

Consensus guideline for the diagnosis and management of pituitary adenomas in childhood and adolescence: Part 2, specific diseases

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Abstract

Pituitary adenomas are rare in children and young people under the age of 19 (hereafter referred to as CYP) but they pose some different diagnostic and management challenges in this age group than in adults. These rare neoplasms can disrupt maturational, visual, intellectual and developmental processes and, in CYP, they tend to have more occult presentation, aggressive behaviour and are more likely to have a genetic basis than in adults. Through standardized AGREE II methodology, literature review and Delphi consensus, a multidisciplinary expert group developed 74 pragmatic management recommendations aimed at optimizing care for CYP in the first-ever comprehensive consensus guideline to cover the care of CYP with pituitary adenoma. Part 2 of this consensus guideline details 57 recommendations for paediatric patients with prolactinomas, Cushing disease, growth hormone excess causing gigantism and acromegaly, clinically non-functioning adenomas, and the rare TSHomas. Compared with adult patients with pituitary adenomas, we highlight that, in the CYP group, there is a greater proportion of functioning tumours, including macroprolactinomas, greater likelihood of underlying genetic disease, more corticotrophinomas in boys aged under 10 years than in girls and difficulty of peri-pubertal diagnosis of growth hormone excess. Collaboration with pituitary specialists caring for adult patients, as part of commissioned and centralized multidisciplinary teams, is key for optimizing management, transition and lifelong care and facilitates the collection of health-related quality of survival outcomes of novel medical, surgical and radiotherapeutic treatments, which are currently largely missing.

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Introduction

In children and young people under 19 years of age (hereafter referred to as CYP), pituitary adenomas (sometimes referred to as pituitary neuroendocrine tumours or PitNETs) are very much rarer than in adults, especially before puberty. In CYP, pituitary adenomas can also differ in their characteristics, be more aggressive or more treatment resistant than adenomas in adults and can present as a sign of genetic disease. Thus, their optimal diagnosis and management need multidisciplinary collaboration from both paediatric and adult pituitary specialists. Their rarity precludes a high-quality evidence base for their management. Therefore, the recommendations in this two-part consensus guideline were developed with Appraisal of Guidelines Research and Evaluation Instrument II (AGREE II)¹ methodology between 2014 and 2022 to generate a best practice reference document of 74 recommendations for the management of suspected pituitary adenomas in CYP to improve the quality of clinical care and thus health outcomes.

Part 1 of this consensus guideline includes 17 general recommendations on neuroimaging, visual assessment, histopathology, genetics, pituitary surgery and radiotherapy relevant to all types of pituitary adenoma in CYP². Here, in Part 2, we detail the 57 recommendations with a total of 69 statements (as some of the recommendations included two or more interrelated statements) pertaining to each adenoma type in CYP: prolactinomas, Cushing disease, growth hormone (GH) excess causing gigantism and acromegaly, clinically non-functioning pituitary adenomas (NFPAs), and thyroid stimulating hormone (TSH)-secreting adenomas (TSHomas) and we also mention the rare functioning gonadotroph adenomas (Supplementary Table 1).

Methodology

For methodology, refer to Part 1 of this publication², which includes the summary of the guideline development process and the literature review flowchart. The detailed evidence tables for Part 2 can be found in Supplementary Table 2.

Recommendations

Prolactinomas

Epidemiology and aetiology. Prolactinomas are the most common adenoma type in CYP, occurring in approximately 0.1 million children every year³. However, prolactinomas are exceptionally rare before puberty, when corticotrophinomas are more common. In a series of 136 CYP presenting with pituitary adenomas before 20 years of age, 53% had prolactinomas, but 93% of these presented after 12 years of age. Pituitary adenomas were 3 times^{4–6} to 4.5 times⁷ more common in female patients than in male patients. Although patients can present with prolactinomas within the first decade of life^{4,5,8}, an adolescent presentation is more typical^{4,6–10}. Median duration of symptom history before diagnosis is 12 months^{3,11}. Of note, macroprolactinomas or giant prolactinomas, which can exert secondary mass effects that compromise growth, puberty and vision, also occur more frequently in CYP than in adults^{6,12}. In a study of CYP with macroprolactinomas, 46% had overweight or obesity at diagnosis and, of these, 23% cited weight gain as one of the reasons for seeking medical advice¹⁰. A small percentage of paediatric prolactinomas are related to familial isolated pituitary adenoma or syndromic disease (multiple endocrine neoplasia type 1 syndrome (MEN1), MEN1-like or pheochromocytoma–paraganglioma-related pituitary disease), even without a known family history¹³. Therefore, genetic testing should be considered (see **Part 1: R11** in ref. 2).

Diagnosis: clinical features.

- **Part 2: R1. Offer serum prolactin measurement in CYP presenting with one or more of the following signs and symptoms: delayed puberty; galactorrhoea; visual field loss; growth or pubertal arrest; or girls with menstrual disturbance** (strong recommendation, moderate-quality evidence).

High serum levels of prolactin inhibit gonadotrophin secretion via inhibition of the hypothalamic hormone kisspeptin¹⁴. Paediatric patients with hyperprolactinaemia might therefore present with delayed (>2 standard deviations (SD) later than mean population age for sex) or arrested puberty, growth failure or short stature, primary amenorrhoea, galactorrhoea, menstrual disturbance or secondary amenorrhoea (in post-menarcheal girls)^{3,6}. Boys might present with gynaecomastia as a result of hypogonadism. Mass effects, occurring more commonly in boys than girls, include headache and visual field loss¹⁵. Obesity, gynaecomastia, constitutional delay in growth and puberty in boys, and menstrual disturbance in girls are common physiological variations that are very rarely caused by prolactinoma. However, the cost of measuring prolactin is offset by the benefits of an early diagnosis and timely treatment.

Diagnosis: biochemical evaluation.

- **Part 2: R2. In CYP with signs or symptoms of hyperprolactinaemia, offer prolactin measurement in a single blood sample collected at any time of day** (strong recommendation, high-quality evidence).
- **Part 2: R3. Consider investigating modestly elevated serum prolactin levels by serial measurements over time to exclude the effect of stress and prolactin pulsatility** (moderate recommendation, low-quality evidence, Delphi 87%).

A single prolactin measurement taken at any time of the day is sufficient to assess hyperprolactinaemia^{16,17}. As prolactin secretion also rises in response to stress, in patients with elevated baseline prolactin (up to five times of the upper limit of normal¹⁸), sampling can be repeated on a different day with two or three samples at 20–60 min intervals, using an indwelling cannula, to differentiate stress-related hyperprolactinaemia from organic disease^{16,18}.

- **Part 2: R4. The diagnosis of hyperprolactinaemia in CYP requires age-specific and sex-specific prolactin reference ranges and the exclusion of confounding conditions such as hypothyroidism, renal and/or hepatic impairment, and use of medications that cause hyperprolactinaemia** (strong recommendation, moderate-quality evidence).

Serum prolactin concentrations vary with age and sex. They are highest in the first 2 years of life and fall to a nadir in mid-childhood, to rise again in adolescence when they are higher in girls than in boys. Paediatric cohort studies of prolactinomas report diagnostic serum prolactin concentrations usually above 4,000 mU/l (188 µg/l)^{4,8,10}, although lower levels can be seen in patients with microprolactinomas³. To rule out mixed prolactin and GH hypersecretion, age-dependent and sex-dependent insulin-like growth factor 1 (IGF1) evaluation should always accompany prolactin assessment in CYP with prolactinomas.

Unexplained, persistently mildly or moderately elevated prolactin in blood samples taken after rest could be due to the stalk effect (disconnection hyperprolactinaemia, pituitary stalk compression from mass lesions disrupting the dopaminergic inhibition of lactotroph cells).

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In adult patients with stalk effect, prolactin levels are reported above the normal range but not higher than 2,000 mU/l; 94 µg/l (ref. 19) or six times above the upper limit of normal¹⁸. Even if no corresponding symptoms of hyperprolactinaemia, hypopituitarism or a pituitary mass are observed, pituitary imaging should be considered. If hyperprolactinaemia is due to a pituitary mass, baseline and dynamic pituitary assessment can identify a potential lack or excess of other anterior pituitary hormones.

Severe primary hypothyroidism can be accompanied by hyperprolactinaemia, probably due to compensatory thyrotropin-releasing hormone hypersecretion and pituitary hyperplasia; care should be taken to distinguish such pituitary enlargement from a true prolactinoma^{20,21}. Severe and prolonged primary hypothyroidism in children can disrupt kidney and liver function as well as delay growth and puberty. In a large cohort of 2,848 adults, hyperprolactinaemia was reported in 43% of women and 40% of men presenting with frank primary hypothyroidism, in 36% of women and 32% of men with subclinical hypothyroidism, and only in around 2% of euthyroid individuals²¹. Hyperprolactinaemia is reported in 30–65% of adult patients with chronic kidney disease due to increased prolactin secretion and reduced renal clearance²². Severe liver disease is also associated with hyperprolactinaemia in adults¹⁸. Intracranial hypotension can cause hyperprolactinaemia¹⁸. Although we could find no parallel data describing the prevalence of hyperprolactinaemia in these clinical scenarios in CYP, the Guideline Development Group (GDG)² recommends the exclusion of confounding diseases. Up to 80% of patients with tetrahydrobiopterin deficiencies (a group of rare neurometabolic disorders characterized by insufficient synthesis of monoamine neurotransmitters, including dopamine) can have hyperprolactinaemia (10–30 fold elevation of prolactin), usually from the teenage years; development of a microprolactinoma has been also described in case reports^{23,24}. While less likely in the CYP population, pregnancy should not be overlooked as a cause of hyperprolactinaemia¹⁸.

Medications are one of the most common causes of hyperprolactinaemia in adults through direct prolactin stimulatory pathways or by antagonizing inhibitory dopaminergic tone²⁵. Medication-induced hyperprolactinaemia is also well described in CYP (Supplementary Table 3). The role of synthetic oral oestrogens (for example, contraceptive pills) in causing mild elevation of prolactin is controversial.

- **Part 2: R5. Assess baseline macroprolactin levels where serum prolactin is found to be mildly or incidentally elevated** (strong recommendation, low-quality evidence, GDG consensus).

In addition to monomeric prolactin (23 kDa), dimeric (48–56 kDa) and polymeric (>100 kDa) forms (usually associated with an antibody) can circulate ('macroprolactin', which has low biological activity), with or without excess monomeric prolactin. No routine assays distinguish between monomeric prolactin and macroprolactin; therefore, prompt and appropriate secondary analysis should be undertaken to detect the possible presence of macroprolactin in the initial investigation of asymptomatic CYP with hyperprolactinaemia^{26,27}. In large retrospective cohorts of adults with hyperprolactinaemia, macroprolactinaemia was present in 10–40% of individuals with hyperprolactinaemia^{17,26,27}, 20% of whom had galactorrhoea, 45% oligo-amenorrhoea and 20% pituitary adenomas. Few patients with macroprolactinaemia are reported in the paediatric literature. In a cohort of five patients aged 11–18 years with an incidental finding of hyperprolactinaemia due to macroprolactinaemia, none developed clinical features of prolactin excess during an observation period ranging from 3 months to 8 years²⁸. In another report, one of six CYP with macroprolactinaemia was asymptomatic; the other five

had either headache, menstrual disturbance, short stature, increased hair growth or early puberty. Four of those with symptoms underwent pituitary MRI and a microadenoma was identified in two (one with headache and one with oligomenorrhoea)²⁹. Given these data and the current widespread clinical practice⁶, the GDG strengthened **R5**.

