Consensus on diagnosis and management of Cushing's disease: a guideline update

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Review

Consensus on diagnosis and management of Cushing's disease: a guideline update

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Introduction

- Cushing's disease requires accurate diagnosis, careful treatment selection, and long-term management to optimize patient outcomes. The Pituitary Society convened a consensus workshop comprising more than 50 academic researchers and clinical experts to discuss the application of recent evidence to clinical practice.

Introduction

- Cushing's disease, the most common cause of endogenous cushing's syndrome, is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary tumour.
- Optimal patient outcomes require accurate diagnosis, careful treatment selection, and management of the disease and its associated comorbidities to optimize patient outcomes. Notably, compared with patients with adrenal causes of cushing's syndrome, longterm quality of life is worse for patients with cushing's disease.

Introduction

- Workshop in October, 2020, to discuss management of Cushing's disease, and Provide recommendations for screening, diagnosis, and treatment and its side effects.

Methods

- Workshop cochairs and steering committee members identified discrete topics related to Cushing's disease diagnosis, complications, and treatment to be addressed.

Laboratory tests

1. LNSC
2. DST
3. LDDT
4. UFC

- In this setting, sensitivity of all tests is higher than 90%; the highest sensitivity rates are obtained with DST and LNSC and the lowest with UFC. Specificity is somewhat lower than sensitivity, with LNSC being the most specific and DST and UFC the least specific.

LNSC

- At least two or three LNSC tests are recommended. Patients with mild Cushing's syndrome may have LNSC just above the upper limit of normal (ULN). Sampling saliva at usual bedtime rather than at midnight could decrease false-positive results.

LNSC

- Specificity is higher when using mass spectrometry while immunoassay has higher sensitivity for Cushing's syndrome. Multiple, periodic, sequential lnsc tests are particularly useful for the longitudinal surveillance needed in distinguishing patients with cyclic Cushing's syndrome who exhibit weeks to months of normal cortisol secretion interspersed with episodes of cortisol excess. By contrast, LNSC should not be done in patients with disruption of the normal day and night cycle, such as nightshift workers.

Overnight 1-mg DST

- Cortisol concentration of less than 1·8 μg/dl (50 nmol/L)

- Values higher than 5 μg/dL

Overnight 1-mg DST

- **False positive results:**

- Rapid absorption or malabsorption of dexamethasone due to increased gut transit time, chronic diarrhoea, or coeliac disease; from concomitant treatment with CYP3A4 inducers (eg, phenobarbital, carbamazepine, St John's wort); and from increased corticosteroid binding globulin (CBG) concentrations caused by oral oestrogens, pregnancy or chronic active hepatitis.

- Measuring dexamethasone concomitantly with cortisol, using laboratory specific ranges of expected values, can reduce the risk for false positive results.

Overnight 1-mg DST

- **False-negative results:**

- Inhibition of dexamethasone metabolism by concomitant medications such as fluoxetine, cimetidine, or diltiazem
- Decreased CBG and albumin
- Nephrotic syndrome

UFC

- At least two or three
- Independent of CBG changes and dexamethasone metabolism or compliance.
- Relies on accurate collection by the patient
- Sex, BMI, age, very high or low urinary volume, and sodium intake can all influence UFC concentrations
- Other screening tests such as LNSC might be preferred for patients with renal impairment (creatinine clearance <60 mL/min) or clinically significant polyuria (>5 L/24 h)

Testing for non-neoplastic hypercortisolism (pseudo-Cushing's syndrome)

- The combined LDDT–corticotrophin-releasing hormone (CRH; DexCRH) test, LDDT, or the desmopressin test might be able to distinguish between ACTH dependent Cushing's syndrome and pseudo-Cushing's syndrome.

Clinical considerations & recommendations for laboratory tests

- We recommend starting with UFC, LNSC, DST, or a combination (high quality, strong recommendation) depending on local availability; multiple LNSCs might be easier for the patient to complete (high quality, strong recommendation).
- If an adrenal tumour is suspected, we recommend starting with DST (moderate quality, strong recommendation) and only using LNSC if cortisone concentrations can be also reported (moderate quality, strong recommendation
- DST might be the preferred test for shift workers and patients with disrupted circadian rhythm due to uneven sleep schedules, but might not be reliable in women treated with oral oestrogen (high quality, strong recommendation).

