RECORDATI
RARE DISEASES

Cushing's syndrome interactive patient journey

START

MA-US-IST-25-00068

RECORDATI
RARE DISEASES

PATIENT JOURNEY
through Cushing's syndrome

START OVER

DISEASE AWARENESS

Cushing's syndrome presents 4:1 more commonly in women, with a mean age at diagnosis of **44 years**[1]

Cushing's syndrome is a rare disease affecting **3.2 patients per million per year**[2,a]

1
Presentation of symptoms to PCP

Symptoms can be **non-specific** which make it challenging to diagnose[3]
Common symptoms include:[4]

- weight gain
- fatigue
- hypertension
- diabetes
- easy bruising
- hirsutism

Presentation is variable and patients may exhibit a wide range of clinical manifestations

2
Referral to specialist

PCPs may not have come across many patients with Cushing's syndrome, therefore may **investigate**

Investigation will usually include referral to other specialists involved in the care of more

3

Patients will undergo **multiple visits to doctors** as investigations continue[3]

Treatment

ABBREV

REFS

START OVER

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ABBREV

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DISEASE AWARENESS

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Cushing's syndrome is a rare disease affecting **3.2 patients per million per year**[2,a]

AGE AT DIAGNOSIS

- The average age of onset is approximately 30 years in females and 37 years in males[10]
- CS presents 4:1 more commonly in women than in men[1]

ABBREV

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DISEASE AWARENESS

Cushing's syndrome presents 4:1 more commonly in women, with a mean age at diagnosis of **44 years**[1]

Cushing's syndrome is a rare disease affecting **3.2 patients per million per year**[2,a]

INCIDENCE

- CS is a rare disease affecting 3.2 patients per million per year[2]
- CS is a chronic and systemic disease caused by endogenous or exogenous hypercortisolism[5]

ABBREV

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SYMPTOMS

- Symptoms of endogenous CS can be specific or non-specific (see Table), and the average number of clinical symptoms experienced by patients is 5[9,11]

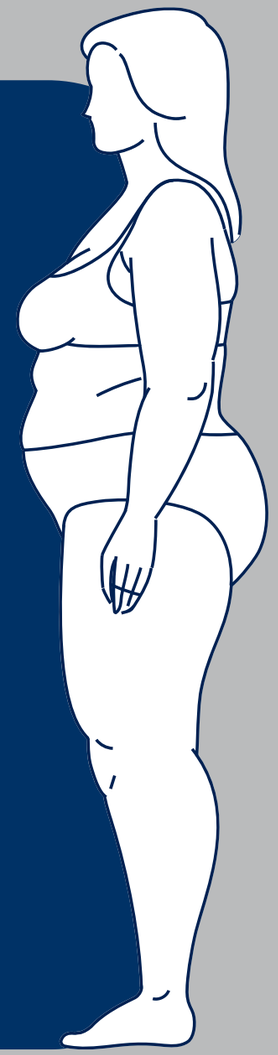
Frequent and non-specific for Cushing syndrome, %	Frequent and specific for Cushing syndrome, %
Recent weight gain, 70–95	Round face, ≤90
Plethora, 70–90	Osteopenia or osteoporosis and fragility fractures, ≤80
Oligo or amenorrhea, 70–80	Muscle weakness, 60–80
Depression, 50–80	
Hypertension, 60–90	
Hirsutism, 50–75	
Sleep disorders, ≈60	
Dyslipidemia, 40–70	
Decreased libido, 25–90	
Cognitive impairment (exact prevalence unknown)	
Vitamin D deficiency (exact prevalence unknown)	

Less frequent and non-specific to Cushing syndrome, %	Less frequent and specific for Cushing syndrome, %
Kidney stones, ≤50	Dorsocervical fat pad, ≈50
Diabetes, ≈30	Purple striae, <50
Atherosclerosis, ≈30	Easy bruising, ≈50
Acne, <50	Thin skin, ≈40
Hair loss, 30	

- The widespread presence of common overlapping symptoms, such as obesity, hypertension, and diabetes in the general population, means that there is often a considerable delay between the onset of symptoms and diagnosis[7]

Symptoms can be **non-specific** which make it challenging to diagnose[3]
Common symptoms include:[4]

- weight gain
- fatigue
- hypertension
- diabetes
- easy bruising
- hirsutism



Presentation is variable and patients may exhibit a wide range of clinical manifestations

ABBREV

REFS

million per year[2,a]

diabetes
easy bruising
hirsutism

Presentation is variable and patients may exhibit a wide range of clinical manifestations

START OVER

2
Referral to specialist

PCPs may not have come across many patients with Cushing's syndrome, therefore may **investigate more common conditions** before considering Cushing's syndrome[3]

Investigation will usually include referral to other specialists involved in the care of more **common conditions**[3]

Average number of doctors consulted **4**[3]

3
Mis-diagnosis and unrelated treatment

Patients will undergo **multiple visits to doctors** as investigations continue[3]

Treatment unrelated to Cushing's syndrome is received[3]

Average time to diagnosis is **3.8 years**[3]

Presentation of additional symptoms and effect on HRQoL

Patients cycle through **multiple rounds of referral** to different specialists and subsequent treatment not targeting the source of Cushing's syndrome, which

As there is diagnostic delay, **other clinical manifestations** often arise[5]

Non-specific clinical manifestations often result in **impaired HRQoL** for patients[5]

ABBREV

REFS

Average number of doctors consulted **4**[3]

