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Angaben zur Veröffentlichung / Publication details:

Antonini, Sonir R., Verena Wiegering, Mariana P. Halah, Luís Eduardo Cruvinel Pinto, Navoda Attapatu, Katja Dumic Kubat, Jorge Elias, et al. 2026. "Diagnostic work-up in paediatric adrenocortical tumours: an international consensus." *European Journal of Endocrinology* 195 (1): R1–22. https://doi.org/10.1093/ejendo/lvag086.

European Journal of Endocrinology, 2026, 195, R1–R22
https://doi.org/10.1093/ejendo/lvag086
Published: 7 July 2026
Unsolicited review

Diagnostic work-up in paediatric adrenocortical tumours: an international consensus

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Received: December 2, 2025. **Revised:** March 20, 2026. **Accepted:** May 11, 2026

Abstract

Objective **Paediatric adrenocortical tumours (pACTs) are rare but potentially life-threatening neoplasms, most of which are hormonally active and frequently present with androgen excess. Although a comprehensive evaluation is recommended, no consensus exists on the optimal diagnostic work-up. The goal of this document is to provide evidence-based recommendations to standardize the diagnostic evaluation of children with suspected pACTs.**

Methods **We applied a modified three-step Delphi process with an international panel of pACT experts to develop consensus on the initial diagnostic work-up. Following a literature review, the steering committee formulated statements, which were distributed electronically to 28 experts from Europe, the Americas, and Asia. Agreement was rated on a six-point Likert scale; ≥70% agreement was defined as consensus. Between rounds, results and feedback were reviewed within the ENS@T-KIDS group. In round one, 33 statements achieved consensus; 12 were revised and re-voted in round 2, with 7 reaching consensus. Five statements were further modified and one reached consensus in round three.**

Results **Response rates were 86% ($n = 24$) in round 1, 82% ($n = 23$) in round 2, and 86% ($n = 24$) in round 3. Forty-one statements received consensus covering 4 domains: (I) General Aspects and Clinical Assessment (17), (II) Endocrine Work-up (15), (III) Imaging (4), and (IV) Genetics (6).**

Conclusion **The diagnostic evaluation of pACTs varies widely between centres and countries, influenced by resources and local expertise. This work delivers the first expert-derived, international consensus statements outlining a practical and standardized diagnostic pathway to support timely and consistent evaluation of children with suspected pACTs.**

Keywords adrenal cortex neoplasms, adrenocortical carcinoma, child, guideline, consensus

Introduction

Paediatric Adrenocortical Tumours (pACTs) are neoplasms that originate from the adrenal cortex. The incidence of pACTs is about 0.2-0.3 cases per million children per year in most countries, with a 15-fold higher incidence in Southern Brazil due to a *TP53* founder pathogenic variant.[1-4] Most pACTs are hormonally active and may excessively produce all 3 classes of steroid hormones physiologically made by the adrenal cortex. Data on long-term outcomes suggest that pACTs that solely produce excess androgens are associated with better long-term survival than tumours that concomitantly produce excess cortisol or are hormonally inactive.[5-7]

In the past, when pACTs were less well understood, most institutions relied on the experience from adult ACTs to establish management. Today, it is well recognized that pACTs differ significantly from adult ACTs in their clinical presentation, biochemical profile, genetics, and prognosis.[8,9] These differences impact clinical practice, leading many institutions to adopt distinct investigations and treatment strategies for paediatric and adult patients. However, some aspects concerning the investigation of these patients remain unclear. Due to the limited number of pACT studies worldwide, these uncertainties fall into 2 categories: (1) characteristics that inherently differ between paediatric and adult ACTs and (2) characteristics that may also exist in pACTs but remain unidentified due to insufficient or inconsistent research findings.

These differences should be considered when applying recommendations from adult studies to the paediatric population and when interpreting associations found in adult-focused research. Apart from the differences stated above, adult and paediatric tumours may have distinct cellular origins,[10] potentially representing an entirely different disease. When a characteristic is consistently observed in adult cohorts but repeatedly absent in paediatric ones, recommendations should differ accordingly between these populations. However, if a characteristic is documented in adult ACT but remains unreported in paediatric cases due to insufficient data, a cautious approach is warranted. In such cases, it is reasonable to follow adult guidelines until more paediatric-specific evidence becomes available.

Although experts recommend a thorough endocrine work-up, there is no consensus on how this work-up should be performed. In addition, there is little guidance on the exact imaging modalities needed to characterize the tumour and potential metastases,[11] nor is there any consensus on genetic investigation. Therefore, the present work aimed to seek international consensus on the initial endocrine and diagnostic work-up in children and young people with pACTs. In the present work, both benign and malignant paediatric adrenocortical tumours are referred to as pACTs. Other adrenal diseases, including primary pigmented micronodular adrenal hyperplasia (PPNAD), primary bilateral macronodular adrenal hyperplasia (PBMAH), aldosteronomas, and pheochromocytoma, are beyond the scope of this consensus.

Methods

This work was conducted within the KIDS working group of the European Network for the Study of Adrenal Tumours (ENS@T; https://ensat.org). A modified three-step Delphi[12] consensus method (estimate-talk-estimate systematic structured communication) (Figure 1) was conducted between January 2024 and March 2025 to develop and finalize statements by an international group of pACT experts (the Delphi panel).

Participants and characteristics

The Delphi panel consisted of 28 participants from 3 continents (Europe, the Americas, and Asia). Experts were identified by their long-standing activity in the field of pACT management, membership in the ENS@T KIDS working group, and/or the International Consortium of Paediatric Adrenocortical Tumours (ICPACT). Participants' main roles as self-identified were as paediatric endocrinologists ($n = 13$), paediatric oncologists

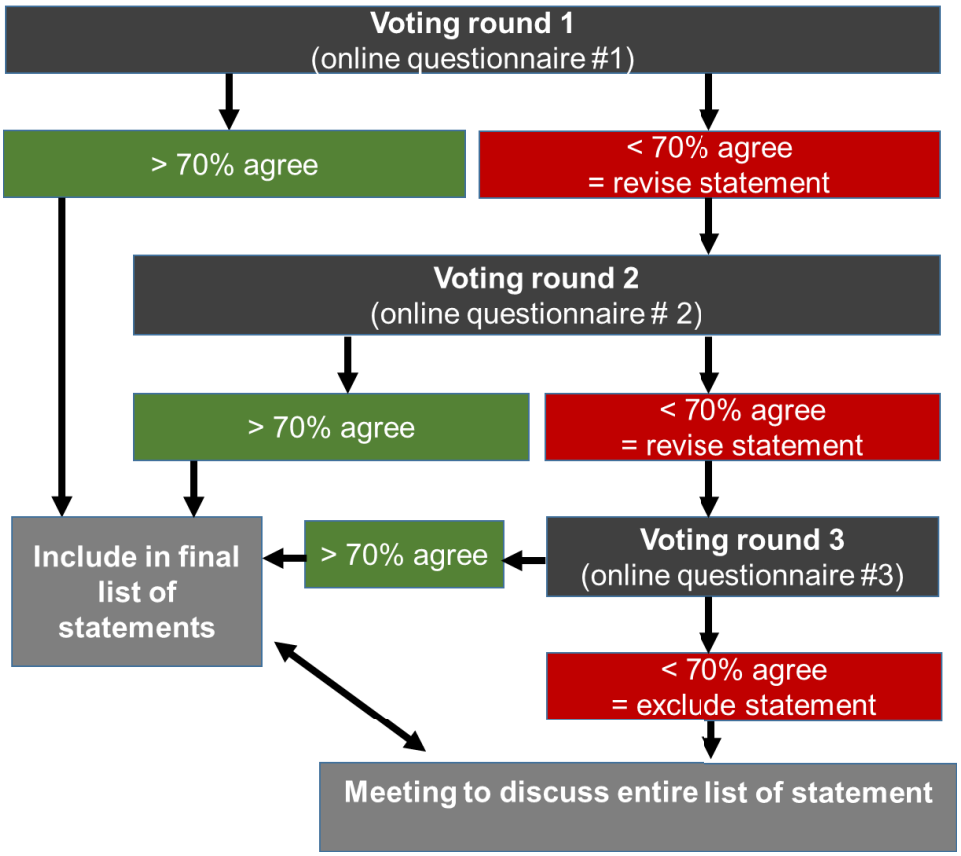

Figure 1 Delphi voting process: results from rounds 1, 2, and 3.

