH-I, 4 belonging to 4 unrelated families (3.1%) tested positive.[59] In addition, 4 other affected children were found among 21 first-degree relatives. Of the 8 affected children, all had high ARRs (>10 ng/dL/ng/mL/h), but only 1 had hypokalaemia. Hypokalaemia was present in <30% of genetically proven affected members of a family with FH-II (caused by a gain-of-function pathogenic variant in *CLCN2*), almost all of whom had raised ARR.[17]

Compared with genetic testing for FH pathogenic variants, the ARR is relatively inexpensive and easy to perform and has the advantage of detecting PA of non-genetic aetiologies. Measurement of aldosterone in a 24-h urine collection is cumbersome and generally not favoured by patients; therefore, collections are often incomplete.

In addition to the ARR, plasma aldosterone and renin concentrations should be assessed separately in order to exclude false positive ARRs due to very low renin concentrations when aldosterone is also low or very high aldosterone concentrations when renin is normal (eg, use of oestrogen-containing oral contraceptives or testing during the proliferative phase of the menstrual cycle).[61,65]

It is suggested to perform screening with drugs that minimally interfere with ARR interpretation.[1,2] However, ARR testing while patients are still on interfering medications can still be informative.[66] For example, a raised ARR with suppressed renin in a patient receiving an angiotensin I converting enzyme inhibitors, angiotensin II receptor blockers, or diuretic would be highly suggestive of PA, whereas a normal ARR in a patient on a beta-blocker would make PA highly unlikely. It should be emphasized that an elevated ARR is not per se diagnostic of PA due to the occurrence of false positives in the grey area between low renin essential hypertension and PA. Therefore, although confirmatory suppression tests lack standardization and validation, they are usually required to obtain a definitive diagnosis of PA.[1,2]

R.1.3. We suggest the diagnosis of PA to be confirmed if the ARR is elevated (with different cut-offs for adults and children)

Rationale. Several studies have demonstrated that the ARR in a healthy normotensive paediatric population is lower than that reported in an adult population.[67-69] This suggests that PA screening in children should be done with a lower cut-off value for the ARR than reported in adults to avoid false negative tests (see Table 2).

Using an ARR cut-off > 10 (aldosterone in ng/dL and PRA in ng/mL/h), all 8 affected persons aged < 20 years of a large kindred of a family with FH-I were correctly identified by ARR screening.[70] In 3 of the 5 adults with FH-I studied, the ARR was >25.[59]

Table 2. Suggested aldosterone:renin ratio cut-offs for screening in children and adults.

	ARR (aldosterone in ng/dL and PRA in ng/mL/h)	ARR (aldosterone in pmol/L and PRA in ng/mL/h)	ARR (aldosterone in ng/dL and DRC in mUI/L)	ARR (aldosterone in pmol/L and DRC in mUI/L)
Cut-off for adults	20	550	2	36
Cut-off for children	10	225	1	18

ARR, aldosterone:renin ratio; DRC, direct renin concentration; PRA, plasma renin activity.

The recommended cut-off value of the ARR in adults is between 20 and 40 (aldosterone in ng/dL and PRA in ng/mL/h) or between 1 and 3.7 (aldosterone in ng/dL and DRC in mU/L). Any chosen cut-off value has to take into account the specific assay characteristics for measurements of aldosterone (automated or non-automated immunoassay or liquid chromatography–tandem mass spectrometry measurement) and renin levels (direct renin concentration or plasma renin activity). The ratio should be considered primarily as a screening test and should be measured at least twice before deciding whether to go on to confirmatory testing for PA[64] (Figure 2).

R.1.4. We suggest performing a confirmatory test in cases where the clinical and/or biochemical diagnosis is unclear after ARR and the age is above 16 years

Rationale. According to the current guidelines, one or more confirmatory tests are recommended in patients with a repeated positive ARR.[1,2] The rationale for the confirmatory testing is that the ARR has a limited positive predictive value for PA, even when performed under ideal conditions and especially when cut-offs are permissive to ensure high sensitivity as is usually required for screening.[64] Confirmatory testing can exclude patients with a falsely positive ARR, thereby avoiding invasive procedures including adrenal vein sampling (AVS). In case of a particularly florid biochemical phenotype and a high a priori suspicion of PA, as indicated by spontaneous hypokalaemia, suppressed renin, a high ARR, and a high absolute aldosterone concentration > 20 ng/dL (555 pmol/L), confirmatory testing can be omitted.[1,2] At the lower end of the spectrum, "mild" forms of PA overlap with low-renin hypertension states, and confirmatory testing is mandatory.