Clinical considerations & recommendations for laboratory tests

- Measuring dexamethasone levels can be useful if a falsepositive DST is suspected due to the clinical scenario (moderate quality, strong recommendation).
- If UFC is used, two or three collections should be obtained to evaluate variability (high quality, strong recommendation).
- If LNSC is used, we recommend at least two or three tests (high quality, strong recommendation)
- (IPSS) should not be used to diagnose hypercortisolism because the centraltoperipheral ACTH gradient in healthy controls and pseudoCushing's syndrome overlaps with that observed in patients with Cushing's disease (high quality, strong recommendation).

Clinical considerations & recommendations for laboratory tests

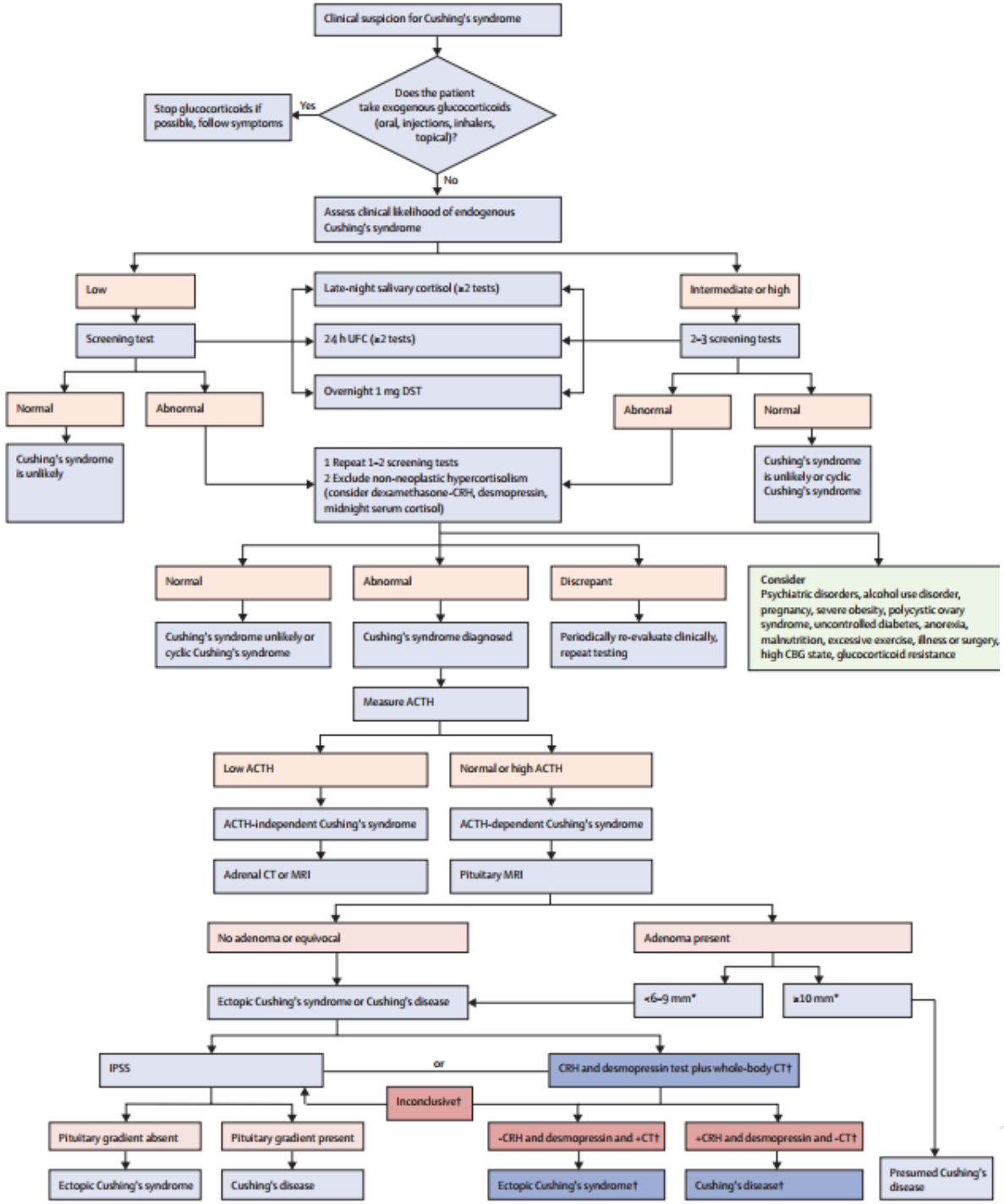
- In classical cyclic Cushing's disease or in patients with unpredictable fluctuating cortisol concentrations, dynamic testing and localisation testing, including IPSS, should be preceded by a confirmatory LNSC or UFC to document that the patients are in the active phase