- **Part 2: R6. Perform serial dilutions of serum for prolactin measurement in CYP with large pituitary lesions and normal or mildly elevated prolactin levels** (strong recommendation, moderate-quality evidence).

Serum prolactin levels directly correlate with prolactinoma size and are important markers of treatment response. Based on adult data, approximately 5% of patients with macroprolactinomas and a paradoxically modest serum concentration of hyperprolactinaemia have grossly elevated prolactin concentrations following serum dilution³⁰. When prolactin is measured in two-site immunoradiometric assays, very high concentrations of prolactin could saturate the signalling antibody, making it less available for binding to the coupling antibody, resulting in artificially low measurements¹⁶. This phenomenon has been described as the 'high-dose hook effect'³⁰ and is well recognized. Some prolactin assay manufacturers have put specific mitigating factors in place, such as large linear ranges or automatic dilution steps, in many modern assays. However, the potential remains for this effect to be a source of anomalous results³¹. Thus, contact with the clinical biochemist to request manual dilution is advised when a discrepancy exists between a large pituitary adenoma on imaging and only modestly elevated prolactin concentrations on initial biochemistry. Of note, inconsistent symptoms and laboratory results can occasionally arise due to biotin exposure or heterophilic anti-animal antibodies¹⁸.

Treatment.

- **Part 2: R7. In CYP with prolactinoma, offer a dopamine agonist as first-line therapy to reduce serum prolactin concentrations and induce tumour shrinkage; cabergoline is the dopamine agonist of choice given its superior effectiveness and lower adverse effect profile** (strong recommendation, moderate-quality evidence).
- **Part 2: R8. In CYP with prolactinoma, offer cabergoline as first-line therapy, even in the presence of visual disturbance and pituitary apoplexy, while carefully monitoring for any deterioration in vision, pituitary function or general status** (strong recommendation, low-quality evidence, Delphi 100%).

Dopamine agonists reduce pituitary-origin hyperprolactinaemia of any cause¹⁸. In adults with prolactinoma, dopamine agonists induce normalization of the prolactin level (median: 68% of patients; range: 40–100%), tumour shrinkage (62%; 20–100%), resolution of visual field defects (67%; 33–100%), normalization of menses (78%; 40–100%), fertility (53%; 10–100%) and sexual function (67%; 6–100%), and resolution of galactorrhoea (86%; 33–100%)^{11,32,33}. In both adults and CYP with prolactinoma, cabergoline is the dopamine agonist of choice^{3,11,12}. Cabergoline has a longer half-life and greater affinity for the dopamine receptor than other dopamine agonists. In a randomized controlled trial of adult women with prolactinoma, cabergoline was superior to bromocriptine in normalizing prolactin (83% versus 59%), resuming ovulatory cycles or achieving pregnancy. Adverse events were more commonly reported with bromocriptine than with cabergoline (72% versus 52%)³⁴.

In studies of CYP with prolactinomas, dopamine agonists lower prolactin concentrations in 60–70% of patients^{3,4,8,10,11,35}, reduce tumour

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size by 80–88%^{3,11}, improve visual deficits³⁶, resolve pubertal delay and eliminate headache¹¹. In an observational study of 28 paediatric patients, CYP with prolactinomas smaller than 13.5 mm in diameter (13 patients) achieved normalization of prolactin levels without surgery, using conventional cabergoline doses (up to 2 mg/week)¹². Moreover, another series of 22 CYP with prolactinomas reported that all tumours of >20 mm diameter required surgery⁶. Although successful dopamine agonist discontinuation has been achieved in CYP, younger patients and those with high serum prolactin concentrations at diagnosis (a marker of adenoma size) are less likely to achieve complete remission and euprolactinaemia^{3,11,37}.

Medication-induced shrinkage of prolactinomas that have invaded sphenoid bone can cause rhinorrhoea after a few months of drug administration (mean 3.3 months, range 3 days–17 months) due to a cerebrospinal fluid leak³⁸, but this adverse effect can also occur during long-term treatment. Detection of β 2-transferrin or β -trace protein (specific to cerebrospinal fluid) in nasal secretions confirms a cerebrospinal fluid leak³⁹. Cerebrospinal fluid leak can require urgent intervention (for example, lumbar drain or surgical repair), with or without a temporary cessation in dopamine agonist therapy⁴⁰. Apoplexy has been described during cabergoline therapy both in adults and CYP⁶.

- **Part 2: R9. For CYP resistant to standard doses of cabergoline, offer graduated dose increments of up to 3.5 mg per week or up to 7 mg per week in exceptional cases** (strong recommendation, moderate-quality evidence, Delphi 100%).

Evidence indicates that adult patients with prolactinoma who are unresponsive to standard dopamine agonist doses (up to 1.5–2 mg of cabergoline per week) might respond to higher doses (3.5–7 mg per week), whilst even higher doses (up to 12 mg per week^{41,42} but below the 21 mg per week dose used for Parkinson disease) have been tried. High-dose cabergoline is reportedly well tolerated and doses of up to 7 mg per week have been used to successfully treat CYP with prolactinoma^{10,11}. However, others report little benefit of cabergoline doses above 3.5 mg per week in adults⁴¹. Patients with cabergoline resistance or intolerance will require adjuvant therapy with surgery or radiotherapy⁴².

- **Part 2: R10.1. Following multidisciplinary discussion, for CYP with prolactinomas offer surgery when the patient is unable to tolerate or is resistant to high-dose cabergoline** (strong recommendation, low-quality evidence, Delphi 95%).
- **Part 2: R10.2. Following multidisciplinary discussion, for CYP with prolactinomas offer surgery when the patient develops deteriorating vision on cabergoline** (strong recommendation, low-quality evidence, Delphi 90%).
- **Part 2: R10.3. Following multidisciplinary discussion, for CYP with prolactinomas offer radiotherapy if surgery is not an option** (strong recommendation, low-quality evidence, Delphi 100%).

Small nocturnal dose increments of cabergoline can effectively diminish the adverse effects of gastrointestinal intolerance and postural hypotension, thereby avoiding trials of less effective dopamine agonists (bromocriptine or quinagolide). Dose-independent psychological intolerance (mood changes, depression, aggression, hypersexuality and impulse control disorder) is similar between agents and described in adults as well as CYP^{37,43}, but the frequency of these adverse events might be higher in CYP than in adults^{11,44}. Dopamine agonist resistance is usually defined in adults and CYP as failure to achieve normoprolactinaemia (biochemical resistance) and less than

50% reduction in tumour area in the coronal plane and/or less than 30% reduction of the longest diameter of the tumour (tumour size resistance, assessed by Response Evaluation Criteria In Solid Tumours (RECIST) criteria) after 3–6 months of maximally tolerated dopamine agonist doses (at least 2 mg per week)^{18,41,45,46}. In a paediatric macroprolactinoma cohort of patients who were unresponsive to 3 months of 15 mg per day bromocriptine, 600 μ g per day quinagolide or 3.5 mg per week cabergoline, 26% were biochemically resistant and 24% were tumour-shrinkage resistant¹⁰. This resistance directly correlated with tumour size and prolactin levels (which in turn were closely correlated) but was independent of *MEN1* mutation status¹⁰.

In CYP with prolactinoma, neurosurgical intervention should be considered if vision deteriorates or does not improve on medical therapy or if dopamine agonist resistance, escape or intolerance occurs. Careful multidisciplinary discussion is needed if the patient expresses a preference for surgery rather than long-term medication or is non-adherent to the latter.

Transsphenoidal surgery induced remission in 30–50% of adults with prolactinomas and any residual post-operative hyperprolactinaemia was subsequently more responsive to dopamine agonists than pre-operatively⁴⁷. Tumour size negatively predicted surgical remission rates, with smaller adenomas being more often cured by surgery alone than larger ones^{47,48}. Paediatric series report lower surgical remission rates than in adults, most likely due to the higher incidence of proportionately larger prolactinomas in CYP, as well as a possible higher frequency of new and permanent pituitary hormone deficiencies after surgery^{43,49–52}. In adults with microprolactinomas or intrasellar macroprolactinomas, surgery is a viable option with an excellent cure rate (83% in microprolactinomas and 60% in macroprolactinomas), especially in high-volume surgical centres, and is certainly an alternative to long-term cabergoline therapy^{18,53}.

Radiotherapy should be reserved for exceptional patients with a growing prolactinoma and where other treatment modalities are not available or have been exhausted; the main indication for radiotherapy is control of tumour growth, whereas normalization of prolactin levels is a secondary objective². After radiotherapy, initially 6-monthly and later 12-monthly follow-up should monitor for the development of hypopituitarism or recurrence. The detailed assessment and treatment of hypopituitarism in CYP is beyond the scope of these guidelines.

- **Part 2: R11. In CYP with prolactinoma, offer an echocardiogram at the start of treatment with a dopamine agonist; offer yearly surveillance echocardiography for patients receiving >2 mg per week cabergoline and every 5 years if on \leq 2 mg per week** (moderate recommendation, moderate-quality evidence).

High-dose and long-term use of dopamine agonists in Parkinson disease pose a recognized risk of cardiac valve regurgitation; however, the doses used in treating prolactinomas are notably lower. A meta-analysis that identified an increased prevalence of echocardiographic tricuspid regurgitation in adults was heavily influenced by a single study, with no reports of increased clinical valvular disease⁵⁴. A subsequent population-based, matched control cohort study in adults failed to identify an excess in hard clinical cardiac endpoints⁵⁵. Nevertheless, the long-term cardiac safety of ergot-based dopamine agonists in CYP requires a balanced judgement against the increasing background rate of cardiac valvulopathy that occurs with age and the often more aggressive nature of prolactinomas in the paediatric age group, who require longer treatment durations and higher cumulative doses than adults. The relative contributions of peak versus cumulative doses

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of dopamine agonists in the aetiology of valvulopathy are unknown. In adults with Parkinson disease and moderate-to-severe valvulopathy, the mean cumulative cabergoline dose was 4,015 mg, with one SD below the mean being 720 mg (ref. 56), yet a critical cumulative dose threshold could not be established⁵⁶. Similar respective cumulative doses in CYP with prolactinoma would require 39 years (4,015 mg) or 7 years (720 mg) of 2 mg per week cabergoline treatment. To date, valvulopathy in CYP treated with dopamine agonists for hyperprolactinaemia has not been reported. A 2019 position statement for adults with prolactinomas treated with dopamine agonists recommends pre-treatment baseline and annual echocardiography with cardiac auscultation for those on >2 mg per week of cabergoline, reduced to 5-yearly echocardiographic surveillance if the cabergoline dose is ≤2 mg per week⁵⁷. Until data specific to CYP emerge, following these recommendations (endorsed by three relevant UK professional societies⁵⁶) seems prudent.

- **Part 2: R12. Temozolomide treatment might need consideration for CYP with aggressive pituitary tumours resistant to medical, surgical and radiation therapy** (weak recommendation, low-quality evidence, Delphi 88%).