Four tests are generally accepted to confirm or exclude PA: the fludrocortisone suppression test (FST), the oral (SLT) and the intravenous saline load test (SIT), and the captopril challenge test (CCT). There is no evidence reporting the test accuracy of SIT, CCT, SLT, or FST to identify patients with FH among those with a positive screening test. We suggest confirmatory testing in patients with suspected FH and repeatedly elevated ARR, especially if the biochemical phenotype is mild (no hypokalaemia, baseline serum aldosterone within the mid-normal range). We analysed the accuracy of the 4 tests in a published literature search and meta-analysis. When restricting the analysis to patients with confirmed unilateral PA, we identified 4 relevant studies conducted in the United States, Australia, Italy, and China,[71-74] the largest number of cases being 65. The optimal thresholds to identify unilateral PA were higher than those reported for overall PA. Thresholds for the diagnosis of PA (irrespective of the subtype) were lower: the estimated optimal threshold across SIT studies was 7.07 ng/dL (sensitivity of 0.86 [95% CI, 0.73–0.93] and specificity of 0.89 [95% CI, 0.78-0.94]). The estimated optimal thresholds across CCT studies for PAC was 10.67 ng/dL (sensitivity of 0.91 [95% CI, 0.82-0.96] and specificity of 0.81 [95% CI, 0.66-0.90]). The certainty of evidence was very low to low. We could not find relevant studies for FST and SLT. Most studies are limited by using imperfect and non-homogenous reference standards.

R.1.5 We suggest adrenal imaging (CT or MRI) in every patient with proven FH

Rationale. Current guidelines suggest imaging of the adrenal glands (by CT scanning or magnetic resonance) in every patient with a definitive biochemical diagnosis of PA. Imaging serves to rule out malignant aldosterone-producing adrenal carcinoma and to provide information for potential AVS.[1,8,64]

Theoretically, all forms of genetically determined FH affect both adrenal glands. Therefore, AVS should be considered futile in the majority, if not all, of patients with FH. This is not the case for situations in which at least 2 patients with PA exist in the same family but without pathogenic variants in the FH-causing genes, in which the causation of PA may be different, and thus at least 1 relative could have unilateral PA. Most FH cases undergo medical therapy; in 2 cases of FH-I, unilateral adrenalectomy was performed but the clinical and biochemical outcomes were not reported.[75] In a patient with a germline *CACNA1H* pathogenic variant, unilateral adrenalectomy was performed to remove an APA where AVS demonstrated lateralized aldosterone production and resulted in a biochemical cure of PA,[24] but the causality of the germline variant is questionable. Adrenal imaging could be useful in patients with FH-III and massive bilateral adrenocortical hyperplasia associated with a severe clinical phenotype and uncontrolled BP despite therapy with multiple anti-hypertensive medications, including high doses of mineralocorticoid receptor antagonists (MRAs), where bilateral adrenalectomy may be performed.[43-45,48,76]

Usually, CT scanning of the adrenals is considered preferable over magnetic resonance imaging for higher spatial resolution.[1,8] However, because most patients with FH are investigated at a young age, magnetic resonance might be preferable, especially in females, to reduce radiation exposure.

R.1.6 We suggest that every patient with early onset hyperaldosteronism should have further testing (genetic, AVS) with consideration of family history, adrenal imaging results, prior likelihood, and age and should be discussed in a multidisciplinary team

Rationale. We suggest that in patients with early onset of PA (ie, age < 20 years), indications for further testing should be obtained after discussion in a multidisciplinary team, in which expert participants will take into account the family history, clinical and biochemical phenotype, and adrenal imaging. Since genetically determined FH is a bilateral disease, AVS should be considered only if debulking surgery with unilateral adrenalectomy is a therapeutic consideration. Due to limited experience and lack of available literature, AVS is not suggested for individuals under the age of 16 years.