Average time to diagnosis is **3.8 years**[3]

START OVER

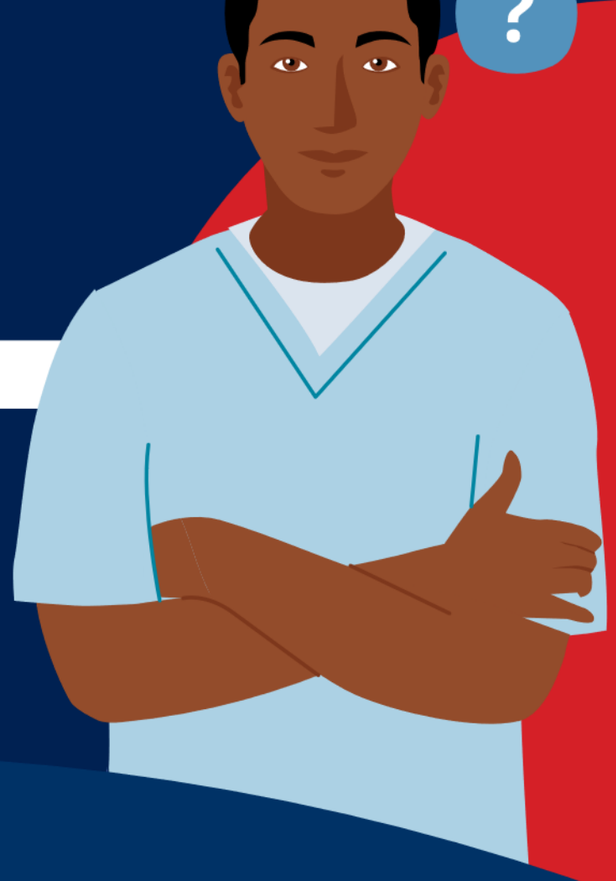
Patients cycle through **multiple rounds of referral** to different specialists and subsequent treatment not targeting the source of Cushing's syndrome, which can allow **additional symptoms to develop** and **greatly impacts HRQoL**[5]

Presentation of additional symptoms and effect on HRQoL

As there is diagnostic delay, **other clinical manifestations** often arise[5]

Non-specific clinical manifestations often result in **impaired HRQoL** for patients[5]

Referral back to PCP



Suspicion of Cushing's syndrome by PCP and referral to **endocrinologist** for screening

ABBREV

REFS

Patients cycle through **multiple rounds of referral** to different specialists and subsequent treatment not targeting the source of Cushing's syndrome, which can allow **additional symptoms to develop** and **greatly impacts HRQoL**[5]

ADDITIONAL SYMPTOMS

- As investigations continue, other clinical manifestations (symptoms or comorbidities) often arise, due to prolonged exposure to elevated cortisol levels[5]
- Multiple visits to doctors and non-specific clinical manifestations also result in impaired HRQoL[5]

ABBREV

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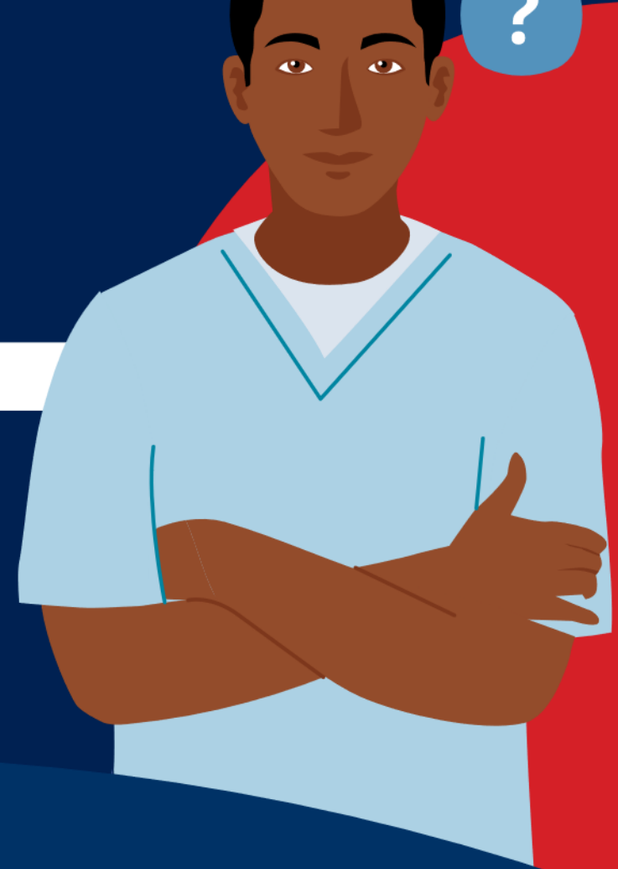
greatly impacts HRQoL

Referral back to PCP



Suspicion of Cushing's syndrome

by PCP and referral to **endocrinologist** for screening

START OVER

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RECORDATI
RARE DISEASES

START
OVER

ABBREV

REFS

RECORDATI RARE DISEASES

START OVER

TESTING AND DIAGNOSIS

of Endogenous Cushing's syndrome[6]