Non-neoplastic hypercortisolism or pseudoCushing's syndrome

- There is no single approach to rule it out.
- We recommend considering the patient's clinical history, particularly the duration of symptoms, and repeating tests to avoid implementing inappropriate treatment if Cushing's syndrome is not present (low quality, discretionary recommendation).
- In most cases patients have mild hypercortisolism and can be monitored for 3–6 months to see whether symptoms resolve; treatment of the underlying condition (such as depression) can restore normal HPA axis function and cortisol concentrations (low quality, discretionary recommendation).

Non-neoplastic hypercortisolism or pseudo-Cushing's syndrome

- LDDT or serial LNSC tests over time correlate with the clinical picture (low quality, discretionary recommendation).
- Desmopressin
- DEX-CRH in this setting could be valuable, but published diagnostic accuracy results have varied; use at an expert centre with measurement of dexamethasone concentrations is advised (moderate quality, strong recommendation)


Clinical suspicion for Cushing's syndrome
Does the patient take exogenous glucocorticoids (oral, injections, inhalers, topical)?
Yes
Stop glucocorticoids if possible, follow symptoms
No
Assess clinical likelihood of endogenous Cushing's syndrome
Low
Intermediate or high
Late-night salivary cortisol (≥2 tests)
24 h UFC (≥2 tests)
Overnight 1 mg DST
Screening test
2–3 screening tests
Normal
Abnormal
Abnormal
Normal
Cushing's syndrome is unlikely
1 Repeat 1–2 screening tests
2 Exclude non-neoplastic hypercortisolism (consider dexamethasone-CRH, desmopressin, midnight serum cortisol)
Cushing's syndrome is unlikely or cyclic Cushing's syndrome
Normal
Abnormal
Discrepant
Consider
Psychiatric disorders, alcohol use disorder, pregnancy, severe obesity, polycystic ovary syndrome, uncontrolled diabetes, anorexia, malnutrition, excessive exercise, illness or surgery, high CBG state, glucocorticoid resistance
Cushing's syndrome unlikely or cyclic Cushing's syndrome
Cushing's syndrome diagnosed
Periodically re-evaluate clinically, repeat testing
Measure ACTH
Low ACTH
Normal or high ACTH
ACTH-independent Cushing's syndrome
ACTH-dependent Cushing's syndrome
Adrenal CT or MRI
Pituitary MRI
No adenoma or equivocal
Adenoma present
Ectopic Cushing's syndrome or Cushing's disease
<6–9 mm*
≥10 mm*
IPSS
or
CRH and desmopressin test plus whole-body CT†
Inconclusive†
Pituitary gradient absent
Pituitary gradient present
-CRH and desmopressin and +CT†
+CRH and desmopressin and -CT†
Presumed Cushing's disease
Ectopic Cushing's syndrome
Cushing's disease
Ectopic Cushing's syndrome†
Cushing's disease†

Panel 1: Clinical considerations and recommendations for Cushing's syndrome diagnosis and monitoring of Cushing's disease recurrence

If Cushing's syndrome is suspected:

- Start with urinary-free cortisol (UFC), late-night salivary cortisol (LNSC), or both; dexamethasone suppression test (DST) could also be an option if LNSC not feasible
- Multiple LNSC might be easier for patient collection

If confirming Cushing's syndrome:

- Can use any test
- UFC average two-to-three collections
- LNSC (two or more tests)
- DST useful in shift workers, not in women on oestrogen-containing oral contraceptives
- Measuring dexamethasone concentration, with cortisol concentration, the morning after 1 mg dexamethasone ingestion improves test interpretability

If Cushing's syndrome due to adrenal tumour is suspected:

- Start with DST
- LNSC has lower specificity in these patients

Monitoring for recurrence:

- Consider which tests were abnormal at initial diagnosis
- LNSC most sensitive, should be done annually
- DST and UFC usually become abnormal after LNSC
- UFC is usually the last to become abnormal

Imaging & tumour localisation

- MRI: choice for detecting ACTH-secreting pituitary adenomas. Most lesions are very small, with use of standard 1·5T MRI only approximately 50% of Microadenomas are clearly depicted.
- PET: an alternative to, or in combination with, MRI for localisation of corticotroph adenomas.
- ^{18}FFDG PET/CT: detecting pituitary lesions. Prior CRH stimulation can increase . FFDG uptake and thus increase detection.

Imaging and tumour localisation

- PET co-registration with volumetric MRI combines functional and anatomical imaging: this technique correctly localised corticotroph adenomas in patients with de novo disease and persistent or recurrent hypercortisolism after primary surgery, most of whom had negative or equivocal standard-spin echo MRI. However, this approach is not available or approved in most countries.
- Alternative strategies (eg, targeting CRH1 receptors on corticotroph tumours) have also recently been proposed, but require further study.

Clinical considerations & recommendations for imaging & tumour localisation

- MRI remains the imaging modality of choice for ACTH-secreting pituitary adenomas (high quality, strong recommendation).
- We suggest 3T instead of 1·5T MRI where available (low quality, discretionary recommendation).

Distinguishing between Cushing's disease and ectopic ACTH-dependent Cushing's syndrome

- Desmopressin and CRH stimulation testing have proven useful in distinguishing between pituitary and ectopic tumors. Increased plasma ACTH and increased cortisol concentrations after CRH or desmopressin administration usually indicates Cushing's disease. Nevertheless, well differentiated neuroendocrine tumours can also express any or all of these receptors, potentially leading to false-positive results.
- High-dose (8 mg) DST, although it has low accuracy overall, is still used in some countries.

Distinguishing between Cushing's disease and ectopic ACTH-dependent Cushing's syndrome

- IPSS, which measures ACTH in pituitary versus peripheral venous drainage, has long been the gold standard to reliably exclude ectopic ACTH production. A central to peripheral ACTH gradient less than 2 before or less than 3 after stimulation suggests an ectopic tumour; however, both false-negatives and false-positives have been reported. Prolactin measurement might improve diagnostic accuracy and it is essential that the patient is hypercortisolaemic at the time of IPSS.

Distinguishing between Cushing's disease and ectopic ACTH-dependent Cushing's syndrome

- A noninvasive approach using a combination of three or four tests, specifically CRH and desmopressin stimulation plus MRI, followed by whole-body CT if diagnosis is equivocal, correctly diagnosed Cushing's disease in approximately half of patients in one series, potentially eliminating the need for IPSS. A positive CT scan, negative CRH and desmopressin stimulation, and negative MRI, had a negative predictive value of 100% for Cushing's disease.

Distinguishing between Cushing's disease and ectopic ACTH-dependent Cushing's syndrome

- GaDOTATATE is a modified (Tyr3) octreotide molecule covalently linked to -tetraazacyclododecane tetraacetic acid (DOTA) combined with the radioactive Ga isotope. The radiopharmaceutical, with a halflife of approximately 1 h, binds to somatostatin receptors with affinity similar to octreotide and can be used as a tracer in PET imaging of ectopic ACTHsecreting neuroendocrine tumours. GaDOTATATE localises about 65% of these tumours, including those not seen or not definitively identified on crosssectional imaging, and images are sharper than with single photon ^{111}InDTPApentetreotide, with greater sensitivity for small tumours. False-positives can occur because of chronic inflammation, and a positive scan does not definitively prove that the neuroendocrine tumour is the source of ACTH, but GaDOTATATE imaging can be useful in guiding clinical management.

Clinical considerations & recommendations for distinguishing between Cushing's disease & ectopic ACTH dependent Cushing's syndrome

- No single laboratory test or combination of tests can absolutely differentiate between pituitary and ectopic ACTH-secreting tumours (high quality, strong recommendation). We recommend using both the clinical context and test results to guide management (high quality, strong recommendation). When prompt access to brain MRI is not available, necktopelvis thin-slice CT scan is useful if suspicion is high for ectopic ACTH syndrome, such as in a male patient with very high UFC, profound hypokalaemia, or both81 (low quality, discretionary recommendation).