($n = 6$), radiologists experienced in paediatric adrenal imaging ($n = 3$), adult endocrinologists ($n = 2$), adult oncologists ($n = 1$), steroid biochemists ($n = 1$), basic researchers ($n = 1$), and expert clinicians in rare endocrine tumours ($n = 1$). Most panellists (96%) manage children and young people with pACTs clinically. Sixty-one percent reported having managed between 5 and 10 patients with pACTs over the last 5 years, and 22% managed 11 or more patients during this period. Most of the experts (83%) conduct clinical research, while 43% conduct basic or translational research in the field of pACTs. Participation was voluntary without financial incentive.

Consensus formation

All members of the panel and the steering committee took part in the voting rounds of the Delphi process. Electronic surveys were created by the steering committee (S.R.A., J.I., and V.W.) and circulated to the Delphi panel. The level of agreement and disagreement was rated on a six-point Likert response scale (1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree; 6, not competent to answer) with the opportunity to give written feedback. After each round, conflicting results were discussed in online meetings of the ENS@T-KIDS group, and questions were redefined if no consensus was reached (Figure 1). Consensus was defined *a priori* as agreement by at least 70% of the participants (Likert scale 1 and 2), or disagreement (Likert scale 4 and 5).[7,12]

Questionnaire

A literature review on the initial work-up in pACT was conducted before the survey (J.I. and S.R.A.), which was provided and discussed during online meetings by the ENS@T KIDS working group. The steering group (J.I., V.W., and S.R.A.) then developed, reviewed, and approved the survey statements. Statements were divided into 3 sections: (1) General Aspects and Clinical Assessment, (2) Endocrine Work-up, (3) Imaging/Radiology, and (4) Genetics. The statements were distributed to the Delphi panel via the online survey platform Online Surveys (JISC). Participants were asked to complete the survey within 28 days and encouraged to provide free-text comments to facilitate further discussions. After participants completed the survey, statements were reviewed (J.I. and S.R.A.) and discussed at a subsequent online meeting of the ENS@T Kids group. Adjustments to statements that did not reach consensus were made based on those discussions and entered the second round of the Delphi process. Of the statements from the first round, 8 statements did not reach consensus (<70%), were revised, and entered the second round. After voting in round 2, one statement did not reach a consensus (<70%) and was modified for entry into the third round when it achieved consensus. In the end, 35 statements reached consensus and are summarized below.

Ethical approval by an independent committee was deemed unnecessary, as there was no direct patient involvement in this process. However, our approach strictly adheres to the tenets outlined in the Declaration of Helsinki.

Table 1 General aspects and clinical assessment in paediatric adrenocortical tumours.

Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Absent
1. All patients should be managed in centres experienced in the management of pACT	**83**	**17**	—	—	—	
2. All children with precocious pubarche should be investigated for pACT	**48**	**35**	9	4	—	4
3. All children and female adolescents with signs of virilization should be investigated for pACT	**70**	**22**	4	—	—	4
4. All children and adolescents with signs of Cushing's syndrome should be investigated for pACT	**61**	**30**	4	—	—	4
5. All children and adolescents with high blood pressure/arterial hypertension should be investigated for pACT	**35**	**43**	9	9	—	4
6. A complete family pedigree, with at least a three-generation history of neoplasms is mandatory in patients with suspected pACT	**57**	**26**	4	4	—	9
7. The duration of the clinical symptoms should be documented in patients with suspected pACT	**78**	**22**	—	—	—	—
8. Tanner pubertal staging is mandatory in all patients with suspected pACT	**70**	**26**	—	—	—	4
9. Weight, height, and BMI should be obtained in all patients with suspected pACT	**87**	**13**	—	—	—	—
10. Weight, height, and BMI trajectories should be obtained in all patients with suspected pACT	**74**	**22**	—	—	—	4
11. The parental target height should be obtained in all patients with suspected pACT	**48**	**43**	4	—	—	4
12. Blood pressure measurement is mandatory in all patients with suspected pACT	**87**	**13**	—	—	—	—
13. Random blood pressure measurements should be done on several occasions and interpreted based on age-, sex- and height-specific reference range	**43**	**39**	9	—	—	4
14. An assessment of cardiac function is indicated only in patients with pACT and elevated blood pressure and/or other cardiovascular risk factors*	**32**	**41**	5	5	9	9
15. An assessment of cardiac function is indicated in patients undergoing chemotherapy, including mitotane treatment*	**61**	**17**	4	—	—	17
16. An ophthalmology assessment, including fundoscopy, is only indicated in patients with pACT and elevated blood pressure*	**30**	**43**	4	9	4	9

List of statements with consensus (≥70% agreement) and the participants' rating results for each statement (in per cent) according to a 5-point Likert Scale (1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree). Participants could also abstain from answering a question if they felt unqualified. (*) These statements were revised and reached consensus in the second round of the Delphi process. All numbers are presented as proportions (%). pACT, paediatric adrenocortical tumour. Bold values represent agreement with the respective statement.

Results and discussion

Tables 1-4 present the recommendations that reached consensus among the Delphi panel. Table 5 provides a summary of the recommended diagnostic work-up in patients with pACT of this international consensus. Each statement is presented and discussed in detail below.

Statements

General aspects and clinical assessment

1. All patients should be managed in centres experienced in the management of pACTs (agreement: 100%)

Comment on statement 1: Given the rarity of this disease, expertise in managing pACTs is limited in most centres. Exceptions occur in settings where care is centralized into high-volume specialist units, or in high-incidence regions such as Brazil, where extensive cumulative experience has facilitated the creation of key diagnostic and treatment protocols. Currently, there is no published data comparing the outcomes of high-volume centres with those of low-volume centres; however, achieving complete surgical resection without capsule rupture has been associated with significantly improved survival rates.[9,13] Centres performing more than 6-7 adrenalectomies annually tend to have shorter hospital stays and a lower incidence of complications.[14] Although specific data regarding paediatric cases are limited, we expect a finding similar to that observed in adults.

Table 2 Endocrine work-up in paediatric adrenocortical tumours.

Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Absent
1. An endocrine work-up is mandatory in children or adolescents presenting clinical signs of pACT	**96**	**4**	—	—	—	—
2. Mass-spectrometry-based assays for the measurement of all steroid hormones should be used	**27**	**43**	4	4	—	22
3. Urinary steroid profiling (gas chromatography—mass spectrometry [GC–MS]) should be used in the work-up of pACTs	**30**	**40**	17	4	—	4
4. Laboratory screening for cell decay parameters (LDH, uric acid), baseline coagulation, and full blood count, including differential blood count, should be performed on all patients diagnosed with pACT	**30**	**43**	17	—	—	9
5. First line assessment of sex steroid hormone excess should include early-morning level of plasma dehydroepiandrosterone sulphate (DHEA-S), androstenedione, 17-OH-progesterone, and testosterone	**68**	**14**	5	—	—	14
6. First-line assessment of sex steroid hormone excess should include an early-morning level of plasma oestradiol in screening patients with suspected pACTs	**30**	**43**	4	9	—	13
7. A prolonged (3-day) oral dexamethasone test to explore autonomous production of androgens is not routinely recommended*	**68**	**14**	—	—	—	18
8. All patients with suspected pACT should be biochemically assessed for cortisol excess, irrespective of clinical signs of hypercortisolism*	**70**	**22**	—	—	—	9
9. If available, 3 consecutive collections of 24 h urine for free urinary cortisol should be obtained*	**26**	**48**	4	9	9	4
10. An early morning sample of plasma cortisol and ACTH should be obtained	**57**	**26**	—	—	4	13
11. A midnight cortisol level (saliva or plasma) should be obtained	**30**	**44**	9	4	4	9
12. An overnight dexamethasone suppression test should be performed	**35**	**35**	4	9	—	17
13. Sodium, potassium, aldosterone, and renin (concentration/activity) should be measured in all patients with suspected or confirmed pACT, regardless of the presence of hypertension	**35**	**38**	9	9	—	9
14. 11-deoxycorticosterone should be measured in patients with suspected or confirmed pACT	**31**	**39**	4	9	—	17
15. The possibility of a phaeochromocytoma should be excluded in the presence of an adrenal mass*	**57**	**30**	9	4	—	—

List of statements with consensus (≥70% agreement) and the participants' rating results for each statement (in percent) according to a 5-point Likert Scale (1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree). Participants could also abstain from answering a question if they felt unqualified. (*) These statements were revised and reached consensus in the second round of the Delphi process. All numbers are presented as proportions (%). pACT, paediatric adrenocortical tumour. Bold values represent agreement with the respective statement.