ABBREV

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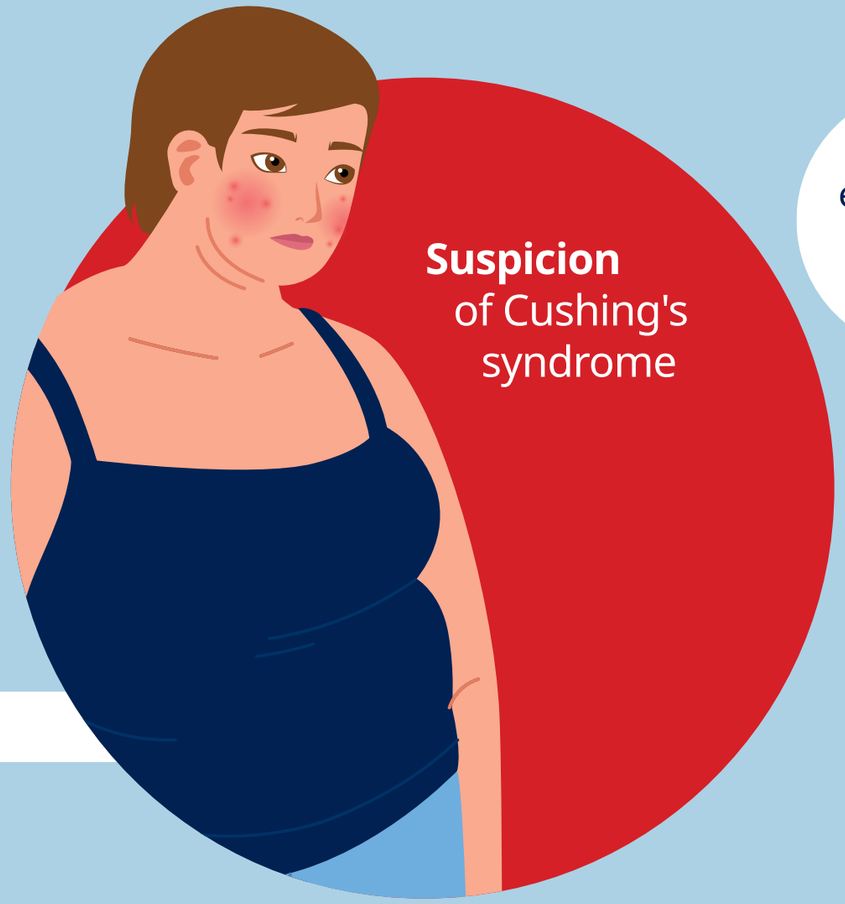


Suspicion of Cushing's syndrome

Exclude exogenous Cushing's syndrome

Perform **2 to 3 screening tests** to measure **cortisol levels**[6]

- LNSC (≥2 tests)[6]
- 24-hour UFC (≥2 tests)[6]
- Overnight 1 mg DST[6]

ABNORMAL RESULTS

>145 ng/dL (4 nmol/L)[7,b]	Above ULN[7]	>1.8 µg/dL (50 nmol/L)[7]

Cushing's syndrome[8]

ACTH test[8]

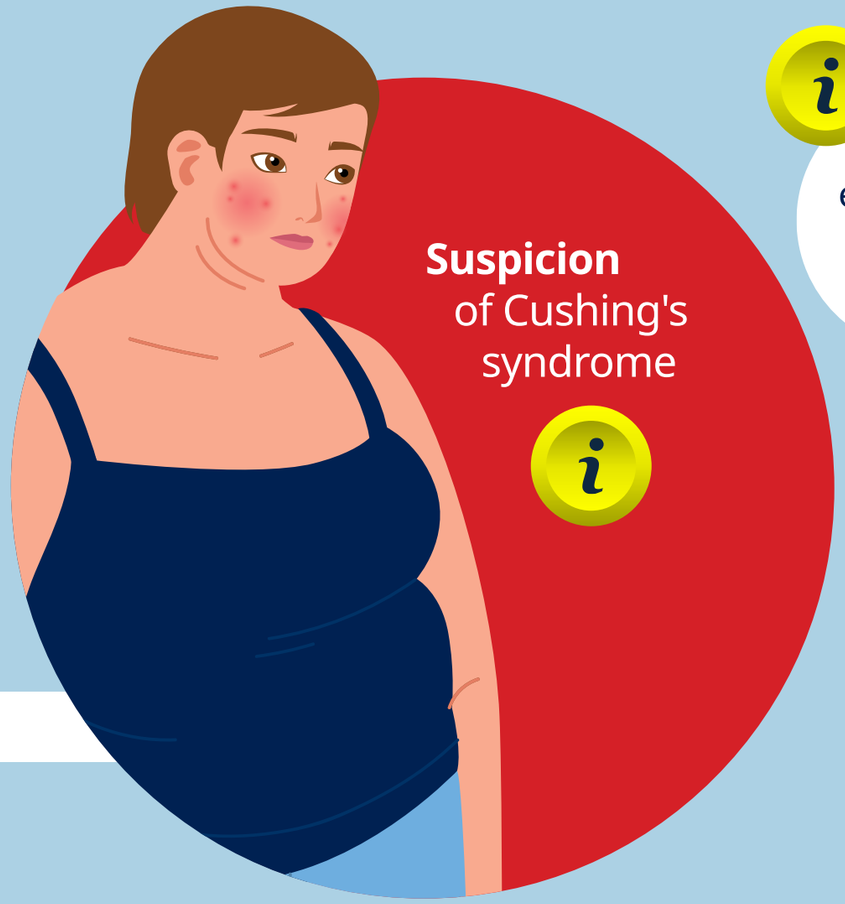
LOW: <10 pg/mL (<2.2 pmol/L) on at least 2 tests performed on different days[9]