Temozolomide treatment for aggressive pituitary tumours and pituitary carcinomas is well described in the adult pituitary literature⁵⁸. These entities are extremely rare in CYP: four patients with pituitary carcinomas are reported to have had disease commencing in childhood^{59–62}. The 2017 European Society of Endocrinology guideline recommends first-line temozolomide monotherapy for aggressive pituitary tumours and pituitary carcinomas unresponsive to standard therapies, with evaluation of responders and non-responders after three cycles of 150 mg/m² per day for 5 days in every 28 days, with dose increases to 200 mg/m² per day in patients with good tolerance⁶³. A minimum of 6 months of treatment is recommended for responding patients. Five paediatric patients receiving temozolomide treatment for pituitary tumours were identified in the literature, with two more paediatric-onset patients receiving temozolomide as adults (Table 1).

Follow-up and surveillance.

- **Part 2: R13. If the serum level of prolactin has been normalized for at least 2 years on medical therapy and there is no visible**

residual prolactinoma on MRI, consider gradual cabergoline dose reduction to maintain normoprolactinaemia and eventual treatment discontinuation, with continued serum prolactin monitoring for at least 2 more years (moderate recommendation, low-quality evidence, Delphi 100%).

The relapse rates of prolactinomas in CYP treated with dopamine agonists are not reported. The Endocrine Society guideline for the treatment of hyperprolactinaemia in adults recommends a trial of therapy discontinuation in those patients with no tumour remnant on MRI and normoprolactinaemia after 2 or more years of medical treatment¹⁸. Studies report variable (26–89%) hyperprolactinaemia recurrence rates under these conditions, largely within the first 2 years of treatment withdrawal^{18,64}. Discontinuation might also be attempted with normoprolactinaemia and a small tumour remnant⁵¹.

Two meta-analyses have examined factors associated with relapse following treatment withdrawal in patients with prolactinoma treated with dopamine agonists. The first (19 studies, 743 patients) concluded that both the use of cabergoline and treatment for more than 2 years were associated with a decreased relapse rate⁶⁵. The second (11 studies, 637 patients) found that tapering doses prior to withdrawal reduced the risk of relapse but that treatment beyond 2 years had no further beneficial effect⁶⁶.

CYP with prolactinomas should be monitored clinically (including assessment of growth, puberty, galactorrhoea, menstrual history, gynaecomastia or loss of libido in puberty) and biochemically by measurement of serum prolactin. For macroprolactinomas, MRI should be repeated 3–6 months after starting cabergoline treatment; for microprolactinomas, re-imaging depends on clinical and biochemical follow-up; imaging is suggested before considering cabergoline withdrawal¹⁸. Longer-term imaging frequency depends on symptoms, biochemical control and the closeness of the pituitary mass to the optic chiasm¹⁸. One observational study (including 11 CYP) reported low bone mineral density (BMD) at diagnosis with modest degrees of recovery after 2 years of dopamine agonist therapy. Assessment of BMD 2 years after diagnosis might be important in patients with prolactinoma⁶⁷; however, the inevitable negative impact of delayed growth and puberty on peak bone mineral accrual will confound definitions of 'osteopenia' in CYP. Thus, repeated longitudinal assessments require interpretation not only alongside cure rates but also with clinical

Table 1 | Paediatric-onset pituitary adenomas treated with temozolomide

Sex	Age at diagnosis (years)	Age at temozolomide treatment (years)	Dose and response to temozolomide	Anterior pituitary hormone staining	Ref.
Male	13	16	200 mg/m ² per day, 5 days per month; good prolactin and size response	Prolactin	Whitelaw et al. ²⁵⁶ ; patient also mentioned in Arya et al. ⁶
Female	8	8	200 mg/m ² per day, 5 days per month	Prolactin	Felker et al. ²⁵⁷
Male	14	18	200 mg/m ² per day, 5 days per month, 40% shrinkage after 6 cycles	Growth hormone and prolactin	Lasolle et al. ²⁵⁸
Male	4 (AIP positive)	4	180 mg per day, 5 days per month	Growth hormone	Dutta et al. ²⁰⁴
Female	9	9	200 mg/m ² per day, 5 days per month	Hormone negative	Guzel et al. ⁶⁰
Female	13	25	75–200 mg/m ² per day, 5 days per month, 50% shrinkage after 12 cycles	Adrenocorticotropin	Lasolle et al. ²⁵⁸
Female	17	27	5 mg per day, 5 days per month	Prolactin	Chentli et al. ²⁵⁹
Male	18	19.75	200 mg/m ² per day, 5 days per month, partial biochemical response, poor tumour size response	Prolactin	Arya et al. ⁶

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pubertal staging, additional sex and adrenal hormone replacement, and at growth completion (epiphyseal fusion) and full pubertal maturation (age 25 years).

The optimal frequency of MRI imaging following cessation of treatment is unknown. Prolactin levels, assessed at 3–6-monthly intervals initially, can be used as markers of tumour relapse, although biochemical relapse is not always accompanied by radiological MRI change.

Cushing disease

Epidemiology and aetiology. Cushing disease is caused by an adrenocorticotropin (ACTH)-secreting pituitary adenoma and is the most common form of ACTH-dependent Cushing syndrome, yet it is rare in CYP. The incidence is approximately 10% of that in adults, of ~0.5 new patients per million individuals per year⁶⁸. Cushing disease accounts for 75–80% of CYP with Cushing syndrome, compared with 49–71% of adults^{69,70}. In fact, corticotroph adenomas are the most common pituitary adenoma diagnosed in early childhood (55% of pituitary adenomas in those aged 0–11 years; 30% in those aged 12–17 years)⁷, with mean age at presentation of 12.3 ± 3.5 years (mean \pm SD; range 5.7–17.8)⁷¹. An overall male predominance exists in CYP, with 63% of patients with paediatric Cushing disease being boys compared with 79% of patients being female in adult series. This discrepancy is driven by prepubertal male predominance (71%)⁷². Boys with Cushing disease tend to have more aggressive disease with elevated BMI, shorter height and higher plasma ACTH levels than girls⁷³. At all ages, microadenomas are the most common cause of Cushing disease, accounting for 98% of cases in CYP, with the adenoma diameter frequently being ≤ 2 mm (refs. 7,68,72,74). Macroadenomas, often showing invasion of the cavernous sinus, are rare in CYP (2–5% CYP versus 10% of adults with Cushing disease)⁷⁵. Genetic associations are described in Part 1 (ref. 2).

Diagnosis: clinical features.

- **Part 2: R14. Offer screening for Cushing syndrome in CYP with obesity but only if weight gain is inexplicable and combined with either a decrement in height SD score (SDS) or height velocity** (strong recommendation, moderate-quality evidence).

The clinical features of Cushing disease in CYP are well documented^{69,73,74,76–78} and demonstrate interesting differences compared with adult patients⁷². CYP might show growth failure (subnormal growth velocity), with respective short stature and weight gain (height SDS below and BMI SDS above the mean for age and sex)^{69,72,74,78,79}. Yet, not all CYP with Cushing syndrome have obesity and few patients with obesity prove to have Cushing syndrome⁸⁰. Consensus statements advise that only CYP with unexplained weight gain and either growth rate deceleration or decrement in height centile over time require investigation, as this combination of features has a high sensitivity and specificity for Cushing syndrome in CYP^{81,82}. The presence of growth failure sensitively discriminates simple obesity from Cushing syndrome in prepubertal CYP⁸³ but is an unreliable indicator in post-pubertal CYP, who require assessment according to adult guidelines⁸².

Diagnosis: biochemical investigations.

- **Part 2: R15. In CYP with suspected Cushing syndrome, offer investigations using established algorithms, first to determine the diagnosis of Cushing syndrome (the presence of hypercortisolaemia), followed by investigations to ascertain its aetiology** (strong recommendation, moderate-quality evidence).

The biochemical investigation of children with suspected Cushing syndrome has been extensively reviewed^{69,76,81,84,85}. The algorithms for testing consist initially of confirmation or exclusion of the diagnosis of hypercortisolaemia and then investigations to determine its aetiology⁸¹.

- **Part 2: R16. Suspected Cushing syndrome in CYP is effectively excluded by either two normal 24-h urinary free cortisol (UFC) measurements and a normal low-dose dexamethasone suppression test (LDDST; 0.5 mg 6-hourly for 48 h or, if patient weight is <40 kg, 30 μ g/kg per day for 48 h); or a midnight sleeping serum cortisol concentration of <50 nmol/l** (strong recommendation, high-quality evidence).
- **Part 2: R17. Two late-night salivary cortisol tests could be a useful alternative for the midnight serum cortisol test as a means of excluding Cushing syndrome, but age-specific and assay-specific normal ranges are not currently available and need to be carefully characterized** (moderate recommendation, moderate-quality evidence).

Diagnosis of hypercortisolism usually includes three tests: dexamethasone suppression testing, 24-h UFC, and late-night salivary or sleeping midnight serum cortisol level (Table 2). None of these tests has 100% diagnostic accuracy and each test has some limitations⁸⁶. It is important to eliminate the effect of exogenous glucocorticoids before biochemical testing.

Dexamethasone suppression testing can be either standard 48-h LDDST or overnight dexamethasone test (25 μ g/kg at 11:00 h or midnight, maximum dose 1 mg). The 1 mg overnight dexamethasone suppression test is now routine in adults⁸² but considerably less data are available in children, where this test has lower sensitivity^{86,87}. Both the 48-h and the overnight dexamethasone tests can be influenced by diarrhoea or coeliac disease, or by medications that increase cortisol-binding globulin levels or influence CYP3A4 activity. Measurements of serum dexamethasone can be used to ensure appropriate blood levels, but data for children are lacking and dexamethasone assays are not widely available. Repeated 24 h UFC measurements in the normal range (corrected for body surface area, micrograms per metre squared per 24 h) can support the lack of hypercortisolism. Physiological increases in UFC excretion can occur in girls in the peri-menarcheal phase. Limitations of the UFC test include difficulties in accurately and repeatedly collecting urinary samples in young children and lower sensitivity in milder cases of hypercortisolism and in severe kidney dysfunction. A sleeping midnight serum cortisol measurement has high sensitivity (94–100%) and specificity (100%) for Cushing disease. The test needs an overnight stay in the hospital and the patient needs to be asleep at the initiation of sampling. By contrast, a late-night salivary cortisol test is easy and cost-efficient, with high sensitivity (93–100%) and specificity (95–100%), but lacks age-specific and assay-specific normal ranges.

Clinical suspicion of Cushing syndrome but normal biochemical test results could rarely be due to periodic Cushing syndrome. In these patients, multiple, periodic, sequential late-night salivary cortisol tests can be helpful in detecting episodes of cortisol excess longitudinally⁸².

- **Part 2: R18.1. In CYP with confirmed Cushing syndrome, Cushing disease can be confirmed by its ACTH dependency, which is supported by a normal or elevated 09:00 h plasma ACTH** (strong recommendation, moderate-quality evidence).