- If a pituitary tumour with a diameter of 10 mm or larger is detected on MRI and dynamic testing results are consistent with Cushing's disease, IPSS is not necessary for diagnosis (moderate quality, strong recommendation). all patients with lesions less than 6 mm should have IPSS and those with lesions of 10 mm or larger do not need IPSS (moderate quality, strong recommendation)

Clinical considerations & recommendations for distinguishing between Cushing's disease & ectopic ACTH dependent Cushing's syndrome

- Expert opinions differ regarding tumors 6–9 mm, but the majority recommended IPSS to confirm the diagnosis in this circumstance (moderate quality, discretionary recommendation)
- Some differences between centres and countries are based on interventional radiology availability. Prolactin measurement can be useful in ruling out a false-negative IPSS (moderate quality, discretionary recommendation).
- Although IPSS has high diagnostic accuracy for localization to the pituitary gland, it is not sufficiently reliable for tumour lateralisation to the right or left side of the gland (moderate quality, strong recommendation).

Clinical considerations & recommendations for distinguishing between Cushing's disease & ectopic ACTH dependent Cushing's syndrome

- A noninvasive alternative using highdose DST and CRH stimulation test predicts Cushing's disease if both tests are positive. However, if tests are discordant, IPSS is necessary (low quality, discretionary recommendation).

- CRH and desmopressin testing with pituitary MRI followed by wholebody CT scan might be a reliable alternative, if assessed by an experienced multidisciplinary team (very low quality, discretionary recommendation).

Complications of Cushing's disease

Hypercoagulability

- Shortened activated partial thromboplastin time and increased fibrinogen, von Willebrand factor, and factor VIII, as well as impaired fibrinolysis mediated by elevated plasminogen activator inhibitor1 and antiplasmin concentrations. Increased thrombin, thromboxane A2, and platelets, with a compensatory increase in anticoagulation factors such as vitamin Kdependent protein C and vitamin Kdependent protein S, have also been implicated in hypercoagulability.

Hypercoagulability

- VTE in patients with endogenous Cushing's syndrome is more than ten times higher versus those with nonfunctioning pituitary adenomas undergoing surgery
- VTE risk persists in the first few months after Cushing's disease surgery, indicating that hypercoagulability is not immediately reversible with cortisol normalisation
- Thromboprophylaxis can decrease the incidence of postoperative VTE, particularly when extended to 30 days.

Cardiovascular disease

- Type 2 diabetes is present in up to 30% of patients and dyslipidaemia, and low HDL, high LDL, and high triglycerides were reported in 16–64% of cases at diagnosis
- Structural cardiovascular changes improve, including left ventricular hypertrophy, concentric remodeling, dilated cardiomyopathy, increased intima media thickness, and increased formation of atherosclerotic plaques, as well as their clinical manifestations, including hypertension and heart failure, but might not fully resolve despite remission of hypercortisolism.

Bone disease

- Vertebral fractures occur in 30–50% of patients, largely correlating with hypercortisolism severity

- Dual Xray absorptiometry of the lumbar spine might show low bone mineral density (BMD), but fractures can occur even in patients with BMD in the normal or osteopenic range

Growth hormone deficiency

- Glucocorticoids, both endogenous and exogenous, inhibit growth hormone secretion, thereby decreasing IGFI production by the liver in patients with Cushing's syndrome.
- Using the insulin tolerance or glucagon stimulation test, prevalence of growth hormone deficiency in adults varies with timing of the diagnosis
- IGFI is an insensitive screening test for diagnosing growth hormone deficiency in adults.
- Compared with other causes of growth hormone deficiency, growth hormone deficiency in patients with Cushing's syndrome is more common in women and young patients; generally, these patients have a higher prevalence of type 2 diabetes, hypertension, low bone mass, fractures, and worse quality of life. Myopathy might be partially related to growth hormone deficiency among patients in remission.