Repeat **1 to 2 screening tests** to confirm diagnosis. Exclude non-neoplastic hypercortisolism[6]

ABBREV

REFS

START OVER



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ABBREV

REFS

SUSPICION OF CS

- Specific symptoms for CS that occur frequently include round face, osteopenia, and muscle weakness. Less frequent symptoms include dorsocervical fat pad, purple striae, easy bruising, and thin skin.[9] However, these symptoms do not occur in all patients with CS[9]
- Common non-specific symptoms include weight gain, plethora, oligomenorrhea or amenorrhea, and hypertension.[9] Other less frequent non-specific symptoms include kidney stones, acne, atherosclerosis and diabetes[9]
- Laboratory abnormalities should also be assessed when CS is suspected. Notably, however, these can vary based on the severity of disease and sensitivity to glucocorticoids[9]
- Testing is recommended for patients with
  - Unusual features for their age. This includes conditions like osteoporosis or hypertension in younger individuals (ie, osteoporosis and vertebral fractures, among those younger than 50 years)[7,9]
  - Multiple or progressive features (ie, diabetes and/or hypertension uncontrolled on multiple agents)[7,12]
  - Adrenal incidentaloma[7]
- No single symptom is pathognomonic for CS, and hypercortisolemia alone is insufficient for diagnosis[9]

ABBREV

REFS

Exclude exogenous Cushing's syndrome

EXOGENOUS CS

- Use of exogenous glucocorticoids (oral, injections, inhalers, topical) should be excluded before diagnostic testing for CS[9]
- Abrupt discontinuation of long-term or high-dose exogenous glucocorticoids can induce adrenal insufficiency[9]

ABBREV

REFS

Perform **2 to 3 screening tests** to measure **cortisol levels**[6]

INITIAL TESTING

- Pituitary Society guidelines recommend the following testing if CS is suspected[6]
  - Start with UFC, late-night salivary cortisol LNSC, or both
  - DST could also be an option if LNSC is not feasible
  - Start with DST if an adrenal adenoma is suspected
- Multiple LNSC tests may be easier for some patients to complete[6]
- Cortisol is secreted in a pulsatile manner with a circadian rhythmicity; therefore, due to an overlap in similar values between healthy individuals and people with CS, morning serum cortisol is not used for the diagnosis of CS[13]
  - Random plasma ACTH levels are also not recommended for diagnosis[7]

ABBREV

REFS

DEXAMETHASONE

- Diagnostic tests for CS assess cortisol secretory status[6]
- A DST is often used if there is a suspicion of mild cortisol excess and is the preferred test in patients suspected of having adrenal adenomas[9]
  - In an overnight test, 1 mg of dexamethasone is given at 11 PM, followed by measurement of fasting plasma cortisol between 8 AM and 9 AM the next morning[14]
  - In a 2-day test, 0.5 mg of dexamethasone is given every 6 hours (starting at 9 AM) for 2 days, with cortisol measurement at the beginning and end of the test[14]
  - A serum cortisol level of >1.8 µg/dL (50 nmol/L) at the end of either test would be considered a positive result for CS[14]
- Using a post-dexamethasone cutoff level of >1.8 µg/dL (50 nmol/L), the DST has a sensitivity of >95% and specificity of 80%–85%[15]
- It should be noted that the test may be unreliable in some patients, including those with[14]
  - Estrogen/mitotane (↑ CBG)
  - Nephrotic syndrome/cirrhosis (↓ CBG)
  - ↓ Dexamethasone metabolism/clearance (cimetidine, fluoxetine, diltiazem, renal insufficiency)
  - ↑ Dexamethasone metabolism (phenytoin, rifampin, carbamazepine)
- A DST may be useful in shift workers, but not in women taking estrogen-containing oral contraceptives (estrogen should be discontinued for 4–6 weeks[16]); measuring dexamethasone concentration, with cortisol concentration, the morning after 1 mg dexamethasone ingestion can also improve test interpretability[6]
- The Pituitary Society Consensus on the diagnosis and management of CD and the Endocrine Society Clinical Practice Guideline for the diagnosis of CS do not provide a recommendation to measure dexamethasone suppression and ACTH at the same time[6,7]

Overnight
1 mg DST[6]