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Table 2 | Recommended protocol for diagnosis of Cushing disease in CYP^a

Type of test	Diagnostic cut-off	Sensitivity ^b	Specificity ^b
Confirmation of Cushing syndrome			
1: UFC excretion (24-h urine collection) for 3 days	>193 nmol/24 h ^c (>70 µg/m ²)	89%	100%
2: Serum cortisol circadian rhythm study (09:00 h, 18:00 h, midnight (sleeping))	≥50 nmol/l ^d (≥1.8 µg/dl)	100% ^d	60% ^d
3: Late-night salivary cortisol	Based on local assay cut-off	95%	100%
4: LDDST; dose 0.5 mg 6-hourly (09:00, 15:00, 21:00, 03:00 h) for 48 h; the dose for patients weighing <40 kg is 30 µg/kg per day; serum cortisol level is measured at 0, 24 and 48 h	≥50 nmol/l (≥1.8 µg/dl)	95%	80%
5: Overnight dexamethasone test; dose 25 µg/kg at 23:00 h or midnight (maximum dose 1 mg); serum cortisol measured at 09:00 h	≥50 nmol/l (≥1.8 µg/dl)	11% (based on 9 patients ²⁶⁰); 75% (based on 4 patients ⁸⁰)	Not applicable
Confirmation of Cushing disease			
1: Plasma ACTH (09:00 h)	>1.1 pmol/l (>5 ng/l)	68%	100%
2: CRH test (1.0 µg/kg intravenously)	Cortisol increase ≥20% ^e	74–100%	Not applicable
4: Pituitary MRI scan	Adenoma detection	63%	92%
5: Bilateral inferior petrosal sinus sampling for ACTH (with intravenous CRH or desmopressin)	Central-to-peripheral ACTH ratio ≥3 (after intravenous CRH or desmopressin)	100%	Not applicable

ACTH, adrenocorticotropic hormone; CRH, corticotrophin-releasing hormone; LDDST, low-dose dexamethasone suppression test; UFC, urinary free cortisol. ^aThe protocol in this table was originally presented in refs. 76,229. ^bData from refs. 78–80,86,91,92,229,260–262. ^cUrinary cortisol values are assay dependent, this value refers to radioimmunoassay data. ^dDiagnostic cut-offs refer to midnight serum cortisol values. ^e≥35% increase in ACTH during CRH testing has also been used as a diagnostic cut-off^{80,85}.

- **Part 2: R18.2. In CYP with confirmed Cushing syndrome, the diagnosis of pituitary-origin ACTH excess is supported by >20% increase in cortisol from baseline during a corticotrophin-releasing hormone (CRH) test** (moderate recommendation, low-quality evidence, Delphi 92%).

Following confirmation of hypercortisolism, the priority is to determine its cause. Cushing disease is most easily confirmed by determination of basal (morning, 08:00–09:00 h) plasma ACTH. In all patients with Cushing disease, ACTH is detectable (>5 ng/l (>1.1 pmol/l); Table 2). In the presence of confirmed hypercortisolism, using a cut-off value of 29 ng/l (6.4 pmol/l), ACTH has a 70% sensitivity and 100% specificity for diagnosing Cushing disease⁸⁵. Based on adult data and guidelines, in ACTH-independent Cushing syndrome, ACTH is always low and usually undetectable.

High-dose dexamethasone suppression tests (HDDST; 80–120 µg/kg, maximum 8 mg) are no longer necessary in the routine investigation of Cushing disease given that, in CYP (as in adults), >30% cortisol suppression during LDDST (but still above 50 nmol/l) correlates with HDDST results and strongly supports the diagnosis of Cushing disease. Furthermore, CYP with ectopic ACTH-secreting tumours might show cortisol suppression on HDDST, while the HDDST itself can induce transient hypertension and hyperglycaemia in CYP^{76,86,88–90}. Therefore, many centres have abandoned HDDST. A CRH test using human sequence CRH (1 µg/kg intravenously) is recommended to support the suspected diagnosis of Cushing disease; in 92% of paediatric patients with Cushing disease (36 of 39 patients), serum cortisol level increased by >20% (range 2–454%) in response to CRH⁷². Ectopic ACTH syndrome is so rare in children that the need for a CRH test is questionable, although a cortisol increase of >20% to CRH has a 97.5% sensitivity and 100% specificity for Cushing disease and can contribute to the diagnosis⁸⁵. As the availability of CRH is not universal, desmopressin (10 µg intravenous) has been used in CYP for bilateral simultaneous inferior petrosal sinus sampling (BSIPSS), with similar cut-off ratios to

the CRH test^{91,92}. A recommended protocol for the diagnosis of Cushing disease in CYP is shown in Table 2. All tests need to be interpreted in the light of the pre-test probability of the disease being present.

Diagnosis: neuroimaging and BSIPSS. In CYP with suspected Cushing disease, pre-operative MRI to localize the pituitary adenoma is strongly recommended, although only 50–63% of corticotroph adenomas were identified on post-contrast images in several large paediatric series^{72,85,93}. This poor visualization rate in children could be explained by the limited spatial resolution of MRI, making small lesions within a small pituitary gland inconspicuous. Therefore, pituitary MRI imaging alone cannot reliably predict the adenoma position or confirm the diagnosis of Cushing disease in CYP.

- **Part 2: R19.1. Offer BSIPSS to CYP with confirmed ACTH-dependent Cushing syndrome and no identified adenoma on pituitary MRI to confirm a central source of ACTH excess** (strong recommendation, low-quality evidence, Delphi 83%).
- **Part 2: R19.2. Offer BSIPSS only in a specialist centre with expertise in such testing and by an experienced interventional radiologist who regularly undertakes this procedure in adults** (strong recommendation, moderate-quality evidence).
- **Part 2: R19.3. Consider confirming hypercortisolaemia immediately prior to BSIPSS to ensure the patient is in an active disease phase** (moderate recommendation, moderate-quality evidence).
- **Part 2: R19.4. During BSIPSS, a pituitary source of ACTH excess is confirmed by a ≥2:1 ratio of central-to-peripheral ACTH before CRH or desmopressin and ≥3:1 ratio after CRH or desmopressin stimulation** (strong recommendation, low-quality evidence, Delphi 100%).
- **Part 2: R19.5. BSIPSS could provide some information on tumour lateralization if the inter-petrosal sinus ACTH gradient after CRH or desmopressin stimulation is ≥1.4 between the two sides** (moderate recommendation, moderate-quality evidence, Delphi 67% and GDG consensus).

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BSIPSS was initially piloted in adults at the National Institute of Health (NIH)⁹⁴ to enable distinction between Cushing disease and ectopic ACTH syndrome. In adult practice, BSIPSS has become routine unless the MRI unequivocally shows a pituitary adenoma that is unlikely to be an incidentaloma. A pituitary source of ACTH excess confirmed during BSIPSS has a high sensitivity for Cushing disease in experienced centres^{72,84,93–95}. Hypercortisolaemia can be confirmed on the morning of the BSIPSS procedure to ensure the few patients with cyclical Cushing disease⁸⁰ are in an active phase. BSIPSS using desmopressin as the stimulant has been reported in five paediatric series, with similar accuracy to CRH stimulation^{91,92}. The reliability of the results of BSIPSS and the incidence of adverse events are related to the experience of the radiology team⁸⁴. To enable the accurate interpretation of the results, medical therapy for Cushing disease (steroidogenesis inhibitors) must be stopped before undertaking BSIPSS; the length of time of treatment discontinuation depends on the half-life of the agent used.

BSIPSS might also help to lateralize pituitary ACTH secretion, where no lesion is visible on MRI⁸¹. If, on BSIPSS, the ACTH gradient between the two sides is greater than or equal to 1.4 after CRH (or desmopressin) stimulation, this finding might indicate lateralization of the tumour^{84,93,94,96–98} with possibly greater accuracy in CYP than in adults with Cushing disease^{75,96}. The first paediatric data were reported in a large NIH series, where the predictive value for lateralization was 75–80%⁶⁹. Similar values have been reported in other smaller series, with surgical concordance of adenoma site in 87–91% of patients^{75,96}. Another NIH study of BSIPSS in 94 paediatric patients reported only 58% concurrence of ACTH lateralization with site of adenoma at surgery, which increased to 70% (51 out of 73) after the exclusion of 18 centrally located and 4 bilateral lesions⁹⁸. Data from 2021 and 2022 confirm similar⁹⁵ or higher (87.5%) percentages⁹³. Based on these data, the GDG strengthened **R19.5**. Theoretically, false lateralization could occur due to altered pituitary blood flow⁹⁴ but, in adult patients with Cushing disease, despite asymmetric internal petrosal sinuses in 11 of 38 patients (39%), both symmetric (100%) and asymmetric (93%) petrosal sinuses gave good lateralization⁹⁹. Prolactin measurements during BSIPSS have been reported to be a useful marker of accurate catheterization, but two studies in adult Cushing disease suggested that prolactin-corrected ACTH concentrations did not substantially increase the accuracy of lateralization^{100,101} and this protocol has not been studied in CYP. Thus, no robust data exist to demonstrate, unequivocally, that lateralization of the tumour on BSIPSS improves surgical outcomes or preservation of residual pituitary function. However, observational studies of CYP suggest that improvements in rates of surgical cure might be related to the introduction of BSIPSS^{75,96}.

Treatment: pituitary surgery.

- **Part 2: R20.1. Offer selective adenomectomy as first-line treatment of choice for CYP with Cushing disease** (strong recommendation, moderate-quality evidence).
- **Part 2: R20.2. Consider repeat surgery for CYP with persistent or recurrent disease** (moderate recommendation, low-quality evidence, Delphi 100%).

Optimal treatment for CYP with Cushing disease is surgical resection by selective removal of the adenoma, performed by a surgeon experienced in paediatric transsphenoidal surgery¹⁰². Selective removal of the adenoma is now considered first-line therapy, maximizing the

potential for normal pituitary tissue to remain in situ^{77,102}. Low rates of post-operative hypopituitarism have been reported in several large studies in CYP^{103,104}. However, selective microadenomectomy can be technically very difficult in children and surgeon experience is a predictor of success^{102,105}.

Early post-operative remission in children was associated with identification of the adenoma at surgery, whilst long-term remission correlated with a younger age, a smaller adenoma, the absence of cavernous sinus or dural invasion, and a morning serum cortisol level of <1 µg/dl (<28 nmol/l) after surgery⁷⁴. Repeat surgery for paediatric Cushing disease resulted in early biochemical remission in 93% of 27 patients⁷⁴. However, recurrence of Cushing disease in adults has been reported up to 15 years after apparent surgical cure, even in individuals who had very low or undetectable post-operative cortisol levels^{106,107}. Therefore, lifelong follow-up for children treated for Cushing disease is essential.

Treatment: pituitary radiotherapy.

- **Part 2: R21. Offer radiotherapy to CYP with recurrent Cushing disease not amenable to curative surgery** (strong recommendation, moderate-quality evidence, Delphi 93%).

A proportion of paediatric patients who undergo transsphenoidal surgery for Cushing disease do not achieve post-operative cure or remission^{87,108,109}. The options for second-line therapy are repeat transsphenoidal surgery, radiotherapy, long-term medical therapy to control hypercortisolaemia and bilateral adrenalectomy. Focal external beam radiotherapy is more rapidly effective in children with Cushing disease than in adults^{108–110} and is often initiated 2–4 weeks after unsuccessful transsphenoidal surgery, when it is clear from circulating cortisol levels that a complete cure has not been achieved¹⁰².

Stereotactic radiotherapy, fractionated proton beam and gamma knife approaches have been proposed and utilized in adult Cushing disease. By contrast, over the past decade, fractionated proton beam radiotherapy with ongoing safety data monitoring has become the standard for focal cranial radiation in CYP with brain tumours generally¹¹¹; however, experience is limited, particularly in children^{112,113}. For fractionated treatment, a total radiation dose of 45 Gy in 25 fractions over 35 days seems effective^{108,114}. A gamma knife stereotactic radiosurgery study in CYP with Cushing disease used a maximum dose of 50 Gy (range, 33–80) and a margin dose of 25 Gy (range, 12.90–27.1)¹¹⁵. The rapid effectiveness of these treatments is shown in Table 3; however, long-term data on adverse late effects are needed.