Indications for genetic testing should consider the age of the patient, the phenotype, the family history, as well as the availability in the centre of candidate genes sequencing, and finally the refundability of the testing by the public health services or insurances. When genetic testing is not possible, clinicians can consider contacting international centres in which these tests are routinely performed. The clinical diagnosis of FH-I can be obtained with a dexamethasone-suppression test (although not with 100% accuracy[77,78]) or preferably with the amplification of the *CYP11B1/B2* hybrid gene by long-polymerase chain reaction[78,79] (Figure 2).

R.1.7 We recommend genetic testing for patients with early onset (age < 20 years) hyperaldosteronism

Rationale. Patients with biochemically confirmed PA and with hypertension diagnosed at age < 20 years should have genetic testing for FH-I to IV (Figure 2). The younger the patient with PA, the higher the probability of an underlying genetic condition. Familial hyperaldosteronism III is usually associated with a more florid and severe phenotype and is therefore diagnosed mainly in paediatric/adolescent patients with hypertension,[21,44,48,49] although some instances of a late diagnosis have been described.[47] Primary aldosteronism, seizures, and neurological abnormalities syndrome was diagnosed only in paediatric patients.[27] In contrast, the diagnosis of hypertension in patients with FH-I, FH-II, and FH-IV was often made in adulthood.[17,24,34,35,80] Therefore, FH cannot be excluded in a patient with a diagnosis of hypertension and PA in adulthood, given the variability in age of onset and the time of diagnosis of hypertension.

Long-polymerase chain reaction for the amplification of the hybrid *CYP11B1/CYP11B2* gene responsible for FH-I[34,79] should be performed for the diagnosis of FH-I. When not available, dexamethasone-suppression testing[77] is an acceptable alternative, but a positive result requires subsequent genetic confirmation. The test is considered positive when cortisol levels are below 4-5 ng/dL after dexamethasone administration (0.5 mg q.i.d. for 4 days).[3,77]

The clinical phenotypes of different FH forms often overlap and do not allow certain determination of the specific FH type. Therefore, in patients with PA and age < 20 years, we recommend sequencing the genes responsible for FH and PASNA syndrome, preferably using next-generation sequencing panels, plus long-range PCR for FH-I. A possible limitation to panel testing is the lack of availability in different public health systems and reimbursement by insurances.

Familial hyperaldosteronism I has some peculiar characteristics: patients display marked suppression of aldosterone concentrations under glucocorticoid administration and increased concentrations of the so-called hybrid steroids 18-hydroxycortisol and 18-oxocortisol.[15,39] Some patients with FH-III also display increased concentrations of hybrid steroids, although not at the levels observed in FH-I. However, the measurement of these steroids is not available in most countries and thus the diagnosis should be performed by sequencing the candidate genes with the exception of FH-I where long-PCR can be performed.

R.1.8 We suggest testing (un)affected family members of patients with genetically proven FH

Rationale. First-degree relatives of a genetically proven patient with FH should be clinically and biochemically tested for the diagnosis of hypertension and PA (Figure 2). Hypertension is a frequent condition with a direct relationship with age, and therefore, a diagnosis of hypertension should not be considered sufficient for the diagnosis of FH. Whenever possible, we suggest performing direct sequencing of the mutated gene in all first-degree relatives independent of the clinical and biochemical phenotype, to allow an early diagnosis and follow-up of patients with FH pathogenic variants. Aldosterone excess causes detrimental effects on cardiovascular and renal tissues,[5] which is in part independent of the effects on BP. In fact, cardiac organ damage has been observed in patients with FH with normal BP levels.[81] Therefore, the early diagnosis of FH is fundamental to treat these patients and prevent cardiovascular and cerebrovascular as well as renal events associated with exposure to aldosterone excess from the early phases of life. However, it should be noted that there is no available evidence that confirms the beneficial effects of early treatment. A case for not performing genetic testing could be made for subjects with normal BP after the age of 60 years, even though evidence is lacking.