Although urgent treatment is recommended, time spent in pursuing appropriate diagnostic procedures and referral to an experienced centre is likely warranted, for more favourable outcomes and prognosis. We believe it is mandatory that patients receive care in centres with experience in managing pACT in high-incidence settings, and in low-incidence settings, patients should be referred to the nearest experienced high-volume centre, whenever feasible. A multidisciplinary team should be available, consisting minimally of a paediatric endocrinologist, paediatric oncologist, paediatric surgeon, pathologist, radiologist, and clinical geneticist, ideally all of whom have experience in the management of pACT. If sufficient expertise is lacking in the paediatric centre, it is advisable to seek guidance from adult adrenal experts.

2. All children with precocious pubarche should be investigated for pACT (agreement: 83%)

3. All children and female adolescents with signs of virilization should be investigated for pACT (agreement: 92%)

Table 3 Radiological work-up in paediatric adrenocortical tumours

Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Absent
1. All patients with suspected pACT who have not completed puberty should have a bone age assessment	**64**	**27**	—	—	—	9
2. In the screening of a patient with suspected pACT imaging studies should be done in parallel to the endocrine/hormonal work-up	**50**	**32**	9	9	—	
3. As the initial imaging investigation of a patient with suspected pact, an abdominal ultrasound should be performed	**55**	**18**	18	5	5	—
4. In a patient with suspected pACT, a contrast-enhanced MRI should be performed	**27**	**46**	4	18	—	5

List of statements with consensus (≥70% agreement) and the participants' rating results for each statement (in per cent) according to a 5-point Likert Scale (1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree). Participants could also abstain from answering a question if they felt unqualified. (*) These statements were revised and reached consensus in the second round of the Delphi process. All numbers are presented as proportions (%). pACT, paediatric adrenocortical tumour. Bold values represent agreement with the respective statement.

Table 4 Genetic work-up in paediatric adrenocortical tumoursdirectly

Statement	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Absent
1. All patients with pACT should undergo genetic testing	**65**	**26**	4	—	—	4
2. *TP53* screening and Li–Fraumeni syndrome prospective screening should be offered for all patients with confirmed pACT	**65**	**26**	4	—	—	4
3. Lynch syndrome should be ruled out in all patients with confirmed pACT	**23**	**51**	9	4	—	13
4. A targeted or whole-exome sequencing panel to assess germline disease-causing variants should be performed in all patients with pACT	**35**	**35**	13	4	—	13
5. Whole-exome sequencing (WES) to assess somatic variants should be performed from a pACT tumour sample	**35**	**35**	13	—	—	17
6. All patients with confirmed pACT should receive genetic counselling	**57**	**17**	9	13	—	4

List of statements with consensus (≥70% agreement) and the participants' rating results for each statement (in per cent) according to a 5-point Likert Scale (1, strongly agree; 2, agree; 3, neutral; 4, disagree; 5, strongly disagree). Participants could also abstain from answering a question if they felt unqualified. (*) These statements were revised and reached consensus in the second round of the Delphi process. All numbers are presented as proportions (%). pACT, paediatric adrenocortical tumour. Bold values represent agreement with the respective statement.

Comments on statements 2 and 3: Although paediatric adrenocortical tumours are the least frequent cause of premature pubarche in European countries,[15] it is not a rare cause in regions with a high incidence of pACT.[9] Regardless of the regional incidence, the aggressive nature of pACTs warrants further investigation in any child or young person presenting with clinical features of hyperandrogenism.

Although most cases of pACT occur in children younger than 5 years,[9,16] Brazilian cohorts consistently report a small number of cases diagnosed in girls with signs of virilization after puberty onset.[17,18] This fraction of teenagers is even higher in non-Brazilian cohorts, reaching 42% in recent European cohorts.[19] Signs and symptoms of virilization reported in children and adolescents diagnosed with pACT include acne, voice deepening, facial hair, hirsutism, increased growth velocity, and hypertrophy of the clitoris or growth of the penis.[20] In low pACT incidence areas, the frequency of pACT as a cause of virilization is remarkably low. However, the diagnosis in adolescents is especially urgent given the aggressiveness of the disease in this age group.[9,21] Currently, no published data exist on the proportion of female virilization attributable to pACT. In male adolescents, virilization is a normal feature of puberty, which makes timely diagnosis more challenging. In this group, suspicion of pACT usually arises from additional clinical manifestations such as Cushing syndrome, abdominal pain, abdominal masses, hypertension, or gynecomastia. In contrast, every female child or adolescent presenting with signs of hyperandrogenism must be investigated for possible pACT.

4. All children and adolescents with signs of Cushing syndrome should be investigated for pACT (agreement: 91%)

Table 5 Summary of the recommended diagnostic work-up for pACT.

Category	Procedures
Laboratory	
Sex steroids	**Mandatory**
	DHEA-S, androstenedione, 17-OH-progesterone, testosterone
	Oestradiol
	Supplementary (if available)
	Urinary steroid profiling (GC-MS)
Glucocorticoids	**Mandatory**
	Morning cortisol + ACTH
	At least 2:
	1. Late-night cortisol (saliva/serum)
	2. Overnight DST
	3. 24-hour UFC (2 subsequent collections)
Mineralocorticoids	**Mandatory**
	Aldosterone, renin/PRA, Na, K,
	Consider
	11-deoxycorticosterone, 11-deoxycortisol
General	Full blood count, coagulation screen, cell decay parameters (LDH, Uric acid)
Imaging	
Ultrasound	Should be used as an initial screening tool
MRI	Preferred diagnostic method for suspected pACT
CT	**Abdomen:** May be used if MRI is not readily available
	Thorax: Indicated for staging and metastasis screening
Others	Bone age assessment
	18F-Fluorodeoxyglucose (FDG) positron emission tomography CT
Genetics	Germline and somatic *TP53* sequencing
	Targeted or whole exome sequencing

ACTH, adrenocorticotropic hormone; CT, computed tomography; DHEA-S, dehydroepiandrosterone sulphate; DST, dexamethasone suppression test; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PRA, plasma renin activity; UFC, urinary free cortisol; .

Comment on statement 4: pACT-derived hypercortisolism leading to Cushing syndrome is the second most frequent mode of presentation in teenagers and the most common cause of Cushing syndrome in pre-pubertal children, often with concomitant hyperandrogenism.[9,22-24] In older children and adolescents, other causes of Cushing syndrome are more frequent, especially ACTH-dependent hypercortisolism. Nevertheless, in children of all ages, despite its rarity in low-incidence regions, adrenocortical tumours accounted for a significant portion of Cushing syndrome diagnoses in a recent report, namely 9.72% of all adrenal-associated causes, and 2% overall.[25]

One of the most relevant clinical signs in children with hypercortisolism is poor height gain. However, patients with pACT-derived hypercortisolism typically present with increased growth velocity driven by excess androgens, regardless of cortisol excess.[22,26]

We recommend investigation for pACT in all children and adolescents with signs of Cushing syndrome with or without signs of androgen excess. Investigations must include the work-up to differentiate between ACTH-dependent and -independent hypercortisolism and done in parallel to investigations for pACT.

5. All children and adolescents with high blood pressure/arterial hypertension should be investigated for pACT (agreement: 78%)

Comment on statement 5: Despite the rise of primary hypertension in children and adolescents, the evaluation for secondary and endocrine causes is advised, in particular in younger and lean children.[27,28] This includes renovascular causes as the most common, followed by cardiac diseases and endocrine causes of hypertension, which account for up to 6%.[27] The prevalence of endocrine hypertension in children is most likely underrated, considering reports on the prevalence of familial hyperaldosteronism.[29,30] Nevertheless, pACT is one of the possible diagnoses in children with unexplained hypertension. There are no published data concerning the proportion of childhood hypertension attributable to pACT. However, data on the frequency of pACT presenting with high blood pressure are available, and most cohorts report hypertension rates between 20% and 56% at diagnosis.[5,17,21,31]

In contrast to aldosterone excess due to hereditary diseases, mineralocorticoid-producing pACTs are particularly rare in childhood, so hypertension is mostly attributed to glucocorticoid excess. Hypertension has also been reported in non-functional tumours, and in these cases, vascular compression is the most plausible explanation.[9,17]

This group reached consensus on the need to investigate for a pACT in all children and adolescents with arterial hypertension.