Table 3 | Radiotherapy in CYP with Cushing disease

Ref.	Number of children included	Number of children cured	Timescale for cure
Jennings et al. (1977) ¹¹⁰	15	12	18 months (10 children within 9 months)
Thoren et al. (1986) ²⁶³	8	7	12 months
Storr et al. (2003) ¹⁰⁸	7	7	0.94 years (range 0.25–2.86 years)
Acharya et al. (2010) ⁹⁹	8	4	9–18 months
Shrivastava et al. (2019) ¹¹⁵	24	19	12 months (range, 2–42 months)

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Treatment: medical therapies.

- **Part 2: R22.1. Offer oral medical therapies, such as metyrapone or ketoconazole, to reduce the cortisol burden in CYP with Cushing disease awaiting definitive surgery or the effect of pituitary radiotherapy** (strong recommendation, low-quality evidence, Delphi 100%).
- **Part 2: R22.2. Due to their adverse effects, metyrapone and ketoconazole have a limited role in the long-term treatment of Cushing disease in CYP** (strong recommendation, low-quality evidence, Delphi 60% and GDG consensus).

Adrenal steroidogenesis inhibitors, such as metyrapone and ketoconazole, are well tolerated and can be highly effective at reducing cortisol levels, either alone or in combination¹⁰². In CYP, these drugs should be prescribed by experienced clinical teams with careful titration (metyrapone: 15 mg/kg every 4 h for 6 doses, alternatively 300 mg/m² every 4 h, usual dose 250–750 mg every 4 h; ketoconazole for patients over 12 years: initially 400–600 mg per day in 2–3 divided doses, increased to 800–1,200 mg per day until cortisol levels normalize and then reaching a maintenance dose of 400–800 mg per day in 2–3 divided doses). However, hypercortisolaemia control can be lost due to the hypersecretion of ACTH and treatment might not be effective in the long term. Common adverse effects of metyrapone include hirsutism, dizziness, arthralgia, fatigue, hypokalaemia and nausea⁸². Prolonged usage can lead to hyperandrogenism and advanced bone age in children. Ketoconazole is associated with hepatotoxicity and liver function should be monitored on therapy. Gastrointestinal disturbance and adrenal insufficiency are recognized adverse effects of both therapies.

The GDG refined **R22.2** after three rounds of an international Delphi consensus, in which only four individuals had the expertise to respond (voting details are provided in Part 1 (ref. 2)). Definitive treatments, which allow rapid normalization of subsequent growth and puberty, such as surgery and/or radiotherapy, are currently recommended for the management of paediatric Cushing disease, whilst medical therapies are currently limited⁸⁷ and not well studied. Nevertheless, given the rarity of this condition in CYP, the effect of these medical agents on growth, and the importance of normalizing childhood growth and puberty, the GDG felt that, in contrast to adults, where long-term medical therapy might have a place after other treatments have failed⁸², their use in CYP should be confined to normalizing cortisol levels in preparation for surgery or while awaiting a biochemical response to radiotherapy.

The effects and safety of osilodrostat, an inhibitor of 11 β -hydroxylase (CYP11B1), are currently being evaluated in a small phase II trial in CYP (NCT03708900)¹¹⁶, while the effects of cabergoline¹¹⁷, mifepristone and pasireotide in children are very limited or unknown. Temozolomide treatment has been used in an adult patient with childhood-onset Cushing disease (Table 1).

- **Part 2: R23. Offer intravenous etomidate treatment in CYP with Cushing disease in an intensive care setting only for the emergency control of severe cortisol excess** (strong recommendation, moderate-quality evidence, Delphi 100%).

Intravenous administration of etomidate has successfully controlled hypercortisolaemia in children with severe Cushing disease, who were either too unwell for transsphenoidal surgery or presented with acute unmanageable symptoms, for example, respiratory failure or severe psychosis¹¹⁸. To enable the accurate assessment of surgical response, oral therapies, if feasible, should be stopped before

surgery, depending on the half-life of the treatment; for example, for metyrapone, 48 h discontinuation should be sufficient.

Treatment: bilateral adrenalectomy.

- **Part 2: R24. Reserve bilateral adrenalectomy only for CYP with severe refractory Cushing disease or for life-threatening emergencies** (strong recommendation, low-quality evidence, Delphi 80% and GDG consensus).

Bilateral adrenalectomy remains a therapeutic option for Cushing disease in life-threatening situations or where transsphenoidal surgery is not possible or not available¹¹⁹. However, corticotroph tumour progression after bilateral adrenalectomy (Nelson syndrome, a potentially life-threatening secondary consequence of bilateral adrenalectomy, in which the pituitary adenoma continues to grow and secrete ACTH) seems to be more frequent in children than in adults and often requires pituitary surgery or radiotherapy^{120,121}.

Follow-up and surveillance.

- **Part 2: R25. Consider dynamic testing for GH deficiency soon after definitive therapy in all CYP in remission from Cushing disease who have not completed linear growth, and closely monitor pubertal progression to identify hypogonadotrophic hypogonadism** (moderate recommendation, moderate-quality evidence).
- **Part 2: R26. Offer prompt initiation of GH replacement to CYP in remission from Cushing disease who are proven GH deficient or fail to show catch-up growth** (strong recommendation, moderate-quality evidence, GDG consensus).
- **Part 2: R27. Consider BMD assessment prior to adult transition in patients at high risk for bone fragility** (weak recommendation, low-quality evidence, Delphi 86%).

Growth failure and resultant short stature are almost always present at diagnosis in paediatric patients with Cushing disease⁶⁹. Virilization from adrenal androgens can lead to pubarche and gonadotrophin-independent pubertal development, accelerating skeletal maturity and further compromising adult height potential¹²². After normalization of cortisol, CYP with growth retardation should be evaluated for GH deficiency with appropriate dynamic testing and receive early GH replacement therapy given the limited window of opportunity to normalize lean-to-adipose mass ratio, promote catch-up growth and attain their normal adult height^{84,123–127}. Given these data and the current clinical practice⁸⁶, a randomized controlled trial of early GH treatment in CYP in remission from Cushing disease is unlikely, and the GDG therefore strengthened **R26**. GH deficiency is well recognized following transsphenoidal surgery¹²⁴ and pituitary irradiation^{106,108,109}. The challenge is to reverse these adverse effects and maximize growth potential to achieve normal adult height and body composition. One approach is to routinely assess for the possibility of GH deficiency soon (up to 3 months)⁸⁶ after surgery or radiotherapy and substitute GH at conventional replacement doses (0.025 mg/kg per day), if deficient. Gonadotrophin-releasing hormone analogue therapy can be added to delay puberty and epiphyseal closure. Results demonstrate that this regimen usually enables adequate catch-up growth and adult height within the range of target height for the majority of patients^{106,128}. Combined treatment with GH and aromatase inhibitors to reduce bone maturation induced by oestradiol could also be a therapeutic alternative in pubertal

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patients¹²⁹. Normal body composition and BMD are more difficult to achieve^{128,130}. Many CYP with Cushing disease have disturbed timing or progression through puberty and require sex steroid replacement to enhance growth velocity and reverse the suppressant effect of cortisol excess on gonadotrophins¹²².

Pituitary function following remission.

- **Part 2: R28. To assess possible recurrence, offer to all CYP in remission from Cushing disease 6-monthly clinical examination, 24 h UFC, electrolytes and morning serum cortisol for at least 2 years and lifelong annual clinical assessment** (strong recommendation, low-quality evidence, Delphi 100%).

Pituitary hormone deficiencies are common after surgical or radiotherapeutic cure of Cushing disease^{106,109,131}. GH deficiency is the most frequent pituitary deficit (see previous section), although recovery in adult life has been reported^{106,132}. During long-term follow-up of patients in remission, gonadotrophin secretion is generally preserved, with normal or true gonadotrophin-dependent early puberty occurring, the latter being well recognized after cranial radiotherapy. After radiotherapy, additional anterior pituitary deficiencies (TSH and permanent ACTH deficits) can rarely develop, typically occurring in combination^{106,132}, with the risk of anterior pituitary hormone deficiencies potentially increasing over time⁸⁴.

Psychiatric and neurocognitive effects.

- **Part 2: R29. In addition to lifelong follow-up for endocrinopathies, consider long-term monitoring for psychiatric and neurocognitive co-morbidities following remission of Cushing disease in CYP** (moderate recommendation, moderate-quality evidence).

Studies of adult patients with Cushing syndrome have reported brain atrophy, cognitive impairment and psychological disease, most commonly depression, associated with excess endogenous circulating glucocorticoids¹³³. A study in 11 patients¹³⁴ also found considerable cerebral atrophy in children with Cushing disease at diagnosis but without IQ differences between patients and control individuals. Interestingly, an almost complete reversal occurred of the cerebral atrophy 1 year after cure with transphenoidal surgery but with a paradoxical decline in cognitive function. Another study shows notable improvements in severe psychiatric and behavioural symptoms after cure; however, long-term cognitive and memory problems were identified in ~25% of patients¹⁰⁶ and this observation is consistent with similar cognitive and memory deterioration in adults¹³⁵. Furthermore, the grey matter volume loss of active Cushing disease reverses 3 months after remission, except in the frontal and temporal lobes, strongly associated with cognition and memory¹³⁶. Children with Cushing disease experience impaired health-related quality of life, which is not fully resolved at 1 year post-treatment¹³⁷.

Relapse of Cushing disease.

- **Part 2: R30. In suspected recurrence of Cushing disease in CYP, offer the same stepwise investigations as at first presentation** (strong recommendation, low-quality evidence, GDG consensus).

Reported recurrence rates after remission of Cushing disease in CYP vary considerably, from 6% to 40%^{74,79,106,138}, and usually occur

within 5 years following definitive treatment. However, relapse can occur later¹⁰⁶, and the percentage of patients who relapse increases with time¹⁰⁷, suggesting that lifelong follow-up is required. This observation is consistent with data from long-term follow-up in adult patients with Cushing disease¹⁰⁷; therefore, the GDG strengthened **R30**.

GH excess: gigantism and acromegaly

Epidemiology and aetiology. A GH-secreting pituitary adenoma arising from somatotroph cells (somatotrophinoma) is the most common cause of acromegaly in CYP and is usually detectable on a contrast-enhanced pituitary MRI. Rarely, CYP with somatotroph hyperplasia due to McCune–Albright syndrome¹³⁹, Carney complex¹⁴⁰, X-linked acrogigantism¹⁴¹ or GH-releasing hormone-secreting tumours (usually associated with MEN1 syndrome in CYP^{142,143}) have been described. GH excess is rare in CYP. Annual incidence rates of GH excess are estimated to be 3–8 cases per million person-years among children aged 0–17 years old, while annual prevalence rates are estimated to be 29–37 patients per million children aged 0–17 years¹⁴⁴. Among surgically treated paediatric pituitary adenomas, 8.8%¹⁴⁵ to 21%¹⁴⁶ are associated with GH excess, with an age-related increase (6.4% at 0–11 years, 9.1% at 12–16 years and 11.8% at 18–19 years). While there are more male patients with gigantism overall^{145,147,148}, more girls (62%) than boys are diagnosed with gigantism in the CYP age group¹⁴⁹.