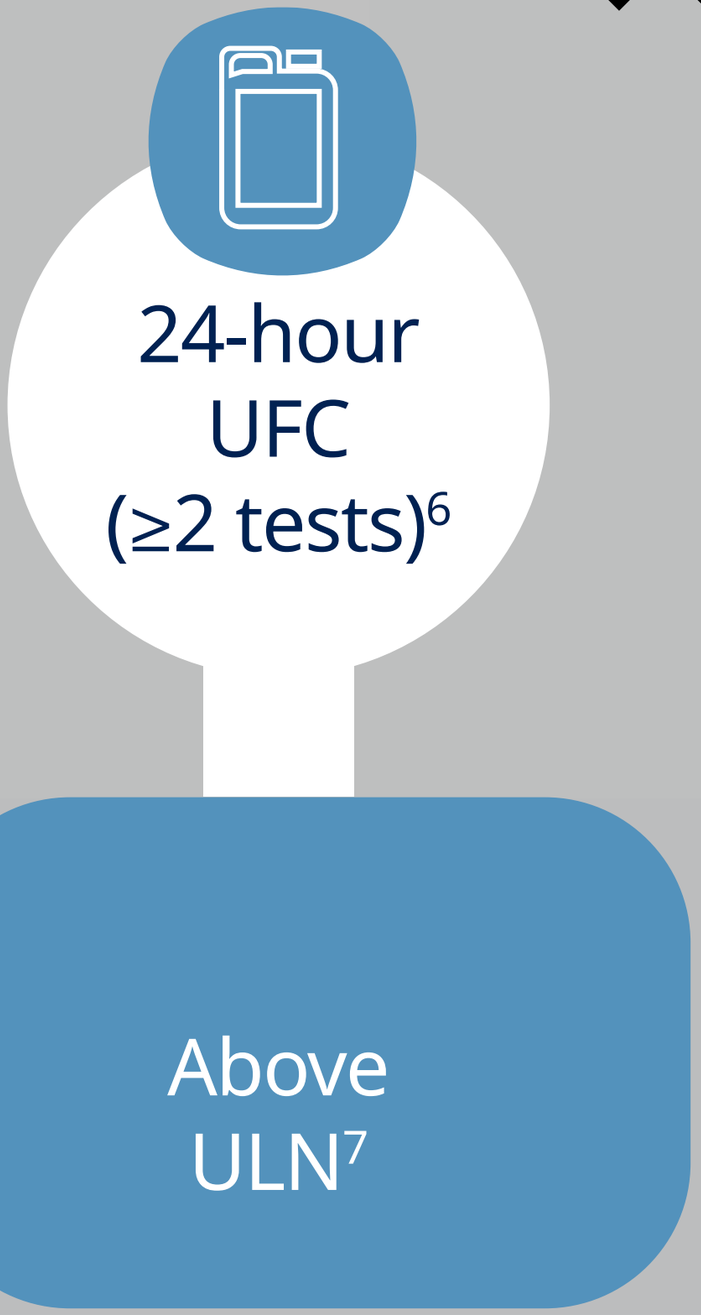
>1.8 µg/dL
(50 nmol/L)[7]

ABBREV

REFS

UFC TESTING

- The UFC test measures the amount of free cortisol excreted in urine over a 24-hour period[9]
- A normal range of cortisol, although assay-dependent, would typically be 20–80 µg/d (20–45 µg/d in most laboratories), and an abnormal cortisol level (>ULN) would indicate the presence of CS[9]
- Notably, however, patients can have varying levels of hypercortisolism that are detected using a UFC test[17]
  - Mild (mUFC ≤2x ULN)
  - Moderate (mUFC >2–5x ULN)
  - Severe (mUFC >5–10x ULN)
  - Very severe (mUFC >10x ULN)
- At least two or three 24-hour urine collections are advised to measure UFC, and results should take into consideration the sex, BMI, age, urinary volume, sodium intake, and renal function of the patient[6,7]
- A UFC test has a sensitivity of 70%–75% and specificity of 40%–90%[15]; it is not as reliable in patients with very mild elevations of cortisol and is not recommended for patients with renal impairment or individuals who have had a high fluid intake.[14] Problems with improper urine collection can also occur during the test[14]
- A UFC test is the last test to show abnormal results when monitoring for disease recurrence[6]
- Patients with suspected cyclic CS are recommended to be tested using UFC or LNSC tests rather than DSTs[7]
  - Multiple serial tests of both UFC and LNSC can be used to monitor treatment outcomes[6]