Other complications

- Increased risk of infection, dysfunction of one or more pituitary axes such as central hypothyroidism, gonadal function impairment, infertility
- Physical and psychological morbidity commonly affects quality of life
- Proximal myopathy

Panel 2: Recommendations regarding complications of Cushing's disease

Hypercoagulability

- There is currently no standard practice for preoperative or postoperative thromboprophylaxis in patients with Cushing's disease. Some experts pause oestrogen therapy in women who are awaiting surgery, but care should be taken if it was being used as contraception, because pregnancy also is associated with increased risk of thrombosis (low quality, discretionary recommendation)
- Prophylactic anticoagulation should be considered for patients at risk for venous thromboembolic events, including history of embolism or abnormal coagulation testing; severe preoperative hypercortisolism; current use of oestrogen or oral contraceptives; poor mobility; extended preoperative or postoperative hospital stay; and high postoperative cortisol concentrations or cortisol over-replacement in patients with adrenal insufficiency (moderate quality, strong recommendation)
- Early postoperative ambulation and use of compression stockings should be encouraged for all patients (high quality, strong recommendation)
- If thromboprophylaxis is administered, there was strong consensus for preference of low molecular weight heparin over oral anticoagulants given the long half-life of the latter and the absence of therapy to reverse their effect, which could be especially concerning in the preoperative setting (low quality, discretionary recommendation)
- Anticoagulants could be discontinued before surgery to minimise intraoperative bleeding risk, although the timing of when to stop and when to reinitiate after surgery is unclear (low quality, discretionary recommendation)
- Among meeting participants, recommended anticoagulation duration in the preoperative setting ranged from 2–4 days to 1–2 weeks, and in the postoperative setting from 1–2 days of the hospital stay up to 2–4 weeks, or even longer, to 2–3 months (low quality, discretionary recommendation)
- Thromboprophylaxis should not be routinely used in paediatric patients because of bleeding risk but is reserved for selected patients

Cardiovascular disease

- Evaluate, monitor, and treat according to current guidelines for patients at high risk of cardiovascular disease (high quality, strong recommendation)
- Management approach should be individualised (high quality, strong recommendation) on the basis of the complications present (eg, hypertension or hyperlipidaemia) and care should be coordinated with primary care and cardiology physicians as needed (very low quality, discretionary recommendation)

Bone disease

- Risk assessment for bone loss and fracture recommended in all patients (high quality, strong recommendation)
- Given the risk for fracture even in patients without osteoporosis, standard dual X-ray absorptiometry alone may not be sufficiently informative; bone quality (microscanner or trabecular bone score) or morphometric vertebral assessment is recommended where available (high quality, strong recommendation) and can be useful in detecting subclinical fractures (high quality, strong recommendation), but might not be practical for all patients. The FRAX tool to assess fracture risk is not validated for Cushing's disease
- Monitor and follow-up as for all adult high-risk populations (high quality, strong recommendation)
- Consider conventional osteoporosis treatments (eg, bisphosphonates) for patients with persistent Cushing's disease, even if bone mineral density is normal, because of increased fracture risk due to cortisol excess (high quality, strong recommendation)

Growth hormone deficiency

- There is currently no standard practice for whether, when, and how to test for growth hormone deficiency in adults with Cushing's disease. As postoperative hypothalamic–pituitary–adrenal (HPA) axis recovery is often delayed, we recommend waiting at least 6–12 months after surgery before considering growth hormone deficiency assessment (moderate quality, strong recommendation)
- Patients with macroadenomas and more aggressive surgical resection are at increased risk of hypopituitarism; patients with three or more pituitary hormone deficiencies are more likely to have growth hormone deficiency and do not need dynamic testing (high quality, strong recommendation)
- Serum insulin-like growth factor I concentration alone is not likely to be a reliable indicator of growth hormone deficiency, because concentrations can be in the lower half of the normal range.
- Accessibility of growth hormone replacement can be an important factor in determining testing and treatment considerations. If growth hormone replacement is implemented earlier than 2 years after pituitary surgery, we recommend retesting periodically to determine whether growth hormone secretion has normalised upon HPA axis recovery (moderate quality, strong recommendation)
- As Cushing's syndrome-associated myopathy does not always spontaneously resolve during remission, physical rehabilitation is recommended for all patients (low quality, discretionary recommendation).
- In children, evaluate for growth hormone deficiency 3–6 months after surgery and immediately initiate growth hormone replacement if needed to ensure proper growth

Thanks for your Attention