6. A complete family pedigree, with at least a three-generation history of neoplasm, is mandatory in patients with suspected pACT (agreement: 83%)

Comment on statement 6: 50%-80% of childhood pACTs are linked to one or more genetic predisposition variants, which is even higher in Brazil as a high-incidence region, reaching more than 90%.[1,6] The most common conditions include Li–Fraumeni syndrome (*TP53 variants,* by far the most prevalent; OMIM#151623), Beckwith–Wiedemann syndrome (11p15 abnormalities; OMIM#130650), Carney complex (*PRKAR1A variants;* OMIM#160980*)*, multiple endocrine neoplasia type 1 (*MEN1 variants;* OMIM#131100), McCune-Albright syndrome (somatic activating *GNAS* variant, OMIM#174800) and Lynch syndrome (hereditary nonpolyposis colorectal cancer; pathogenic variants in mismatch repair genes, OMIM#120435).[9] In high-incidence settings, most cases of pACT are linked to the presence of the germline *TP53* p.R337H pathogenic variant, and these carriers exhibit a behaviour significantly different from those with other hotspot *TP53* variants[32]; however, it is debated whether these patients should be categorized as Li-Fraumeni, given their different natural clinical course.[4,33] Carriers of the *TP53* p.R337H variant were initially thought to have sporadic pACT,[4,34] but studies

over the last 2 decades have suggested otherwise.[4] Furthermore, the role of other germline genetic variants like those in *BRCA2* or *CHEK2* still need to be fully established, as well as the role of variants associated with a worse prognosis in *TP53* p.R337H carriers, such as *XAF1* variants.[35,36] Nevertheless, patients with pACT and their families are at increased risk of developing other tumour subtypes. We therefore recommend that clinicians perform a complete pedigree for every patient with pACT, and provide genetic testing, counselling, and follow-up for families.

7. The duration of the clinical symptoms should be documented in patients with suspected pACT (agreement: 100%)

Comment on statement 7: Clinical manifestations of pACT are usually due to hormone excess and less often to mass effect.[9] A minority present at birth with signs such as abdominal mass or virilization, but most develop symptoms within the first 4 years of life.[9,19,20,31,37-42] Mineralocorticoid secretion is rare.[9,19,20,37-39,41,43] Median symptom duration before diagnosis is typically 4-8 months,[19,20,31,39,44] but it can be shorter,[19,45] but also symptoms up to 5 years until a diagnosis was established are reported.[46]

Prolonged hormone excess can cause severe virilization, growth disturbances (variable degrees of growth acceleration [tall stature] with reduced adult height [short stature]), emotional instability, Cushingoid features, hypertension, stroke, or peripheral and central precocious puberty (CPP).[37,47,48] Diagnostic delays >6 months have been associated with larger tumours, which may relate to poorer prognosis, though size alone does not predict malignancy.[20] Tumour size, however, correlates with disease-free survival,[20] and adenomas may have longer symptom duration than carcinomas.[43] CPP does not appear to be linked to symptom duration.[44]

8. Tanner pubertal staging is mandatory in all patients with suspected pACT (agreement: 96%)

Comment on statement 8: Most pACTs are hormone-secreting tumours and present with virilizing features.[9,19,20,31,37-42] Feminization is a rare manifestation of pACT, even though oestradiol secretion seems to be more common than previously thought.[20,31,37] Patients may therefore present with premature pubarche, pre-pubertal girls with premature thelarche or males with gynecomastia.

A cohort study by Stecchini et al. demonstrated an increased frequence (58%) of CPP in patients with pACTs during follow-up; tall stature, older age at pACT diagnosis, recurrence, and/or metastasis at pACT diagnosis were associated with a higher risk.[44]

We therefore recommend that Tanner staging should be assessed in all patients to evaluate the clinical manifestations of the tumour and the complications associated with excess hormone production and advanced bone age.

9. Weight, height, and BMI should be recorded in all patients with suspected pACT (agreement: 100%)

10. Weight, height, and BMI trajectories should be obtained in all patients with suspected pACT (agreement: 96%)

11. The parental target height should be obtained in all patients with suspected pACT (agreement: 91%)

Comment on statements 9-11: Patients with pACT frequently present with growth and weight disturbances. Virilising and mixed tumours are associated with taller stature SDS compared with target height and population norms,[19,20,31,44,49] and tall stature at diagnosis may indicate a risk for gonadotrophin-dependent CPP.[44] Weight and BMI are often above the 50th percentile, reflecting both excessive androgen and/or cortisol secretion,[19,20,31,38,44,49] with many patients being overweight or obese at diagnosis. Cortisol-secreting tumours cause visceral adiposity and centripetal fat distribution; more than one-third present with weight gain.[20,31] Isolated cortisol secretion is rare (<10%) and may present with decreased growth velocity,[38] whereas androgen/oestrogen excess leads to rapid growth and premature epiphyseal closure.[20,31] Bone age is often advanced; however, post-treatment catch-up growth results in adult height within the target range, even in patients with CPP.[9,20,44]

12. Blood pressure measurement is mandatory in all patients with suspected pACT (agreement: 100%)

13. Random blood pressure measurements should be done on several occasions and interpreted based on age-, sex-, and height-specific reference range (agreement: 82%)

14. An assessment of cardiac function is indicated only in patients with pACT and elevated blood pressure and/or other cardiovascular risk factors (agreement: 73%)

15. An assessment of cardiac function is indicated in patients undergoing chemotherapy (including mitotane) treatment (agreement: 78%)

16. An ophthalmology assessment, including fundoscopy, is only indicated in patients with pACT who have elevated blood pressure (agreement: 73%)

Comments on statements 12-16: Hypertension is reported in 13%-68% of children with pACT, most often due to hypercortisolism.[9,19,20,31,37-39,42-44,49] Autonomous aldosterone secretion, particularly pure hyperaldosteronism, is rare.[19,20,43] In some cases, hypertension results from renal artery compression.[5,9,38] Severe

complications have been described, including hypertensive crises, stroke, encephalopathy, or even death.[31,37] Diagnosis should follow paediatric hypertension guidelines,[50] with BP measured on ≥3 visits, classification by age/sex/height, and consideration of ambulatory blood pressure measurements (ABPM), particularly in suspected white coat, masked, or secondary hypertension.[51] ABPM may better correlate with cardiac changes but is limited by availability and lack of normative data in children <5 years. Echocardiography (ECG) is recommended if pharmacological treatment is planned,[52] whereas ECG has poor sensitivity.[53] Fundoscopy is reserved for severe hypertension or associated neurological symptoms.[27,54,55]

Endocrine work-up

17. An endocrine work-up is mandatory in children or adolescents presenting with clinical signs of pACT (agreement: 100%)

Comment on statement 17: pACT is hormone-secreting in more than 80% of the cases.[7,9] Androgens are the most frequently produced steroid hormones (60%-80%), followed by glucocorticoids (15%-40%), oestrogen (7%), and mineralocorticoids (1%-4%). When subclinical hypercortisolism is taken into account, mixed tumours with cortisol and androgen secretion account for 42% of pACTs[9,14] Clinical signs alone have good sensitivity for diagnosing pACT, with smaller cohorts reporting near 100% presence of signs of hormone hypersecretion. The predictive value of the clinical assessment depends on the regional incidence, but the association with imaging studies can improve accuracy. However, a small portion of patients may have subclinical hormone production. This is particularly significant in pubertal children, since symptoms can be misinterpreted as normal, making the clinical diagnosis of pACT more challenging.[19]

Apart from their diagnostic relevance, the hormone profiles of pACT have prognostic implications. Non-secreting tumours in children, albeit rare, have been associated with poorer outcomes compared to hormone-secreting pACTs,[16] which is different compared to adult ACTs.[56] There are still uncertainties regarding the prognostic implications for each specific hormonal excess subtype, but pACT patients presenting with isolated hyperandrogenism have better long-term survival than those presenting with excess glucocorticoid, mineralocorticoid, or mixed secretion.[16,57]

Finally, the hormonal profile may indicate the need for glucocorticoid replacement during and after surgery. A small portion of patients with (subclinical) excess cortisol production at presentation may develop central adrenal insufficiency requiring glucocorticoid replacement after surgery.[38] Therefore, the panel strongly recommends performing a comprehensive endocrine work-up in all children with pACT.