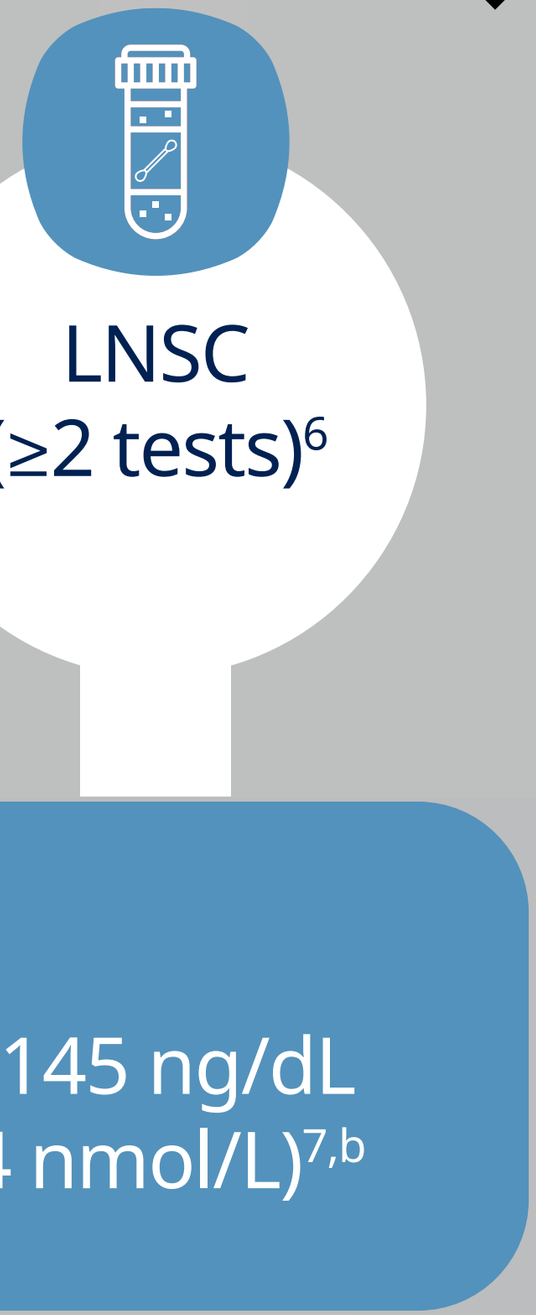


ABBREV

REFS

LNSC TESTING

- An LNSC test measures elevated nighttime cortisol levels, which are abnormal in people with CS[6]
- Salivary cortisol is collected using a cotton swab before bedtime, usually between 11 PM and midnight, with at least 2 or 3 LNSC tests recommended for the diagnosis of CS[6,7]
- LNSC testing has a sensitivity of 90%–98% and specificity of 90%–100%,[15] and an abnormal salivary cortisol level (>145 ng/dL [4 nmol/L]) indicates the presence of CS[7,14]
- The test is not recommended for use in individuals with abnormal sleep/wake cycles, such as shift workers,[7] and false positives can also be seen in people who smoke or chew tobacco, are of older age, and have hypertension or diabetes[15]
- LNSC is the recommended first test to determine recurrence in patients after surgery, as the circadian rhythm is typically the first to become disrupted[6,18]



ABBREV

REFS

Repeat **1 to 2 screening tests** to confirm diagnosis. Exclude non-neoplastic hypercortisolism[6]

CONFIRMATION OF DIAGNOSIS

- The Endocrine Society and Pituitary Society recommend[6,7]
  - Repeating 1 to 2 screening tests to confirm diagnosis
  - Excluding non-neoplastic hypercortisolism
- If multiple tests produce normal results, CS is unlikely[6]
- When results are discrepant or yield inconsistent results, the Pituitary Society recommends to periodically reevaluate the patient clinically and repeat testing[6]; additional second-line tests such as a desmopressin or dexamethasone-CRH (not available in the US) can also be performed for these patients[9]
  - The desmopressin test has a high specificity for CD and is less complex and expensive than the dexamethasone-CRH test, but both tests have shown good diagnostic performance in distinguishing CS from non-neoplastic Cushing's syndrome in some studies; when both tests were done, they showed excellent agreement[6]
- Non-neoplastic hypercortisolism occurs when the HPA axis is activated due to conditions that are non-cancerous or related to abnormal tissue growth; these can include psychiatric disorders, alcohol use disorder, pregnancy, severe obesity, polycystic ovary syndrome, uncontrolled diabetes, anorexia, malnutrition, excessive exercise, illness or surgery, high CBG state, or glucocorticoid resistance[6]

ABBREV

REFS

Cushing's syndrome[8]

ENDOGENOUS CS CONFIRMED

- With CS confirmed, the next step is to determine the source of hypercortisolemia, whether it be adrenal, pituitary, or ectopic[9]

ABBREV

REFS

START OVER

ACTH test[8]

Cushing's syndrome[8]

Repeat **1 to 2 screening tests** to confirm diagnosis. Exclude non-neoplastic hypercortisolism[6]

LOW:
<10 pg/mL
(<2.2 pmol/L)
on at least 2 tests performed on different days[9]

ACTH-INDEPENDENT

NORMAL:
10–20 pg/mL
(2.2–4.4 pmol/L)[9]

HIGH:
>20 pg/mL
(>4.4 pmol/L)[9]

ACTH-DEPENDENT

Pituitary MRI[8]

Adrenal CT or MRI[6]

Unilateral adrenal adenomas

Lower native fat density (<10 HU)

ually smaller with rapid contrast washout*

ABBREV

Adrenocorticol carcinomas

Higher native fat density (≥10 HU)

REFS

Inhomogenous tissue pattern with delayed contrast washout*

Primary bilateral macronodular

No visible adenoma or <6–9mm[c,8]

Adenoma ≥10 mm[c,8]

IPSS or CRH[d] and/or desmopressin test plus

No pituitary gradient

Pituitary gradient present

ACTH test[8]

ACTH TEST

- ACTH is produced by the pituitary gland and regulates cortisol production in the adrenal glands[9]
- Plasma ACTH is critical to the differential diagnosis of CS and is a good predictor of localization of the disease[9]
- ACTH levels are used to distinguish between ACTH-independent (due to an adrenal source) and ACTH-dependent (due to a pituitary or ectopic tumor) causes of CS[9]
- ACTH testing in the blood should ideally take place between 8 AM and 9 AM[9]
- Because ACTH is pulsatile in the body, multiple tests are recommended[9]
- The sensitivity and specificity of ACTH below 10 pg/mL for adrenal CS are 92% and 94%, respectively. The sensitivity and specificity of ACTH above 30 pg/mL for ACTH-dependent CS are 69% and 100%, respectively[19]

ABBREV

REFS

LOW:
<10 pg/mL
(<2.2 pmol/L)
on at least 2 tests
performed on
different days[9]

ACTH-INDEPENDENT

Adrenal
CT or MRI[6]

ACTH-INDEPENDENT

- A suppressed morning plasma ACTH concentration <10 pg/mL (<2.2 pmol/L) on at least 2 tests performed on different days indicates a corticotropin-independent adrenal CS, such as adrenal adenoma, primary bilateral adrenal hyperplasia, or adrenal carcinoma[9]
- Adrenal CS is confirmed by imaging of the adrenal gland[6]
- Further classifications of adrenal CS may be determined using tumor morphology and HU when imaged through contrast-enhanced CT.[9] The presence of bilateral hyperplastic nodules may indicate adrenal hyperplasia.[9] Unilateral tumors with <10 HU may indicate the presence of an adrenal adenoma.[9] Unilateral tumors with >10 HU may indicate the presence of an adrenocortical carcinoma[9]