R.1.9 We recommend electrocardiography and echocardiography in all patients with FH and documented hypertension and/or hypokalaemia

Rationale. We suggest early identification of potential cardiac damage in patients with FH, since prompt diagnosis and initiation of specific treatment may prevent the development of structural and functional changes. It should be noted that formal evidence that early detection of cardiac damage improves disease prognosis is lacking. Left ventricular hypertrophy (LVH) in patients with hypertension is the most important predictor of adverse events in patients with hypertension and its regression predicts a more favourable prognosis.[82]

A meta-analysis of observational studies showed that left ventricular mass, interventricular septal, and posterior wall thickness were significantly increased in patients with PA relative to individuals with essential hypertension. This association was independent of BP, age, and sex.[6]

Aldosterone-mediated cardiac damage also includes impaired diastolic function and subclinical systolic dysfunction.[83] It has been reported that patients with PA display subclinical myocardial dysfunction as evidenced by lower magnitude of global longitudinal strain as compared with subjects with essential hypertension.[83]

The clinical phenotypes of different FH types often overlap, and most affected individuals develop severe hypertension in early life resulting in the development of LVH and an increased risk for cerebrovascular events and other cardiovascular complications.[2,9,49]

Several studies reported different degrees of severity of hypertension in patients with FH. However, increased left ventricular wall thickness and reduced diastolic function were also described in normotensive patients with FH-I, providing evidence of the BP-independent effect of aldosterone excess.[81]

R.1.10 We suggest to perform out-of-office BP measurements in patients with FH

Rationale. An analysis of 66 studies including patients adrenalectomized for unilateral PA showed substantial deficiencies and inconsistencies in office BP measurements and that the diagnosis and follow-up of patients were based mostly on office BP measurements. This may explain why, in contrast to

excellent biochemical outcomes, clinical results in terms of improved postoperative BP control in patients with PA have been less gratifying.[84]

Therefore, appropriate measurement methodology and the use of accurate BP measuring devices are important in the assessment of patients with PA before and after the institution of specific treatment. Current guidelines, including the 2021 European Society of Hypertension (ESH) practice guidelines and 2023 ESH guidelines for the management of arterial hypertension, recommend widespread use of ambulatory and home BP measurement methods to detect uncontrolled and resistant hypertension, assess BP variability, and detect nocturnal hypertension and non-dippers.[82,85]

Since several studies have reported a wide spectrum of BP values in patients with FH, ranging from normotension to severe or resistant hypertension, standard use of out-of-office BP measurements may improve proper diagnosis of hypertension and early initiation of antihypertensive treatment, independently of early initiation of specific treatment of FH[86] and support optimal management during follow-up.

R.1.11 We suggest to measure eGFR and urine ACR in all patients with FH

Rationale. We suggest that in all patients with FH, serum creatinine, estimated glomerular filtration rate (eGFR), and albumin:creatinine ratio (ACR) should be evaluated.

Clinical studies indicate that PA is associated with kidney damage, a relationship at least partly independent of BP levels. However, early involvement of the kidney in PA is characterized by functional changes that are largely reversible by treatment.[87]

A meta-analysis of observational studies demonstrated that patients with PA compared with hypertensive individuals without PA show higher eGFR suggestive of glomerular hyperfiltration. It has been documented that this parameter was diminished by specific treatment—either unilateral adrenalectomy or medical treatment with MRA.[7] In the large multicentre, cross-sectional PAPY study, 24-h microalbuminuria was higher in patients both with unilateral and bilateral PA compared with individuals with essential hypertension.[88] A study with short-term (6 months) follow-up showed a decrease in urinary albumin excretion after adrenalectomy in patients with PA and unilateral disease.[87] A second study with long-term (6.4 years) follow-up reported that albuminuria was higher at baseline in patients with PA as compared with those with essential hypertension. The subsequent restoration of normal albumin excretion after causal treatment was independent of BP levels.[89]

Therapy in FH

R.2.1 We recommend reduction in sodium intake in all patients with FH and hypertension (good clinical practice)