18. Mass-spectrometry-based assays for the measurement of all steroid hormones should be used (agreement: 70%)

Comment on statement 18: Mass-spectrometry (MS)-based techniques for steroid hormone measurement have become standard in all areas of clinical endocrinology in many countries. Their advantages include: the capacity to (1) simultaneously determine a spectrum of various steroid hormones, (2) to measure a wide range of concentrations concurrently, and (3) to reveal much more specificity than direct immunoassays.[58,59] In case mass spectrometry-based methods are not accessible preference should be given to immunoassays using extraction or chromatographic steps.[60]

19. Urinary steroid profiling assessed by gas chromatography (GC–MS) should be used in the work-up of pACTs (agreement: 70%)

Comment on statement 19: Urinary steroid profiling (USP) based on GC-MS has its role in delineating (inborn) errors of steroid metabolism, as it can simultaneously quantify the most comprehensive range of metabolites of active steroid hormones, their precursors, enabling the gathering of an extensive metabolic "fingerprint" of (adrenal) steroid hormone synthesis and catabolism.[61] There is robust evidence in adults that urinary steroid profiling (USP) with gas–chromatography (GC)–MS has high sensitivity and specificity to distinguish between adrenal cortical adenomas and carcinomas.[62] The EURINE-ACT study, a prospective multi-centre study with more than 2000 participants,[63] was based on these findings and used liquid chromatography-tandem mass spectrometry (LC–MS/MS), concluding that it improves diagnostic accuracy compared to imaging alone.[64] It may also be a valuable tool to detect ACC recurrence.[65] Recent data show that urinary GC–MS steroid metabolome analysis in children allows fairly good separation between pACCs and pACAs.[66] However, as pACAs and pACCs do not differ in all metabolic parameters, they may form a continuum. Furthermore, biomarkers in children differ from those in adults; in particular, Δ5-steroids do not differentiate between pACCs and pACAs.[66]

As pACTs require separate consideration from adult ACTs, the panel acknowledges that caution should be exerted in urinary steroid analytics and preference should be given to the much more comprehensive and specific technique of GC–MS. Thus, findings from LC–MSMS-based urinary studies in adults, eg, the EURINE-ACT study, cannot be transferred to children. More data are needed to decide if LC–MSMS will be suitable for characterizing childhood ACTs at all. The panel currently advises the use of USP (GC–MS) in conjunction with serum hormone measurements and imaging, particularly when the standard biochemical phenotype is unclear or mixed. USP should therefore be considered as a supportive and complementary tool within the comprehensive diagnostic work-up, not a standalone test.[67] GC–MS-based USP should be limited to highly specialized supraregional laboratories that possess both highly sophisticated analytical technology and the necessary expert knowledge in steroid metabolism.

20. Laboratory screening for cell decay parameters (LDH, uric acid), baseline coagulation tests, and a comprehensive blood count, including differential white blood cell count, should be performed on all patients diagnosed with pACT (agreement: 73%)

Comment on statement 20: Although comprehensive blood counts and cell decay parameters are routinely obtained in pACT, their findings are rarely reported, and their clinical relevance is unclear. Lactate dehydrogenase may be elevated in some patients, but its prognostic value is inconsistent, and haematologic abnormalities such as erythrocytosis are rare.[37,41,68,69] Blood count and coagulation screen remain an essential component of preoperative assessment and prior to administration of cytotoxic chemotherapy. In adult ACT, inflammation-based scores, particularly the neutrophil-to-lymphocyte ratio (NLR), have been linked to poor outcomes.[70-73] In paediatric tumours, these markers require validation; only one study has associated the monocyte-to-lymphocyte ratio (MLR) with adverse prognosis.[74] In summary, the panel supports performing complete blood count, baseline coagulation tests, and cell decay parameters in all newly diagnosed pACT cases.

21. First-line assessment of sex steroid hormone excess should include early-morning level of plasma dehydroepiandrosterone sulphate (DHEA-S), androstenedione, 17-OH-progesterone, and testosterone (agreement: 82%)

22. First-line assessment of sex steroid hormone excess should include an early-morning level of plasma oestradiol in screening patients with suspected pACTs (agreement: 73%).

23. A prolonged (3-day) oral dexamethasone test to explore autonomous production of androgens is not routinely recommended (agreement: 82%)

Comments on statements 21-23: The initial diagnostic evaluation for suspected pACT should include a general work-up for other causes of childhood androgen excess.[75] Nearly all patients have markedly elevated DHEA-S, often exceeding levels seen in idiopathic adrenarche/pubarche.[15,20] In high-incidence regions, further evaluation is warranted if no alternative cause is identified or if high-risk features are present (eg, rapid pubarche with growth acceleration, associated Cushing syndrome, age <4 years). In adolescents and older prepubertal girls, slightly raised DHEA-S may also occur in more common conditions such as idiopathic premature adrenarche, adolescent polycystic ovary syndrome, non-classic congenital adrenal hyperplasia (CAH), or Cushing's.[13] Moderate or high DHEA-S elevations should prompt further investigation. Most patients also have elevated testosterone and androstenedione, and some secrete excess 17-OH-progesterone, potentially mimicking non-classic CAH; therefore, early-morning DHEA-S, androstenedione, testosterone, and 17-OH-progesterone should be measured. The dexamethasone androgen suppression test, historically used to distinguish tumours from ACTH-dependent hyperandrogenic conditions in adults,[76,77] lacks validation in paediatric subjects and is rarely required, but it may be useful in cases of mild DHEA-S elevation with unclear aetiology.

Feminizing pACTs are rare,[14,78] and oestradiol is often measured only when clinical signs are present, despite reports of subclinical excess in some patients.[47,79] While feminizing tumours in adults are linked to poor prognosis,[80] paediatric data are limited, and a recent study did not confirm this association.[21] The panel therefore recommends including early-morning plasma oestradiol in the initial work-up for suspected pACT, even without overt feminization.

24. All patients with suspected pACTs should be biochemically assessed for cortisol excess, irrespective of clinical signs of hypercortisolism (agreement: 92%)

25. If available, 3 consecutive collections of 24-hour urine for free urinary cortisol should be obtained (agreement: 74%)

26. An early morning sample of plasma cortisol and ACTH should be obtained (agreement: 83%)

27. A late-night cortisol level (saliva or plasma) should be obtained (agreement: 74%)

28. An overnight dexamethasone suppression test should be performed (agreement: 70%)

Comments on statements 24-28: Cushing syndrome is the second most frequent presentation of pACT, and ~10% of patients without overt signs have biochemical cortisol excess.[9] As cortisol overproduction may worsen prognosis[80] and cause bilateral adrenal suppression, all suspected pACT cases should be biochemically screened for hypercortisolism, regardless of phenotype. Steroid replacement is indicated postoperatively in such patients. No pACT-specific data exist comparing diagnostic methods; therefore, recommendations follow general paediatric Cushing guidelines.[23]

Early morning cortisol and ACTH are often initial tests; although not diagnostic, they are useful to exclude exogenous cortisol exposure.[81] Late-night salivary or plasma cortisol is a precise screening tool[18,82] and should be collected with appropriate timing, repeated to account for cyclicity, and, in children, preceded by venous access to reduce stress-related false-negative results.[23]

Twenty-four-hour urinary free cortisol (UFC) is an excellent screening option, though challenging in younger children, especially girls.[23,83] The overnight 1 mg (or 20 µg/kg) dexamethasone suppression test (DST) is accurate, simple, and stress-independent, though malabsorption and cortisol-binding globulin changes may yield false positive results; measuring dexamethasone concomitantly can help.[83] The panel recommends combining at least 2 methods to minimize false negatives and optimize perioperative management. The choice of methods

may depend on local availability, logistics, and acceptability for both clinical teams and families.