If GH excess occurs before epiphyseal fusion, the patient develops tall stature or gigantism. The definition of pituitary gigantism is arbitrary^{150,151} (Box 1). Gigantism can be exacerbated by delayed puberty due to gonadotrophin inhibition by co-secretion of prolactin from the adenoma, hyperprolactinaemia from stalk compression or mass effects causing gonadotrophin deficiency. Gigantism has an identifiable genetic basis in almost 50% of patients currently, so genetic assessment and testing are particularly important in CYP (see Part 1, Genetics section²).

Diagnosis: clinical features.

- **Part 2: R31. Offer testing for GH excess to CYP with excess height (more than 2 SDS) or consistently elevated height velocity and acromegalic features, with or without delayed or arrested puberty or family history of pituitary adenoma** (strong recommendation, moderate-quality evidence, Delphi 100%).

Box 1

Definitions of pituitary gigantism in CYP

The following definitions for pituitary gigantism have been used in various studies. GH–IGF1 excess associated with:

- Accelerated growth velocity >+2 SDS or
- Abnormally tall stature defined as +2 or +3 SDS above the country-specific, age-appropriate and sex-appropriate mean height or +2 SDS above the mid-parental height

CYP, children and young people under 19 years of age; GH, growth hormone; IGF1, insulin-like growth factor 1; SDS, standard deviation score.

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The most prominent clinical feature of GH excess in CYP before epiphyseal closure is increased growth velocity. Serial heights and photographs are useful for timing the onset of disease¹⁵².

Ethnicity-adjusted height of >2 SDS above age-adjusted and sex-adjusted normal values or 2 SDS above mid-parental target height, persistently elevated growth velocity (>2 SDS), acral enlargement, headache, visual field defects, pubertal delay, delayed bone age and joint pain are common signs of GH excess in CYP. Other features, typical of adult-onset GH excess, can also develop, including coarsened facial features, prognathism, dental malocclusion, teeth separation, frontal bossing, sweating, kyphosis, insulin resistance and occasionally secondary diabetes mellitus, hypertension, sleep disturbance, sleep apnoea, carpal tunnel syndrome, galactorrhoea, pituitary apoplexy, left ventricular hypertrophy and diastolic dysfunction^{105,145,149,153–160}, while joint hypermobility has occasionally been observed¹⁶¹.

X-linked acrogigantism is characterized by tall stature onset before 5 years (usually before 2 years) in all patients^{141,147,148,162,163} and disproportionately enlarged hands, feet, teeth separation, acanthosis nigricans, increased BMI and increased appetite^{141,162}. In McCune–Albright syndrome¹³⁹, early-onset (3 years onwards) GH excess, café-au-lait pigmentation, fibrous dysplasia and precocious puberty (or other hormone excess conditions) are prominent clinical features, while in Carney complex¹⁴⁰ typical skin pigmentation, myxomas, testicular and adrenal disease are characteristic, in addition to other pleiotropic manifestations.

Diagnosis: biochemical investigations.

- **Part 2: R32. A diagnosis of GH excess is supported by an elevated serum IGF1 level in relation to the age-adjusted, sex-adjusted and Tanner stage-matched normal range** (strong recommendation, moderate-quality evidence).

Elevated Tanner stage-matched and age-adjusted circulating serum IGF1 concentration is a reliable marker for GH excess, but marginal or mild elevation in adolescence, during the peak growth spurt, needs cautious interpretation. IGF1 values might be falsely normal or low in CYP with a GH-secreting adenoma and concurrent severe hypothyroidism, malnutrition or severe infection^{164–166}, or might be falsely elevated in CYP without GH-secreting adenoma in poorly controlled diabetes mellitus, hepatic and/or renal failure. Oral oestrogens can also confound detection accuracy by reducing IGF1 generation by the liver¹⁶⁷, whilst local Tanner stage-matched, sex-matched and age-matched normal ranges for the IGF1 assay must be established to avoid notable inter-assay variability¹⁶⁸.

- **Part 2: R33. Consider the diagnosis of GH excess in CYP whose serum GH levels fail to suppress below 1 µg/l in response to an oral glucose load (cut-off based on adult population); however, complete suppression of GH can be difficult to achieve in normal adolescence** (moderate recommendation, moderate-quality evidence, Delphi 100%).

Algorithms for assessing GH excess in CYP are based on those established in adult patients^{150,169}. In healthy adults, serum levels of GH should be suppressed after an oral glucose load: cut-off GH nadirs are 1 µg/l or, using sensitive GH assays, 0.4 µg/l (refs. 170,171). GH nadir after glucose load in CYP undergoing puberty is sex and pubertal stage specific: the highest levels were observed in mid-puberty (Tanner stage 2–3) in girls more than in boys (mean ± 2 SD GH nadir after 2.35 g/kg, maximum 100 g glucose load: in girls 0.22 µg/l ± 0.03–1.57,

in boys 0.21 µg/l ± 0.09–0.48)¹⁷². However, an earlier study reported a lack of GH suppression (defined as <1 µg/l following 1.75 g/kg, maximum 75 g glucose load) in approximately 30% of children with tall stature (+3.1 ± 0.8 height SDS)¹⁷³, rendering the diagnosis of GH excess by these criteria challenging in this patient group. An elevated serum IGF1 concentration, with apparently normal serum GH values, might reflect early disease¹⁷⁴. We suggest that biochemical results should be interpreted within a clinical assessment of phenotype that includes height velocity, pubertal stage and bone age.

From adult data, serum IGF1 levels correlate linearly with GH levels only up to 4 µg/l and plateau at about 10 µg/l (refs. 175,176). Baseline GH levels are predictive of surgical outcome (higher GH levels predict a lower likelihood of remission after surgery)¹⁷⁷ and are key to monitoring the hormone-producing activity of the adenoma¹⁷⁶. Thus, both GH and IGF1 should be monitored at baseline and during follow-up in CYP with GH excess.

- **Part 2: R34. In CYP with GH excess, offer dynamic pituitary assessment of possible hypofunction and hyperfunction of other anterior pituitary hormones** (strong recommendation, high-quality evidence).

Hypofunction of other pituitary hormones caused by tumour mass compression or prolactin co-secretion has been noted in 25–35% of patients with somatotrophinomas^{105,149}. Hypogonadism and consequent bone age delay are particularly relevant to GH excess as they increase the time window for longitudinal growth. Co-secretion of other anterior pituitary hormones is common in both adults and CYP with GH excess. A review of 137 published cases of CYP with acromegaly found that 65% had hyperprolactinaemia at presentation, while half showed both GH and prolactin immunostaining in the adenoma tissue¹⁰⁵. Furthermore, 34–36% of CYP with gigantism had prolactin co-secretion in two large cohorts^{147,149}. TSH can also be co-secreted by somatotrophinomas but less frequently than prolactin. Patients require assessment and treatment of complications of GH excess such as glucose intolerance and hypertension.

- **Part 2: R35.1. Pituitary adenomas can be associated with syndromic diseases; offer clinical evaluation for associated syndromic causes of somatotrophinomas to CYP with GH excess** (strong recommendation, low-quality evidence, Delphi 93%).
- **Part 2: R35.2. Offer biochemical screening for pituitary hormone excess to all CYP with Carney complex, McCune–Albright syndrome, and patients with MEN1 or MEN1-like disease** (strong recommendation, high-quality evidence, Delphi 100%).

Several syndromes, including McCune–Albright syndrome, Carney complex, MEN1 or, rarely, MEN1-like diseases (MEN4, MEN5) and pheochromocytoma–paraganglioma-related pituitary disease² can be associated with childhood-onset pituitary adenomas, including GH excess. The biochemical diagnosis of GH excess in the context of such syndromes is identical to sporadic cases of acromegaly^{139,141,147,149,151,178,179}. In CYP with Carney complex, biochemical alterations of the GH axis without overt clinical acromegaly can often be observed. GH-releasing hormone-secreting pancreatic tumours should also be considered as a cause of GH excess in CYP with MEN1 syndrome^{142,143}. GH hypersecretion, usually transient, occurs in 10% of infants and children with neurofibromatosis type 1 and optic pathway hypothalamic gliomas¹⁸⁰; some of these patients have been treated temporarily with somatostatin analogues or pegvisomant^{180–182}. GH excess is probably a result of hypothalamic dysregulation of the GH axis. Data on the aetiology of

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temporary GH excess in CYP with optic glioma, therapeutic interventions, the effects of GH excess on glioma growth itself and the observed evolution from GH excess to GH deficiency remain unexplained and poorly understood. The GDG suggested the establishment of a collaborative neuroendocrine oncology research study to gather evidence for these questions.

Treatment: pituitary surgery.

- **Part 2: R36. Offer surgery to reduce GH burden as the treatment of choice in the majority of CYP with GH-secreting adenomas, even where surgical cure is unlikely** (strong recommendation, moderate-quality evidence, Delphi 93%).
- **Part 2: R37.1. Consider pre-operative medical therapy with somatostatin analogues and/or GH receptor antagonists to rapidly control signs and symptoms and support perioperative airway management** (weak recommendation, low-quality evidence, Delphi 75%, GDG consensus).
- **Part 2: R37.2. Consider pre-operative medical therapy with somatostatin analogues and/or GH receptor antagonists to reduce height velocity, particularly if pituitary surgery is delayed** (weak recommendation, low-quality evidence, Delphi 100%).

The goals of any therapy for GH excess include normalization of growth velocity, prevention of excessive height and suppression of IGF1 into the normal range; adenoma shrinkage and visual preservation with potential restoration of other hormone function; and prevention of long-term morbidity. Surgery performed by an experienced neurosurgeon offers the prospect of complete remission and is therefore recommended as the first-line treatment for CYP with gigantism or acromegaly^{159,183–185}, as for adults^{150,186–188}. Even if remission is thought to be unlikely following surgery, tumour debulking can reduce the circulating GH burden and facilitate more successful medical therapy and/or radiotherapy. In an experienced pituitary neurosurgical unit between 2003 and 2016, the surgical success rate in 17 CYP with GH excess was ~50%¹⁸⁹. Re-operation could be considered in patients with notable residual tumour and inadequate response to somatostatin analogue therapy or if considerable tumour re-growth occurs.

A role for somatostatin analogues in safely reducing pre-operative GH levels in adults with macroadenomas, with favourable effects on short-term cure, has been suggested by a systematic review, although long-term outcomes require further study¹⁹⁰. Patients with severe cardiac and/or respiratory complications from GH excess might benefit from pre-operative reduction of GH levels. Pre-operatively, patients should be assessed for enlargement of the upper airway soft-tissue structures, including the tongue and epiglottis as well as jaw deformity, to prevent perioperative airway difficulties^{191,192}.

In the absence of prospective trials, factors predicting outcome of surgery in CYP with gigantism or acromegaly are limited, although retrospective studies and case reports suggest that a rapid reduction in growth velocity might be a favourable predictor^{105,149,153}.

In patients with genetic causes of acromegaly, the whole gland could be affected (typically in McCune–Albright syndrome, Carney complex and X-linked acrogigantism). Selective adenomectomy¹⁹³, radical surgery¹⁶² or hypophysectomy^{139,194} have all been described as surgical approaches in these conditions.

Treatment: medical therapies.

- **Part 2: R38. Offer monotherapy or combination medical therapy in CYP with GH excess and post-operative residual disease** (strong recommendation, moderate-quality evidence, Delphi 100%).
- **Part 2: R39. Assess efficacy of medical treatment in CYP with GH excess by both auxological measurements and serum levels of GH and IGF1** (strong recommendation, moderate-quality evidence, Delphi 100%).