ABBREV

REFS

NORMAL:
10–20 pg/mL
(2.2–4.4 pmol/L)[9]

HIGH:
>20 pg/mL
(>4.4 pmol/L)[9]

ACTH-DEPENDENT

ACTH-DEPENDENT

- Normal (2.2–4.4 pmol/L or 10–20 pg/mL) or elevated (>4.4 pmol/L or >20 pg/mL) morning plasma ACTH concentration in a patient suggests a corticotropin-dependent CD or ectopic CS[9]
- Extremely elevated ACTH levels, such as those exceeding 250 pg/mL, are more common in ectopic CS than in CD, but there is substantial overlap in corticotropin values between the 2 conditions[9]
- Patients with ACTH-dependent CS account for approximately 70% of endogenous CS cases[9]

ABBREV

REFS

ACTH-DEPENDENT

Adrenal CT or MRI[6]

Unilateral adrenal adenomas

- Lower native fat density (<10 HU)
- Usually smaller with rapid contrast washout*

Adrenocorticol carcinomas

- Higher native fat density (≥10 HU)
- Inhomogenous tissue pattern with delayed contrast washout*

Primary bilateral macronodular adrenal hyperplasias

- Bilateral nodules
- Hyperplastic or atrophic cortex between nodules[9]

*When scanned with contrast-enhanced CT

No visible adenoma or <6–9mm[c,8]

Adenoma ≥10 mm[c,8]

IPSS or CRH[d] and/or desmopressin test plus whole-body CT[e]

No pituitary gradient with IPSS[8]

Pituitary gradient present with IPSS[8]

Negative CRH or desmopressin test and positive CT[8]

Positive CRH or desmopressin test and negative CT[6]

Adrenal Cushing's syndrome[6]

Ectopic Cushing's syndrome[6]

Cushing's disease[6]

Presumed Cushi disease[6]

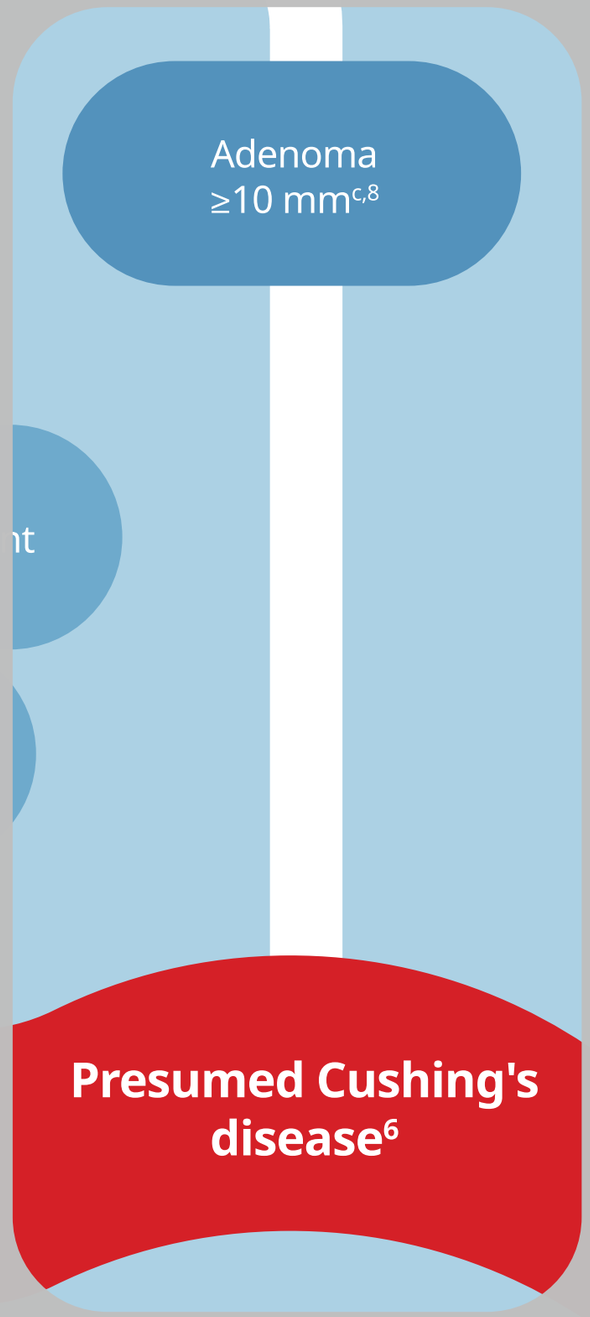
START OVER

ABBREV

REFS

PITUITARY TUMOR

- MRI remains the imaging modality of choice for ACTH-secreting pituitary adenomas[6]
- 1.5T MRI with gadolinium contrast identifies pituitary tumors in approximately 50% of patients with ACTH-dependent CS, thereby indicating a presumed CD[8]
- Pituitary Society guidelines currently recommend that 3T MRI be used over 1.5T where available[6]