29. Sodium, potassium, aldosterone, and renin (concentration/activity) should be measured in all patients with suspected or confirmed pACT, regardless of the presence of hypertension (agreement: 73%)

30. 11-deoxycorticosterone should be measured in patients with suspected or confirmed pACT (agreement: 70%)

Comments on statements 29-30: Mineralocorticoid-producing tumours are the rarest functional pACT subtype,[14] and interpretation is complicated by the absence of paediatric reference ranges for renin concentration or plasma renin activity (PRA). Suppressed renin may indicate mineralocorticoid excess due to other disorders of primary hypertension, such as primary hyperaldosteronism or congenital adrenal hyperplasia due to 11-beta hydroxylase deficiency. It is unknown whether aldosterone hypersecretion in pACT occurs without clinical signs. Given that subclinical cortisol excess is found in ~10% of pACT cases, a similar phenomenon may exist for aldosterone; therefore, the panel recommends mineralocorticoid assessment in all suspected or confirmed cases.

pACTs may also produce steroid precursors with mineralocorticoid activity, such as 11-deoxycorticosterone (11-DOC), and glucocorticoid precursors like 11-deoxycortisol.[84] Elevated 11-deoxycortisol has been linked to worse outcomes in adults[85] and in one paediatric and adult study.[21] Most adult studies linking 11-DOC, 11-deoxycortisol, and other precursors to carcinoma–adenoma distinction[86] are of limited applicability to children, where histopathological classification is less reliable.[87] Weak mineralocorticoid overproduction (11-DOC, corticosterone) without aldosterone excess has been described in adults[88,89] but not studied in children. In view of these gaps, the panel recommends including 11-DOC measurement in pACT if reliable methods for its quantification are available.

31. The possibility of a phaeochromocytoma should be excluded in the presence of an adrenal mass. (agreement: 87%)

Comment on statement 31: This statement reflects the panel's consensus on considering pheochromocytoma in the differential diagnosis of an adrenal mass. However, no consensus was reached on measuring plasma or urinary fractionated metanephrines in all suspected or confirmed pACT cases. Due to the frequency of incidentalomas, adult guidelines recommend metanephrine assessment for almost all adrenal incidentalomas,[87] a scenario uncommon in children.[9,14] Routine testing in all pACT patients is therefore not warranted.[9] The panel recommends assessing metanephrine secretion when an adrenal mass shows no biochemical evidence of steroid hormone excess. Hypertension can be attributed to pACT when there is clinical or biochemical hyperandrogenism or hypercortisolism.[31] To date, no cases of pACT with catecholamine co-secretion have been reported; thus, except in steroid-negative tumours, pheochromocytoma can be clinically distinguished from ACT in children.

Imaging

Table 6 presents an overview of the advantages and disadvantages of imaging studies in the diagnosis of pACTs. The subsequent sections present each of the panel's recommended statements on imaging in the diagnostic work-up of pACT.

32. All patients with suspected pACT who have not completed puberty should have a bone age assessment (agreement: 91%)

Comment on statement 32: Bone age assessment is recommended in patients with pACTs, considering that most tumours secrete sex steroids, which in turn impact skeletal growth. Most patients with pACT present with advanced bone age and reduced predicted adult height at diagnosis.[20,31,44] However, the final heights in these patients do not differ from their target heights, and, after tumour resection, both bone age and height standard deviation scores normalize.[22,90] Secondary CPP has been previously described in the follow-up of patients with pACTs in the context of excess sex steroid secretion and bone age advancement.[44] A previous cohort study demonstrated that the majority (37/63) of patients with pACTs developed CPP or progressive early puberty, especially those with tall stature, older age at diagnosis, and metastasis and recurrence.[44] Despite isolated bone age advancement or initial tall stature, puberty disorders did not alter final height[44]

33. In the screening of a patient with suspected pACT, imaging studies should be done in parallel to the endocrine/hormonal work-up (agreement: 82%)

Comment on statement 33: Most children (more than 85%) with a pACT present with excess hormone production and associated clinical characteristics, such as virilization and hypercortisolism. In the presence of such symptoms, it is appropriate to perform imaging studies to confirm or exclude the presence of an adrenal mass. The median duration of symptoms until diagnosis of pACT is 4 to 6 months.[19,20,31,39,44] In order to avoid delays in diagnosis, imaging studies should be performed in parallel to the endocrine laboratory work-up. In pACT, imaging studies should demonstrate the presence of an adrenal mass, and radiological characteristics can also point to the possible diagnosis as well as differentiate it from other conditions.[91] Characteristic imaging findings in CAH, such as enlarged adrenal glands, cerebriform surface, and stippled echogenicity, can also help in determining the diagnosis in a patient with suspected pACT[91] while the laboratory work-up is under way. However, it is important to consider that radiologists with experience in paediatric adrenal imaging should be involved in this evaluation. Paediatric adrenals, in particular at infancy or young toddler age, are

Table 6 Characteristics of imaging studies on the diagnosis of paediatric adrenocortical tumours.

Imaging method	Advantages	Disadvantages
Ultrasound	• Non-invasive • No ionizing radiation • Can evaluate adrenal gland prenatally and in infants • Can distinguish between the cortex (large and hypoechoic) and the medulla (small and hyperechoic) • Can evaluate vascularity and assess the relationship between adjacent vessels and inferior vena cava involvement	• Examiner-dependent • Cannot differentiate tumour type • Fails to adequately assess deeper lesions (>10 cm) • Not useful for staging • Not useful for older children
Computed tomography	• Better resolution in comparison to ultrasound • Better imaging for evaluation of small vessels when compared with MRI • More available and lower cost • Does not necessarily demand sedation of the patient	• Decreased sensitivity for detecting tumour deposits and bone marrow involvement • Radiation concerns • Lipid content and washout contrast are not criteria that are validated in children or adolescents to differentiate benign for malignant tumours
Magnetic resonance imaging	• Increased resolution for soft tissue, good lesion detection and characterization • No ionizing radiation exposure • When contrast-enhanced, can characterize the tumour and evaluate vascular involvement	• Need for sedation • Higher cost and lower availability • As with CT and US, also cannot differentiate between benign and malignant tumours in children or adolescents
18F-FDG-PET	• Detect distant metastasis	• Higher cost and lower availability

18-F-FDG-PET, 18F-fluorodeoxyglucose (FDG) positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound.

proportionally larger than their adult counterparts, which should be considered when adrenal imaging is performed in paediatric patients.[92]

34. As the initial imaging investigation of a patient with suspected pACT, an abdominal ultrasound should be performed (agreement: 73%)

Comment on statement 34: An abdominal ultrasound scan (USS) can be an initial imaging modality to evaluate a child with suspicion of an adrenal mass.[93] It can confirm the presence of a lesion while determining whether the adrenal mass can be an anatomical anomaly, a simple cyst, or secondary to haemorrhage.[91] USS is the primary imaging modality to evaluate adrenal glands prenatally (after 13 weeks of gestational period) and in neonates because of the larger size of normal adrenal glands in this period of life when compared with older children and adolescents.[90,94] In infants, it is also possible to distinguish between the cortex (large and hypoechoic) and the medulla (small and hyperechoic).[91] Furthermore, ultrasound is a non-invasive modality, free from ionizing radiation, does not usually require sedation and is widely accessible in paediatric centres. It is also advantageous to evaluate vascularity and assess the relationship between adjacent vessels and inferior vena cava involvement.[20]

However, abdominal USS has technical limitations: it depends on the examiner and their expertise, it cannot determine tumour type, fails to adequately assess deeper lesions (>10 cm from skin), and is not useful for staging or to fully assess response to treatment. Therefore, despite being a good imaging method to initiate investigation and to evaluate infants,[45] some tumours may go unnoticed by USS, and MRI or CT must be performed in patients with a high level of suspicion of pACT, especially those with hormonal excess in whom the USS was not able to find the tumour.

35. In a patient with suspected pACT, a contrast-enhanced MRI should be performed (agreement: 73%)

Comment on statement 35: An MRI has increased resolution for soft tissue while lacking ionizing radiation exposure. A contrast-enhanced MRI is preferable to characterize the tumour and evaluate vascular involvement.[93] In younger children, the performance of an MRI is complicated by the need for sedation or general anaesthesia. Moreover, MRI cannot differentiate between benign and malignant tumours in children or adolescents.[95] Adenomas tend to be circumscribed and uniform with homogenous low signal on T1 and T2-weighted images, have homogeneous contrast-enhancement and less calcification. However, these characteristics do not rule out the possibility of carcinoma since they overlap between tumour types.[91,95-97]

Despite the lack of studies specifically evaluating the diagnostic accuracy of MRI for paediatric adrenal masses, 2 relevant points should be noted. First, in children, the prevalence of benign lesions (mainly adenomas) is low; therefore, a significant proportion of adrenal masses will be malignant. Second, certain MRI features are strongly associated with malignancy: large size,

ill-defined or infiltrative margins, signal heterogeneity (particularly on T2), and heterogeneous enhancement after intravenous contrast. The presence of these features, individually or in combination, should trigger further investigation. The panel did not reach consensus on employing other imaging modalities routinely; these are discussed in the following sections.