Rationale. Aldosterone regulates sodium and potassium homeostasis. Activation of the mineralocorticoid receptor (MR) also causes inflammation and fibrosis of the heart, fibrosis, and remodelling of blood vessels, as well as tubulointerstitial fibrosis and glomerular injury in the kidney.[90-92] Prior to the development of fibrosis, aldosterone causes monocyte and macrophage infiltration, increased expression of inflammatory markers,[93,94,95] and generation of reactive oxygen species.[96,97] High salt intake potentiates these effects, in part by activating the Rho family member Rac1,[98,99] indicating that the Rac1 pathway may account for MR activation under conditions of high salt intake. Furthermore, 24-h urinary Na^+ excretion correlates with LV mass and with degree of proteinuria in patients with PA.[100,101] Patients with untreated PA consume on average more dietary salt than patients with essential hypertension or normotensive subjects. Specific treatment (adrenalectomy in unilateral PA and MRA therapy in bilateral PA) is associated with a reduction in salt consumption. An explanation could be impaired salt-tasting sensitivity due to aldosterone excess and improvement of the salt sensitivity threshold following treatment.[102,103] A moderate dietary salt restriction improved BP levels in patients with PA.[104]

Therefore, reduction in sodium intake (to <2.3 gr of sodium/day ~5.8 gr of salt) is strongly recommended in the management of patients with FH and hypertension.[64,96-99] The World Hypertension League, Resolve to Save Lives, and International Society of Hypertension are committed to support reductions in dietary sodium as a high priority and have recently developed consensus guidelines recommending reductions in dietary sodium.[105]

R.2.2 We recommend aiming for normalization of BP and of the ARR and potassium in the treatment of FH (+OOO)

Rationale. The treatment objectives in patients with FH include the resolution of hypokalaemia and the prevention of morbidity and mortality associated with hypertension.[106,107] The cause of FH dictates the optimal treatment option. It is essential for clinicians to understand that normalization of BP is not the only goal. In the presence of sodium, excessive autonomous secretion of aldosterone is associated with an increased risk of cardiovascular disease and morbidity.[106,107] This recommendation places a relatively higher value on reduction of BP and normalization of serum potassium concentrations and ARR with consequent abrogation of the vascular, cardiac, and renal effects of aldosterone with the minimum number of pharmacological agents.[106,107] It should be emphasized that studies investigating the optimal BP target are lacking in FH.

R.2.3 We recommend dexamethasone in FH-I and MRA as first-line treatment for patients with FH-II to IV and PASNA syndrome (+OOO)

Rationale. Outcomes of long-term treatment and side effects in FH-I have been seldom reported.[108] Studies comparing different drugs do not exist (see also section review Appendix). Familial hyperaldosteronism I should be treated medically with a glucocorticoid to partially suppress pituitary ACTH secretion (Figure 2). In patients with FH-I, the use of low-dose glucocorticoid treatment is recommended as first-line therapy rather than an MRA, which is the first alternative in patients who do not tolerate glucocorticoids and in children (<16 years). We recommend the use of a synthetic glucocorticoid that is longer acting than hydrocortisone, such as dexamethasone or prednisone, with most publications using dexamethasone (0.125-2.0 mg daily). Renin and aldosterone concentrations may be helpful in assessing the effectiveness of treatment and in the prevention of overtreatment.[1,107,109] Overtreatment with exogenous steroids should be avoided; iatrogenic Cushing syndrome and impaired linear growth in children have resulted from such overdosing. In general, the lowest possible dose of glucocorticoid that normalizes BP and/or serum potassium concentration should be used.[109]

Treatment with a glucocorticoid may not always normalize BP, and the addition of an MR antagonist should be considered in these cases. The use of eplerenone may be preferred in the case of affected children, in whom there may be concerns with respect to growth retardation and anti-androgenic effects of glucocorticoids and spironolactone, respectively.

In FH-III, some patients were well controlled with spironolactone only. MRAs appear to be effective at controlling BP and provide BP-independent target organ protection in patients with PA (Figure 2). For more than 5 decades, spironolactone has been the agent of choice in the medical treatment of PA. Several observational studies in patients with bilateral PA have reported a mean reduction in systolic BP of 25% and diastolic BP of 22% in response to spironolactone 50-400 mg/d for 1-96 months.[1,107] The incidence of gynecomastia with spironolactone therapy is dose related, at 12.5-50 mg daily, the incidence is 10%-15% while at doses of >100-150 mg daily exceeds 50%,[3] while the exact incidence of menstrual disturbances in premenopausal women with spironolactone therapy is unknown. A small dose of a thiazide diuretic, triamterene, or amiloride can be added to attempt to avoid a higher dose of spironolactone, which may cause side effects. The starting dose for spironolactone should be 12.5-25 mg daily in a single dose. The lowest effective dose should be determined by gradually titrating upward if necessary to a maximum dose of 100 mg/day.