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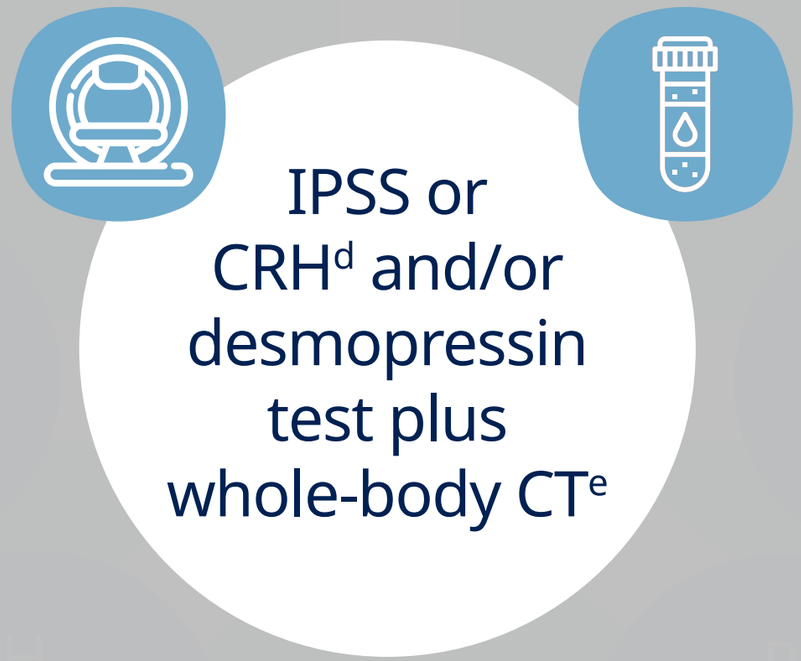

NO PITUITARY TUMOR

- For patients with no visible adenoma or smaller tumors on MRI scan, IPSS or CRH and/or desmopressin plus whole-body CT are commonly used[8]
- IPSS, which measures ACTH in pituitary versus peripheral drainage, has long been the gold standard to reliably exclude ectopic ACTH production[6]
- The test measures serial central and peripheral ACTH samples before and soon after CRH or desmopressin administration with central measurement of ACTH in pituitary via the inferior petrosal veins and peripheral measurement of ACTH via peripheral venous drainage[6,20]
- Differences in the central-to-peripheral ACTH gradient indicate diagnostic results[6,20]
  - Pituitary source of ACTH: pituitary gradient present (gradient of ≥2 before stimulation or ≥3 after stimulation)
  - Ectopic source of ACTH: pituitary gradient absent (gradient <2 before stimulation or <3 after stimulation)
- Improper placement of the catheter or asymmetrical or anomalous venous drainage can lead to a false negative result with the test[21]
- A non-invasive approach using a combination of 3 or 4 tests, specifically CRH and desmopressin stimulation plus MRI, followed by whole-body CT if diagnosis is equivocal, correctly diagnosed CD in approximately half of patients in one series, potentially eliminating the need for IPSS[6,22]
  - A positive CT scan, negative CRH and desmopressin stimulation, and negative MRI had a negative predictive value of 100% for CD[6,22]
  - Currently, this combination of laboratory and imaging testing as a non-invasive approach to distinguish between pituitary and ectopic ACTH-secreting tumors is likely to be limited to specialized centers[6,23]

ABBREV

REFS

Primary bilateral macronodular adrenal hyperplasias

Bilateral nodules

Hyperplastic or atrophic cortex between nodules[9]

*When scanned with contrast-enhanced CT

with IPSS[8]

test plus whole-body CT[e]

with IPSS[8]

Negative CRH or desmopressin test and positive CT[8]

Positive CRH or desmopressin test and negative CT[6]

START OVER

Adrenal Cushing's syndrome[6]

Ectopic Cushing's syndrome[6]

Cushing's disease[6]

Presumed Cushing's disease[6]

[a]True incidence and prevalence rates for Cushing's syndrome in the United States are unknown. Estimated data are pooled rates based on a meta-analysis of global Cushing's syndrome epidemiology; [b]Cutoff values may vary between labs because different methods used to measure cortisol give different reference ranges; [c]There is consensus that all patients with lesions <6 mm should have IPSS and those with lesions of ≥10 mm do not need IPSS, but expert opinions differ for lesions between 6–9 mm in diameter; [d]CRH test may not be available; [e]This alternative option does not have clear consensus and needs further research.

This material is not to be used for the treatment or diagnosis of hypercortisolemia in patients with Cushing's syndrome, nor is it a substitute for clinical judgment or guidelines. For patients suspected of having Cushing's syndrome, the clinical work-up begins by determining if hypercortisolemia is present.

ABBREV

REFS

RECORDATI
RARE DISEASES

START OVER

ABBREVIATIONS

ACTH = adrenocorticotropic hormone

BMI = body mass index

CBG = cortisol-binding globulin

CISS = constructive interference in the steady state

CRH = corticotropin-releasing hormone

CS = Cushing's syndrome

CT = computed tomography

DST = dexamethasone suppression test

FLAIR = fluid attenuation inversion recovery

HPA = hypothalamic-pituitary-adrenal

HRQoL = health-related quality of life

HU = Hounsfield unit

IPSS = inferior petrosal sinus

LNSC = late-night salivary cortisol

MRI = magnetic resonance imaging

mUFC = mean urinary free cortisol

PCP = primary care physician

SPGR = spoiled gradient–recalled

T = Tesla

TSE = turbo spin echo

UFC = urinary free cortisol

ULN = upper limit of normal

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