Computed tomography (CT)

Current CT technology allows for rapid acquisition, which typically obviates the need for sedation, while offering improved visualization of small vessels relative to MRI. However, the sensitivity for detecting tumour deposits and bone marrow involvement is decreased. There are radiation concerns,[91,98] especially in children and in patients with cancer predisposition syndromes, which are common in patients with pACT. A retrospective cohort study showed an increased risk of brain tumours and leukaemia after cumulative doses of radiation (> 50mGy) due to CT scans performed in childhood.[98]

Initial imaging with a multiphasic contrast-enhanced CT should be avoided if an MRI is available. Despite being widely used in adults to differentiate between adenomas and carcinomas, lipid content and washout contrast in multiphasic CT are not validated criteria in children or adolescents. Nevertheless, if MRI is unavailable for diagnosis, an abdominal CT scan can be performed following adequate protocols,[93] including ALARA (As Low As Reasonably Achievable) principles, exposing the patient to minimal radiation.[99,100] Advanced imaging protocols are in development with ultra-low dose acquisitions and noise correction using deep learning and artificial intelligence-based denoising techniques.[101]

In previous cohort studies, paediatric patients with adrenocortical tumours did not present with central nervous system metastases.[9,20,31] Therefore, it is not beneficial to perform brain imaging at diagnosis to screen for metastatic disease in the absence of neurological symptoms. However, in patients with pathogenic *TP53* variants associated with Li-Fraumeni syndrome, a central nervous system MRI should be performed at follow-up to look for other primary tumours, since the incidence of other brain tumours is higher.[102] Moreover, there have been reports on the occurrence of brain metastasis in Beckwith-Wiedemann patients with ACC in the absence of liver or lung involvement.[103]

Considering the risk of malignancy and the impossibility of differentiating between benign and malignant lesions in ultrasound, CT, and MRI, all patients should undergo a contrast-enhanced chest CT to evaluate for lung metastasis.[93-95,97] Of note, the lungs, in addition to the liver, are the most common sites of metastasis in pACT.[104] As suggested by the COG Diagnostic Imaging Committee/SPR Oncology Committee, if the patient is sedated for MRI, a chest CT should be performed first to avoid atelectasis, which is common in children under anaesthesia and can conceal pulmonary metastasis. A contrast-enhanced CT is not necessary to detect pulmonary nodules, but it is useful to assess the hilar regions and mediastinum.[93] However, this panel did not reach a consensus on recommending that a low-dose non-contrast-enhanced chest CT should be performed in all patients with suspected pACT.

Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT)

Most imaging studies in pACTs cannot differentiate adenomas from carcinomas unless metastases are detected.[95,97] Recent advancements in the radiological evaluation of ACTs include 18F-FDG PET/CT, which assesses glucose metabolism in tumours.[105,106] However, the high cost and low availability limit its use in clinical practice.[93] 18F-FDG PET/CT has been performed for the preoperative stratification of paediatric patients with ACC and also to evaluate malignancy and metastasis in adult patients.[105,107] In adults, 18F-FDG PET/CT is a valuable tool to help distinguish adrenal adenomas from carcinomas. Low uptake supports adenoma, while high uptake (especially with adrenal-to-liver SUV ratio >1.8) strongly suggests malignancy. However, overlap exists, so interpretation should always be integrated with CT/MRI features, clinical presentation, and biochemical findings.[105,108,109] Although its use may vary across institutions, 18F-FDG PET/CT remains an especially informative modality for post-radiointervention surveillance of metastatic adrenal lesions, allowing robust identification of residual or persistent metabolically active disease.

Pheochromocytomas have a high uptake of 18F-FDG and cannot be differentiated from ACC with an 18F-FDG PET/CT alone. The use of metomidate-based imaging, which can differentiate between cortical and non-cortical lesions and also detect metastases, could be an answer to this problem.[110] However, it is even in adults still an experimental method and is not systematically investigated in children.

Although this expert panel recognizes the potential future usefulness of 18F-FDG PET/CT, it did not reach a consensus to recommend its routine use.

Bone scintigraphy

In previously reported cohorts, the frequency of bone metastasis was very low, and most of the time was undetected in all evaluated cases. Ribeiro *et al.* previously reported that none of the 8 patients who underwent bone scintigraphy with 99 m Tc-MDP had bone metastasis, and the tracer was only taken up by 3 primary tumours.[111] Antonini *et al.* reported that despite all patients undergoing routine bone scintigraphy in the investigation of metastatic paediatric ACT, none presented with bone metastases.[9] Therefore, it is not justifiable to perform bone scans for all patients with paediatric ACT, unless bone metastases are highly suspected, and thus this expert panel did not recommend bone scintigraphy in pACT patients.

Genetic evaluation

36. All patients with pACT should undergo genetic testing (agreement: 92%)

Comment on statement 36: Cancer predisposing genetic syndromes are found in more than 50% of patients with pACT, and

Table 7 Genetic syndromes associated with adrenocortical tumours.

Genetic syndrome	Clinical presentation	Genetic abnormalities
Li–Fraumeni[113-115]	Multiple cancers: sarcomas, breast cancer, central nervous system tumours, and leukaemia	*TP53*
Beckwith–Wiedemann[116,117]	Organomegaly, omphalocele, and childhood tumours, including Wilms tumour and hepatoblastoma	Chromosome 11q15 anomalies; imprinting of *H19*, *KCNQ1OT1* and *CDKN1C*; Paternal isodisomy and loss of heterozygosity of *IGF2*
Lynch (hereditary nonpolyposis colorectal cancer)[116-118]	Nonpolyposis colorectal cancer and other primary cancers, including adrenocortical	Mismatch repair genes: *MLH1, MSH2, MSH6,* and *PMS2*
Carney complex[116,117,119]	Spotty skin pigmentation, endocrine and non-endocrine tumours, myxomas	*PRKAR1A*
Multiple endocrine neoplasia type 1[116,117]	Tumours: parathyroid glands, anterior pituitary, and the neuroendocrine tissue of stomach/intestines/pancreas	*MEN1*
McCune–Albright[117,119]	Polyostotic fibrous dysplasia, peripheral precocious puberty, and *café-au-lait* spots	*GNAS* (somatic)

they include Li–Fraumeni syndrome, Beckwith–Wiedemann syndrome, Carney complex, multiple endocrine neoplasia type 1, McCune-Albright syndrome, and Lynch syndrome (Table 7).[3,9,20,112]

Li–Fraumeni syndrome, caused by germline pathogenic variants in the *TP53* gene, was first described in 1969 and is characterized by the development of several tumours besides ACT, such as sarcomas, breast cancer, central nervous system tumours, and leukemia.[120] Early childhood onset ACT is found in 1%-3% of patients with the syndrome who can also present as the index case.[4,121-123]

The *TP53* p.R337H variant is associated with ACT development and predispose to other types of cancer, but it may also be an isolated manifestation that does not lead to the development of classic Li-Fraumeni syndrome,[1,4] in which case it can be considered as Li–Fraumeni-like syndrome. Patients in the southeastern regions of Brazil have a 10-15 fold increase in incidence of pACT in comparison with the rest of the world due to the high prevalence of the *TP53* p.R337H germline pathogenic variant, which is widespread due to a founder effect.[1,4,124,125] In this population, this variant has a low penetrance of ACT, which suggests that other genetic and epigenetic modifications can contribute to the development of the disease.[125,126] For example, somatic *ATRX* pathogenic variants occurring in the context of a germline *TP53* variant can lead to larger tumours, advanced disease, and worse prognosis.[112]

Beckwith–Wiedemann syndrome is associated with organomegaly, omphalocele, and paediatric tumours, including ACTs in approximately 3% of these patients.[112,127] The genetic alterations include genetic or epigenetic changes in chromosome 11p15, leading to the imprinting of the following genes: *H19*, *KCNQ1OT1*, and *CDKN1C*, and paternal isodisomy and loss of heterozygosity of *IGF2*.[127] Expression of *IGF2* is important in sporadic cases of ACT as well.[40] In adults, but not in paediatric patients, IGF2 overexpression was more prevalent in carcinomas and was associated with a worse prognosis.[128,129]

In patients with the Carney complex, although rare, ACT can be a clinical manifestation. *PRKAR1A* pathogenic variants were found in 10% of adenomas but not in carcinomas, while 17q22-24 loss of heterozygosity was found in both adenomas and carcinomas.[130] *PDE11A* somatic variants were found in 19% of adenomas and 16% of carcinomas.[131]

In the context of multiple endocrine neoplasia type 1 (MEN1), abnormal function of menin can predispose to the development of ACTs. Bilateral non-secreting tumours or hyperplasia of the adrenals can be found in 20%-40% of these patients.[132] However, MEN1 is a very rare cause of pACT.