Studies of medical therapy in patients with post-operative residual GH excess have been conducted primarily in adults, although case series and case reports also confirm their utility in CYP^{105,139,147,149,153–155,160,162,195}. Adjunctive post-operative long-acting somatostatin analogues reduce serum concentrations of GH to 'safe' levels and normalize serum levels of IGF1 in approximately 35% of adult patients with GH-secreting adenoma¹⁹⁶ with less predictable tumour shrinkage in up to 40%. Retrospective studies have also confirmed the tumour-shrinking effect of somatostatin analogues in adolescents with gigantism^{139,147,149,153,162}. While no formal dosing recommendation exists for children, the dose of long-acting somatostatin analogues can be titrated to normalize IGF1 levels. In adults, the starting monthly dose of lanreotide autogel is 60 mg and of octreotide-LAR 10 mg whereas, for very young children, the dose needs to be individualized. In CYP with acromegaly, numerous reports of the failure of somatostatin analogues to normalize IGF1, satisfactorily reduce GH levels or initiate tumour shrinkage suggest that treatment resistance is more common in CYP than in adults^{147,149,156,160,162}. CYP with *AIP* or *GPR101* mutations have more aggressive disease and are less responsive to first-generation somatostatin analogue therapy^{147,149,162}, whereas the response to medical treatment in patients with Carney complex and McCune–Albright syndrome is more promising¹³⁹. The second-generation somatostatin analogue pasireotide has also been used in adult patients with childhood-onset GH excess, with mixed results^{197,198}.

Regardless of the presence or absence of prolactin co-secretion, dopamine agonists (primarily cabergoline) can be used alone in CYP with mild GH excess, co-administered with somatostatin analogues where GH hypersecretion is not adequately controlled, or substituted for the latter where poorly tolerated^{199–202}. However, the GH-lowering effect of dopamine agonists is only modest^{105,155,156,160} and doses required in acromegaly are often high (see **R11** on cabergoline use).

Several studies and case reports have been published of the GH receptor antagonist pegvisomant normalizing serum IGF1 levels in CYP with acromegaly or gigantism when used in adequate doses^{105,139,147,149,154,160,162,203–205}. This medication can suppress growth velocity, a clinical priority in CYP with gigantism, suggesting that earlier introduction could be beneficial. The dose of pegvisomant should be started at 10 mg daily and titrated until serum IGF1 levels normalize. Patients treated with pegvisomant require only IGF1 measurements during follow-up. As pegvisomant has no direct pituitary action, careful radiological tumour monitoring is required. Tumour expansion described during pegvisomant treatment^{105,152} might represent the natural history of the tumour rather than being secondary to reduced negative feedback from reductions in IGF1. Combination therapy with pegvisomant and somatostatin analogues has also been successfully tried in CYP with GH excess^{149,203–205}. Temozolomide therapy has been reported in a CYP patient with a GH-secreting tumour and another with a GH–prolactin co-secreting tumour (Table 1).

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Treatment: pituitary radiotherapy.

- **Part 2: R40.1. Offer pituitary radiotherapy to CYP with GH-secreting adenoma and uncontrolled tumour growth and incomplete surgical and medical response, except for patients with skull base fibrous dysplasia** (strong recommendation, low-quality evidence, Delphi 75%).
- **Part 2: R40.2. After radiotherapy in CYP with GH-secreting adenoma, offer intermittent dose reduction or withdrawal of medical therapy to assess radiation efficacy on GH hypersecretion** (strong recommendation, low-quality evidence, Delphi 100%).

Radiotherapy might be useful for CYP with gigantism or acromegaly who have post-operative residual tumour bulk and in whom surgery and medical therapy have failed to control GH-IGF1 levels (see Part 1, Radiotherapy section²). Conventional conformal, stereotactic and proton beam radiotherapy have all been used successfully to control tumour growth and lower serum GH levels in CYP^{105,115,149,152}, although adult data indicate that it might take up to 10 years for radiotherapy to be fully effective in suppressing GH²⁰⁶. Therefore, medical therapy is probably required, at least as a temporary measure, in CYP who receive pituitary radiotherapy. Intermittent interruption of medical therapy for 1–3 months (to allow clearance of the drug) might be required to allow biochemical assessment of the efficacy of radiotherapy. After radiotherapy, at first 6-monthly and later 12-monthly follow-ups should monitor the patient for the development of hypopituitarism or recurrence.

GH excess in the context of McCune–Albright syndrome is typically accompanied by fibrous dysplasia of the craniofacial bones. In one study of patients with this syndrome, 6 of 112 patients, 3 of whom had prior pituitary irradiation, developed a skull base sarcoma¹³⁹. While a causal link to pituitary radiation is not proven, the risk of sarcomatous transformation is higher in McCune–Albright syndrome than in isolated fibrous dysplasia²⁰⁷. Almost half of the patients with McCune–Albright syndrome are CYP (46%) at the time of diagnosis of GH excess. Given the uncertain transforming effect of GH-IGF1 on dysplastic bone^{208–210}, alternative medical and surgical treatments, rather than radiotherapy, might be considered in this condition to control GH excess and preserve vision.

Follow-up and surveillance.

- **Part 2: R41. There is no evidence to suggest that CYP with GH excess require routine screening for colonic polyps during childhood** (strong recommendation, low-quality evidence, Delphi 92%).
- **Part 2: R42. Consider avoiding corrective surgery for jaw, spine and joint abnormalities in CYP with gigantism or acromegaly until GH and IGF1 are at safe levels** (weak recommendation, low-quality evidence, GDG consensus).

While good evidence indicates an increased risk of colonic polyps in adults with acromegaly, such data are lacking in CYP, and the Delphi panel returned a 92% consensus against routine colonoscopy in CYP with GH excess.

Bone overgrowth induced by GH excess does not reverse with successful treatment of acromegaly and, while jaw and dental deformity can be troublesome, corrective surgery should be deferred until GH-IGF1 levels are adequately controlled and jaw changes have stabilized²¹¹.

Late recurrence of GH excess, up to 10 years after apparent remission, has been described²¹². Thus, long-term annual serum

IGF1 monitoring is necessary with repeat biochemical (oral glucose tolerance tests) and radiological (MRI) assessment if recurrence is suspected. Due to the high rates of persistent post-operative disease in CYP with GH excess, many will receive long-term medical therapy or radiotherapy. Monitoring of their efficacy and adverse effects, together with management of secondary pituitary deficits and medical complications, requires experienced specialist support within a dedicated pituitary multidisciplinary team. Close interaction between paediatric and adult endocrine services is required to coordinate long-term medical care and the transition to adult services.

TSHoma

Epidemiology. TSH-secreting adenomas are extremely rare in children and the literature is limited to case reports. In adults with TSHoma, the incidence has been estimated to be 0.26 cases per million per year; co-secretion of other pituitary hormones occurs in 25–42% of cases²¹³. Co-secretion of GH was also noted in an adolescent with gigantism and secondary hyperthyroidism²¹⁴.

Diagnosis.

- **Part 2: R43. Consider assessment for TSHoma in CYP with hyperthyroxinaemia and an unsuppressed TSH, particularly in the presence of clinical thyrotoxicosis and neurological or visual deterioration** (moderate recommendation, moderate-quality evidence).
- **Part 2: R44. Consider assessment for thyroid hormone resistance and euthyroid hyperthyroxinaemia in the differential diagnosis of TSHoma in CYP** (moderate recommendation, low-quality evidence, Delphi 100%).

Patients with TSHomas present with elevated thyroid hormone levels and unsuppressed TSH, differentiating them from primary hyperthyroidism. Usually, children have symptoms of hyperthyroidism but some are reported to be asymptomatic²¹⁵. Most TSHomas reported in children have presented as macroadenomas; thus, mass effects can cause optic nerve compression and deficiency of other pituitary hormones^{215–217}. Following the diagnosis of a TSHoma, investigation for pituitary hypofunction and hyperfunction with baseline and dynamic pituitary testing is recommended. Prompt treatment of any cortisol, GH or sex steroid deficiency is recommended to optimize surgical, growth and well-being outcomes.

An unsuppressed TSH in the setting of hyperthyroxinaemia can occur due to assay interference and due to genetic causes of euthyroid hyperthyroxinaemia such as familial dysalbuminaemic hyperthyroxinaemia and resistance to thyroid hormone. Of note, a case of TSH-secreting microadenoma and resistance to thyroid hormone in a child has been reported²¹⁸.

Treatment.

- **Part 2: R45. Consider pre-operative somatostatin analogue treatment to normalize thyroid function in CYP with confirmed TSHoma** (moderate recommendation, low-quality evidence, Delphi 73% and GDG consensus).
- **Part 2: R46. Offer transsphenoidal surgery as the treatment of choice in CYP with TSHomas** (moderate recommendation, low-quality evidence, Delphi 93%).

In adults with TSHoma, somatostatin analogues improve the symptoms of thyrotoxicosis, decrease serum-free T₄ and TSH concentrations,

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and can cause pre-operative tumour shrinkage²¹⁹. In one paediatric patient, somatostatin analogues reduced thyroid hormone levels and tumour size, thereby postponing definitive surgery^{215,220}. Out of 44 patients aged 11–73 years on pre-operative somatostatin analogue treatment, 84% had normalization of thyroid function levels and 61% showed tumour shrinkage²²¹.

Surgery offers a potentially definitive cure. Even partial tumour debulking can be worthwhile in reducing TSH and free T₄ levels, decompressing the optic apparatus or improving the effectiveness of subsequent medical therapy^{216,217,221,222}.

Follow-up and surveillance.

- **Part 2: R47. Disease monitoring with regular thyroid function tests and regular MRI surveillance, similar to the protocol described for NFPA, is suggested in CYP with confirmed TSHomas** (weak recommendation, low-quality evidence, GDG consensus).

There is no evidence base to inform a surveillance schedule in CYP with TSHoma and the natural history of disease progression is unknown. We therefore suggest a pragmatic approach to biochemical and MRI surveillance to detect secondary hyperthyroidism and to identify those with rapid tumour progression or recurrence early, even if asymptomatic. We suggest monthly thyroid function tests for 6 months after initial treatment but, given the uncertainty regarding tumour progression, biochemical and MRI surveillance should be individualized.

- **Part 2: R48. Consider pituitary radiotherapy in CYP with post-operative tumour remnant and resistance to medical therapy or relapsing TSHomas if re-operation is not an option** (moderate recommendation, low-quality evidence, Delphi 92% and GDG consensus).

If surgery is unsuccessful or contraindicated and the paediatric patient with TSHoma fails to achieve normal thyroid function or shows tumour growth despite somatostatin analogue therapy, radiotherapy could be considered^{222,223} (see Part 1, Radiotherapy section²). After radiotherapy, at first 6-monthly and later 12-monthly follow-ups should monitor for the development of hypopituitarism or recurrence.

Incidentalomas and NFPA

Epidemiology and aetiology. Clinically non-secreting pituitary adenomas account for 4–6% of all paediatric pituitary adenomas^{224,225} and for 10% of cases in a surgical series²²⁰, in stark difference to adult pituitary patients where NFPA account for 15–30% of clinically relevant pituitary adenomas and 50–60% of cases in a surgical series²²⁶. Depending on case selection criteria, NFPA represent 13–56% of incidentally discovered pituitary lesions (incidentalomas) in large retrospective radiological series of CYP^{227–229}. NFPA also represent 25% of *MEN1*-associated pituitary lesions in CYP, and small lesions detected by screening can be seen in patients with *AIP* variants^{151,230,231}. NFPA in CYP usually present in the second decade of life, with increasing incidence thereafter^{9,228,230,232}. There is no consistent male or female predisposition^{9,230,232–236}, although a 2019 surgical series in CYP reported a slight female predominance²²⁰.