Eplerenone is a newer, selective MRA without antiandrogen and progesterone-agonist effects[110] and is thus less likely than spironolactone to cause adverse endocrine side effects. Eplerenone has 60% of the MR antagonist potency of spironolactone. Its superiority tolerability profile needs to be balanced against its higher cost and lower efficacy. Reflecting its shorter half-life, eplerenone should be given twice daily for optimal effect. The starting dose for eplerenone is 25 mg twice daily and can be uptitrated to a maximum dose of 100 mg twice daily. In patients with stage III chronic kidney disease (ie, glomerular filtration rate <60 mL/min*1.73 m^2), spironolactone and eplerenone should be used with caution because of the risk of hyperkalaemia and should be avoided in those with stage IV disease or higher.

Esaxerenone, a new non-steroidal MRA, and aldosterone synthase inhibitors may be other options for treatment in the future;[111-113] other MRAs (finerenone, apararenone, and ocedurenone) have not been tested in patients with PA).

R.2.4 In FH-I, we suggest adding very low doses of dexamethasone in children in cases where the ARR or potassium concentrations are not completely normalized with MRA (+OOO)

Rationale. In patients with FH-I, treatment with glucocorticoids suppresses hybrid gene expression, which results in the amelioration of hyperaldosteronism and hypertension.[106] Dexamethasone doses in the order of 0.5-2.0 mg daily are recommended for the treatment of hypertension due to FH-I.[106,114-116] Previously, it has been reported that long-term treatment with dexamethasone in doses as low as 0.5 and 0.75 mg daily is sufficient in some patients to cause marked, continuous suppression of ACTH.[117] It was shown that in patients with genetically proven FH-I, glucocorticoid doses of 0.125-0.25 mg dexamethasone daily or 2.5-5 mg prednisolone daily were sufficient to maintain normal BP throughout 0.5-3.8 year of follow-up without the need for additional antihypertensive medication. Adequacy of hypertension control was supported by the demonstration of normal and stable (or falling) left ventricular mass index values on echocardiography.[106] We recommend using the lowest possible dose of dexamethasone to reduce long-term undesirable effects. Careful monitoring should be dedicated to the detection of any adverse effects to prompt reduction/withdrawal of glucocorticoids and substitution with an MRA.

R.2.5 We suggest that amiloride be considered in patients with FH in cases where the ARR or potassium concentrations are not completely normalized with MRA and/or low dose glucocorticoids (in FH-I) (+OOO)

Rationale. Amiloride antagonizes the aldosterone effects by blocking the renal sodium channel ENaC. Being a potassium-sparing diuretic, amiloride can ameliorate both hypertension and hypokalaemia in patients with PA and is generally well tolerated. It lacks the sex steroid-related side effects of spironolactone but does not provide the beneficial effects on endothelial function.[1,118,119] For more than 5 decades, the MRA spironolactone has been the agent of choice in the medical treatment of PA. However, a small dose of a thiazide diuretic (with control of potassium concentrations to avoid hypokalaemia) or amiloride can be added to avoid a higher dose of spironolactone, which may cause side effects.[1]

Amiloride should be considered as a second-line treatment in FH-II, FH-III, and FH-IV.[120,121] Mussa et al.[122] described a patient with FH-III due to the G151E KCNJ5 pathogenic variant (c.452G>A) successfully treated with canrenone and amiloride, resulting in prompt normalization of electrolytes and complete normalization of BP. When BP is not optimally controlled by MRAs and/or amiloride or these drugs are not tolerated, calcium channel blockers should be considered.[3]

R.2.6 In female FH patients contemplating pregnancy, we recommend normalization of BP levels before pregnancy and strict follow-up of potassium and BP levels during pregnancy