Lynch syndrome (hereditary nonpolyposis colorectal cancer) is associated with variants that alter genes involved in DNA repair (for example, *MLH1* and *MSH6*) and can lead to the development of ACTs in adults and very rarely in children.[133]

Although the most common presentation of Cushing's syndrome in McCune-Albright patients is associated with macronodular adrenal hyperplasia, the development of pACT has been described.[134,135]

Impaired beta-catenin degradation has been described in adult patients with ACTs and could be associated with a worse prognosis. The frequency of somatic *CTNNB1*-activating pathogenic variants is lower in paediatric patients, but apparently it is associated with shorter survival.[18,112]

The high prevalence of underlying molecular alterations in patients with pACT justifies the need to perform genetic testing in all patients, since it can determine the appropriate follow-up, including screening for other types of cancer, and lead to the identification of other family members through cascade genetic testing. Additionally, recent data in the literature shows that some pathogenic variants can be associated with a worse prognosis.

Genetic testing for germline pathogenic variants can be performed on specific genes based on a gene candidate-based approach, especially for *TP53*. However, whenever available, a targeted next generation sequencing panel or whole-exome sequencing (WES) should be offered. Importantly, as for all genetic testing, detailed counselling with explanation of the benefits, limitations and potential risks should be offered to all patients

with pACT, but the decision to proceed or not must rest with the patient and the family.

37. Screening and Li–Fraumeni syndrome prospective screening should be offered for all patients with confirmed pACT (agreement: 91%)

Comment on statement 37: Paediatric ACT is an exceedingly common condition in patients with Li–Fraumeni or Li–Fraumeni-like syndrome when compared to the general population.[3,4,121-123] Approximately 70% of patients with this syndrome present with germline *TP53* pathogenic variants, and the most common alleles are p.R175H, p.G245S, p.R248Q, p.R248W, p.R273H, and p.R282W.[3] Previous cohorts have demonstrated a prevalence of 22%-80% of *TP53* pathogenic variants in patients with ACT.[2,4,18,20,39,42,45] Due to a founder effect, the highest estimates (80%) are in the Brazilian cohorts, which overestimate the prevalence compared with other series of patients (50%).[2-4,18,20] Moreover, *TP53* mutations seem to decrease in prevalence as the patient's age at diagnosis increases.[3]

In Brazil, a large proportion of patients with pACT have a mutation in the *TP53* gene (p.R337H allele), and the phenotype of the affected families often presents as a Li–Fraumeni-like syndrome. However, not all patients with ACT have a positive familial history of cancer.[4] Therefore, all patients should undergo genetic testing and be evaluated for *TP53* pathogenic variants.

38. Lynch syndrome (hereditary nonpolyposis colorectal cancer) should be ruled out in all patients with confirmed pACT (agreement: 74%)

Comment on statement 38: Lynch syndrome is an autosomal dominant cancer-predisposing syndrome that is associated with altered expression of genes implicated in DNA repair (mismatch-repair genes). Approximately 3% of patients with ACC have clinical criteria for the diagnosis of Lynch syndrome. Of note, the occurrence of pACT is extremely rare in this condition. The syndrome should be considered especially in adult patients with the diagnosis of ACC, in which *TP53* mutation is less common.[133,134]

39. A targeted or whole-exome sequencing panel should be performed to assess germline disease-causing variants in all patients with pACT (agreement: 70%)

40. Whole-exome sequencing (WES) to assess somatic variants should be performed from a pACT tumour sample. (agreement: 70%)

Comments on statements 39 and 40: Previous studies including the Paediatric Cancer Genome Project have demonstrated that WES analysis are useful in the evaluation of paediatric patients with ACTs.[112] In the presence of germline *TP53* pathogenic variants and somatic *ATRX* mutations, patients present with larger tumours, higher prevalence of stages 3 and 4 disease, and worse prognosis (poor event-free survival and higher risk of relapse and death).[112] Patients with the p.R337H variant in *TP53* that acquired a somatic variant in *ATRX* also showed a more aggressive phenotype. Somatic TP53 variants were infrequent, and *CTNNB1* somatic mutations were found in patients with wild-type *TP53*.[7]

Therefore, tumour WES can identify somatic mutations that are associated with specific phenotypes and outcomes, enhancing our understanding of tumour aggressiveness and prognosis. WES of pACT tumour samples is typically performed in highly specialized centres based on research protocols rather than as a universal standard of care. Clinical use is expanding through precision oncology programmes.

Epigenetic regulation is recognized as a key factor influencing the development and prognosis of various types of cancer. The most common epigenetic mechanism regulating gene transcription is DNA methylation.[136] For over a decade, epigenetic aberrations at specific loci have been linked to adrenal tumorigenesis.[137] Large-scale DNA methylation analyses have been employed to assess global differences in adult ACT.[138-141] However, the use of large-scale methylation assays in pACT is relatively recent, with the first studies emerging only in the past few years.[6,142]

Methylation profile analysis is a promising tool for the prognostic evaluation of ACT,[143] which is particularly valuable in pACT, since traditional histopathological analysis is unreliable for distinguishing benign from malignant paediatric tumours.[87] Recent studies have identified 2 distinct prognostic groups based on the methylation profiles of tumour samples from children with ACT.[6,142] This approach could aid in therapeutic decision-making, especially when clinical and histological analyses alone are insufficient to predict individual outcomes.

Nevertheless, the applications of methylation profiling in pACT are still in their early stages and have not yet been fully implemented in clinical settings. Furthermore, integrating data from different populations presents significant methodological challenges, and findings from one study may not be universally applicable.[144,145] Considering these factors, the board did not agree on recommending DNA methylation profiling for all patients with pACT.

41. All patients with confirmed pACT should receive genetic counselling (agreement: 74%)

Comment on statement 41: Cancer predisposition syndromes have long been associated with ACTs in both children and adults. However, many childhood cases were initially considered sporadic, particularly when no significant family history of cancer was present. In the latter half of the 20th century, reports of children developing multiple tumours led to the hypothesis that genetic predisposition played a role in the development of pACTs.[136,146]

With advancements in molecular biology techniques at the end of the 20th century, many of the genetic foundations of pACT were clarified. The most significant breakthrough was the identification of the *TP53* p.R337H variant.[1,2] This discovery

helped to explain the unusually high incidence of pACT in southern Brazil, where the condition occurs at least 15 times more frequently than in the rest of the world.[9] However, even after the identification of this variant, most pACT cases were still considered sporadic.

The *TP53* R337H variant is present in approximately 1 in 400 newborns in southern Brazil. However, despite an increased risk compared with the general population, most carriers do not develop ACT.[113,126] The absence of a family history of cancer in many of these patients further supported the hypothesis that most pACT cases occur sporadically.

Over the past 2 decades, numerous other genetic variants and epigenetic alterations have been linked to the occurrence and prognosis of pACT, with more likely to be identified in future studies. This growing body of research has steadily reduced the frequency of so-called sporadic tumors.[3,21,40,114,137] These findings highlight that *TP53* status and family history alone are not sufficient predictors of cancer development in patients diagnosed with pACT and their families. Furthermore, as long-term follow-up of R337H carriers became possible, the previously considered "mild" variant was found to be associated with other types of cancer.[4]

Despite significant progress in understanding the molecular basis of pACT, many aspects remain unclear. The fact that a pattern of cancer predisposition was identified more than 15 years after the first description of the *TP53* R337H variant, along with the growing number of studies uncovering new molecular links to pACT, underscores the need for comprehensive genetic counselling. The board recommends that genetic counselling be offered to every patient diagnosed with pACT, as well as their families, even in the absence of a known cancer predisposition syndrome or an identified predisposition variant.

Authors' Contributions

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Conflicts of interest

The authors have no conflict of interest to declare regarding this document.

Funding

This work was supported by grant funding from the National Institute of Health and Care Research, UK (Clinical Lectureship to J.I.) and the Birmingham Women's Hospital Charity and Birmingham Children's Hospital Chatiry and Children's Hospital Charity (Project Grant SRP004.24). SRA receives funding from FAPESP, CNPq and Fundação de Apoio ao Ensino, Pesquisa e Assistência (FAEPA) HCFMRP-USP.

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