Presentation. CYP with NFPA, by definition, do not have features of a hypersecretory syndrome. Symptomatic NFPA are macroadenomas, whereas microadenomas are usually discovered as a coincidental

finding on an MRI scan. The clinical features of macroadenomas at presentation result from mass effects on surrounding structures. These include headache, visual field defects, pituitary apoplexy (probably more common than in adult NFPA^{235,236}) with or without mild prolactin elevation, or hypopituitarism manifesting as secondary amenorrhoea, delayed puberty, hypothyroidism, hypocortisolaemia, growth failure and/or hyperprolactinaemia^{9,220,228,230,232–234}. Headache, visual impairment and hypogonadism were the most common presenting features in a surgical series in CYP²³⁶. Immunohistochemistry for pituitary hormones in 14 NFPA, from CYP aged 12–19 years, revealed 6 silent plurihormonal tumours, 3 silent lactotrophs, 1 each of a silent gonadotroph and a corticotroph, and 3 hormone-negative tumours (transcription factor staining not reported)²³⁶. These proportions are different from those in adult patients, where silent gonadotrophinomas represent the majority of NFPA. Non-functioning pituitary microadenomas do not usually cause hypopituitarism or visual abnormalities²²⁷.

Diagnosis and investigation.

- **Part 2: R49. Identification of a pituitary incidentaloma or NFPA requires exclusion of clinical or laboratory evidence of pituitary hormone hypersecretion (except mild hyperprolactinaemia from pituitary stalk disruption); exclusion of elevation of serum level of α -fetoprotein (AFP) and β -human chorionic gonadotrophin (β HCG) and the absence of other suprasellar and intracranial lesions** (strong recommendation, low-quality evidence, Delphi 100%).
- **Part 2: R50. Offer baseline and dynamic evaluation of pituitary function to assess hypopituitarism and exclude hormone excess in all CYP with suspected NFPA** (strong recommendation, low-quality evidence, Delphi 100%).

If a pituitary mass is suspected on MRI, baseline and dynamic pituitary investigations should be undertaken as indicated clinically to confirm the absence of pituitary hormone excess from a functioning adenoma or the presence of hormone deficiency. The MRI appearance of a small Rathke cleft cyst or pars intermedia cyst can present a differential diagnosis for a clinically non-functioning microadenoma. Stalk compression from macroadenomas, or rarely microadenomas²³⁷, can cause mild hyperprolactinaemia, usually below 2,000 mU/l (94 μ g/l)¹⁹.

Intracranial germ-cell tumours, more common in the adolescent age group than NFPA, can present with similar MRI appearances^{238,239}. AFP and β HCG (markers of germ-cell tumours) should be measured in the serum and, if clinically or radiologically indicated, also in the cerebrospinal fluid²⁴⁰.

Hypopituitarism is common in children with symptomatic non-functioning pituitary macroadenoma^{9,220,228,230,232,233}. Basal and dynamic pituitary assessment is recommended following diagnosis of an NFPA together with prompt replacement therapy of any cortisol, thyroid hormone, sex steroid and GH deficiency to optimize surgical, growth and well-being outcomes. Arginine vasopressin deficiency (also known as central diabetes insipidus) is an extremely infrequent finding at diagnosis of an NFPA unless the tumour has undergone apoplexy^{9,220,228,230,232,233}, and its presence strongly suggests an alternative diagnosis such as a craniopharyngioma, histiocytosis or germ-cell tumour^{111,240}.

Visual deterioration is a well-described presentation of NFPA in CYP^{9,228,232,233} and an urgent indication for surgery to decompress the optic apparatus if sight is threatened. Thus, early assessment of visual acuity and visual fields is mandated¹¹¹.

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- **Part 2: R51. There is no evidence to suggest a benefit of routine diagnostic biopsy in CYP of incidental pituitary masses whose radiological features are typical of a pituitary adenoma with no other intracranial abnormalities** (strong recommendation, low-quality evidence, GDG consensus).

A pituitary biopsy is not required in clinically non-functioning lesions with MRI appearance strongly suggestive of a pituitary adenoma and no other intracranial abnormality, which remain asymptomatic, without visual or pituitary function compromise, unchanged in size over time, and negative for serum β HCG and AFP. In these patients, the risk of a biopsy harming pituitary function is greater than the likelihood of achieving a 'tissue' diagnosis or a diagnosis requiring alternative management²⁴⁰. MRI surveillance should be instituted if the optic apparatus is not compressed.

Treatment.

- **Part 2: R52. Offer treatment to CYP with NFPA only if the patient is symptomatic (hypopituitarism), the visual pathway is threatened or there is interval tumour growth on MRI** (strong recommendation, low-quality evidence, Delphi 94%).
- **Part 2: R53. Offer transsphenoidal surgery as the treatment of choice in CYP with NFPA needing surgical intervention** (strong recommendation, high-quality evidence, Delphi 100%).

The majority of non-functioning microadenomas in CYP are asymptomatic and detected incidentally or as part of a screening programme, with little data on their frequency, natural history or complication rates. By contrast, macroadenomas enlarge in over 40% of adult patients at 5 years²⁴¹, while there are no equivalent data in CYP. Surgical removal of a growing macroadenoma is an effective intervention to prevent further damage to surrounding tissues and cranial nerves^{9,228,229,230,232–234}.

- **Part 2: R54. There is insufficient evidence to recommend medical therapy, including cabergoline, in CYP with NFPA** (moderate recommendation, low-quality evidence, Delphi 80%).

No data are available to suggest that medical therapy (for example, dopamine agonists or somatostatin analogues) can induce tumour shrinkage in CYP with NFPA, and these medications are not recommended in adult guidelines. Some inconsistent reports of effectiveness in adults with NFPA receiving somatostatin analogues²⁴² or dopamine agonists^{243–245} suggest that dopamine agonists might reduce tumour growth in some recurrent cases^{244,245}.

- **Part 2: R55. Consider second surgery or radiotherapy for CYP with recurrent or symptomatic NFPA** (moderate recommendation, low-quality evidence, Delphi 94% and GDG consensus).

Both surgery and radiotherapy have been used to treat recurrent NFPA^{9,146,246–248} and the optimal treatment modality for CYP is not clear. The specialist age-appropriate pituitary multidisciplinary team should make an individual treatment recommendation, accounting for tumour location and any hypothalamic or cavernous sinus invasion, ease of surgery, and the age of the child. Local tumour control after radiotherapy for NFPA in CYP ranges from 80% to 97%²⁴⁹. After radiotherapy, at first 6-monthly and later 12-monthly follow-ups should monitor for the potential development of hypopituitarism or recurrence. Temozolomide treatment was reported for one childhood-onset

hormone-negative tumour (Table 1). Based on results from adults²⁵⁰ and the above data, the GDG strengthened R55.

Follow-up and surveillance.

- **Part 2: R56. Following NFPA surgery in CYP, offer post-operative MRI surveillance at a minimum of 3 and 6 months, and 1, 2, 3 and 5 years after surgery** (strong recommendation, low-quality evidence, Delphi 89%).
- **Part 2: R57. In CYP with incidental NFPA, offer MRI surveillance for microincidentalomas: at 12 months and, if stable, at 1–2 year intervals for 3 years with gradual reduction thereafter; for macroincidentalomas: at 6 months and, if stable, annually for 3 years with gradual reduction thereafter** (strong recommendation, low-quality evidence, Delphi 100%).

Although evidence in CYP following pituitary surgery for NFPA is lacking, data in adults show a recurrence rate of non-irradiated operated pituitary adenomas of up to 38% of those with a visible residuum on post-operative MRI over a follow-up period of 5 years. A post-operative MRI at 3 months will assess the extent of residual tumour, with a further scan at 6 months to assess for recurrence and, if stable, a gradual reduction in the annual scanning frequency as above, with screening continuing lifelong^{251,252}.

The natural history of NFPA in CYP is unknown and could vary. In adults, macroadenomas tend to have higher growth rates than microadenomas (12.5 macroadenomas grow over 100 patient-years versus 3.3 microadenomas)²⁵³. Microadenomas seem to follow a benign course in children²²⁷, and follow-up can be gradually reduced and stopped^{227–229}. For macroadenomas, we recommend lifelong clinical surveillance (as in adults), with an individualized radiological (MRI) surveillance strategy to identify those with rapid tumour progression or post-operative recurrence early, even if asymptomatic.

Visual surveillance in patients with either operated or incidental macroadenomas should be adjusted to their individual needs. Retrospective pituitary imaging studies in CYP highlight the need to recognize that physiological pubertal pituitary hypertrophy can occur and draw attention to the lack of progression of microadenomas^{227–229}. As more comprehensive data on incidentalomas or non-gonadotroph silent tumours in CYP are lacking, we suggest following adult guidelines for follow-up as above^{251,252}. While the radiological surveillance of stable non-functioning microadenomas can cease after 1–3 years, macroadenomas need to be followed in the long term^{251,252}. We suggest a decreasing scanning interval for adenomas proven stable over the years. Concerns regarding repeated gadolinium administration over prolonged imaging follow-up are discussed in the Radiology section of Part 1 (ref. 2).

Gonadotrophinomas in CYP

Functioning gonadotroph adenomas are exceedingly rare in CYP. They can result in isosexual precocious puberty or ovarian hyperstimulation syndrome^{254,255}. Germ-cell tumours secreting β HCG can represent a differential diagnostic dilemma as symptoms can overlap with those of functioning gonadotrophinomas. Silent gonadotrophinomas are discussed above.

Conclusions

Children and young people are at a disadvantage compared with adults in accessing age-appropriate, highly specialized pituitary care for pituitary adenomas. The incidence, type, symptomatology, aggressiveness and aetiology of their disease not only differ from that of adults

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but their impact, treatment choice and timely remediation can carry far greater consequences on the developing body and brain as well as on secondary health, intellectual, visual and psychosocial adult outcomes. These can limit the quality of adult relationships and represent challenges for parenting and employment over a long lifespan. The purpose of these recommendations – the first comprehensive consensus guideline of its kind – is to equalize and optimize health care for CYP with pituitary adenomas, raise awareness of diagnostic and treatment delays with potentially life-limiting complications, and improve access to modern pituitary-specific specialist centres, novel therapies, research and monitoring of long-term health and well-being outcomes. The latter must encompass the transition to adult services; closer integration of paediatric and adult pituitary services and data sets can only benefit CYP.

Key developments have occurred over the past few years regarding the diagnosis and treatment of pituitary adenomas – genetic testing, intraoperative MRI and the introduction of pegvisomant are just a few examples. Due to the rarity of pituitary adenomas in CYP, data have necessarily been gathered from retrospective studies, case series, anecdotal case reports and experience from the adult population for most of the management recommendations we present here and in Part 1 (ref. 2) (Supplementary Table 1). Facilitating referral and service pathways so that CYP can access centralized speciality pituitary multidisciplinary advisory panels across the age range and establishing national and international data registries of morbidity outcomes are in the best interest of CYP and vital to informing future best practice recommendations and to improving the long-term quality of life of these children and young people.

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