Rationale. Currently, no formal recommendations for the therapeutic management of pregnant women with PA have been proposed due to a lack of evidence.[123] The key point of management is to achieve BP control, in order to prevent hypertension-associated maternal and foetal morbidity and mortality, and to correct hypokalaemia. Women with treated FH-I should withdraw dexamethasone that crosses the placenta and carefully monitor BP values and serum K^+ concentrations during the first trimester.[124] If BP becomes uncontrolled, methyldopa, long-acting nifedipine, and labetalol are treatments of choice for non-PA pregnancies.[125] If BP rises during the second and/or the third trimester, low to very low dose dexamethasone can be used with the aim of normalizing BP, aldosterone, renin, and serum K^+ concentrations.[124] Women with FH-I do not seem to have a large increased risk of preeclampsia during pregnancy, while women with FH-I and chronic hypertension might be at an increased risk for an exacerbation of their hypertension during pregnancy.[126]

Treatment with MRAs and potentially teratogenic antihypertensive drugs should be stopped 4-6 weeks before conception, and treatment with first-line medications (such as α-methyldopa, labetalol, and nifedipine) should be started. In a patient with PA and severe hypertension and hypokalaemia seeking pregnancy, a switch from spironolactone to

eplerenone at the lowest effective dose could be considered, since eplerenone has been reported not to be associated with adverse outcomes.[123] When PA is diagnosed during pregnancy, standard anti-hypertensive therapy with first-line drugs should be commenced, postponing confirmation testing and subtype diagnosis until after delivery. In cases of poor BP control and/or refractory hypokalaemia, eplerenone or amiloride might be considered, while spironolactone should be avoided, especially in the first trimester, because of its anti-androgenic side effects.[123]

R.2.7 We recommend not to perform surgery in FH since it is a bilateral disease and only consider it in FH-III when BP is not normalized after optimal therapy

Rationale. Other than in patients with FH-I, medical treatment of FH does not significantly differ from non-heritable forms of PA.[127] In families and patients with FH-III, several studies have shown that different germline *KCNJ5* pathogenic variants result in phenotypic variability, ranging from spironolactone-responsive hyperaldosteronism to massive adrenal hyperplasia with drug-resistant hypertension.[128,129] This variability is attributed to the type of *KCNJ5* pathogenic variant, with a severe phenotype associated with pathogenic variants: p.Gly151Arg,[48] p.Thr158Ala,[21,43] p.Ile157Ser,[45] and p.Tyr152Cys.[47] Broadly, the majority of reported cases of FH-III have been resistant to aggressive antihypertensive therapy including aldosterone receptor blockade and amiloride, thus ultimately requiring bilateral adrenalectomy to control BP. Removed adrenal glands have demonstrated massive bilateral hyperplasia of the adrenal cortex.[21,45,48] In contrast, patients with the p.Gly151Glu pathogenic variant show aldosteronism early in life, but this can be treated successfully with MRA.[48,49]

Recommendations: follow-up of patients with FH

R.3.1 We recommend clinical and biochemical follow-up every 3-6 months

Rationale. Patients with FH should be followed up regularly, preferably at 3-6 monthly intervals, with detailed clinical and biochemical evaluation to determine effective management following the introduction of treatment. Follow-up management should be undertaken by an experienced multidisciplinary team. Blood pressure should be normalized and plasma aldosterone and renin activity levels should be measured as an indication of biochemical response.[1] With increasing age, depending on the clinical phenotype and BP control, follow-up timing can be less strict.

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Supplementary material

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Authors' contributions

Paolo Mulatero (Conceptualization [lead], Data curation [lead], Methodology [equal], Project administration [lead], Supervision [lead], Writing—original draft [lead], Writing—review & editing [lead]), Ute Scholl (Data curation [equal], Writing—original draft [equal], Writing—review & editing [equal]), Carlos Fardella (Data curation [equal], Writing—original draft [equal], Writing—review & editing [equal]), Evangelia Charmandari (Data curation [equal], Writing—original draft [equal], Writing—review & editing [equal]), Andrzej Januszewicz (Data curation [equal], Writing—original draft [equal], Writing—review & editing [equal]), Martin Reincke (Data curation [equal], Writing—original draft [equal], Writing—review & editing [equal]), Celso Gomez-Sanchez (Data curation [equal], Writing—original draft [equal], Writing—review & editing [equal]), Michael Stowasser (Data curation [equal], Writing—original draft [equal], Writing—review & editing [equal]), and Olaf Dekkers (Conceptualization [lead], Data curation [lead], Methodology [lead], Project administration [lead], Supervision [lead], Writing—original draft [lead], Writing—review & editing [lead])

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