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Consensus on biomarker utility for ACTH-dependent Cushing syndrome: a Pituitary Society Modified Delphi Panel

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Abstract

Context **Biochemical test results are central to clinical decision-making for the diagnosis and management of Cushing syndrome (CS). With emerging research and increasing availability of different tests, updated consensus on the utility of these biomarkers is warranted.**

Objective **To establish an updated consensus on the role of biomarkers in the diagnosis and monitoring of adrenocorticotropic hormone-dependent CS, address novel therapeutic approaches, and identify areas for future research.**

Design **A modified 2-round Delphi panel was conducted. Consensus was defined as ≥70% agreement/disagreement for Likert-scale statements or ≥70% selection of the same option for single-choice questions.**

Setting **Participants represented a range of international expertise.**

Participants **Forty-one participants took part in the Delphi panel, with no attrition between rounds (one nonclinician was not required to complete the second round). An 8-member Steering Committee guided statement development.**

Results **Of statements designed to reach consensus, 45% (14/31) and 44% (11/25) statements reached consensus in Rounds 1 and 2, respectively. Notably, most panelists reported the use of late-night salivary cortisol for diagnosis of mild CS and for monitoring following pituitary surgery or medical or radiation therapy. Most panelists responded that block-and-replace therapies can be considered in patients with cyclical or severe CS, and consensus was reached that restoration of circadian rhythm is a treatment goal for patients with CS.**

Conclusion **Areas of alignment among experts on the diagnosis and monitoring of CS are presented. The findings from this study are intended to support clinicians in their clinical decision-making and highlight priority areas for future research.**

Keywords Cushing syndrome, adrenocorticotropic hormone, cortisol, late-night salivary cortisol, 24-hour urinary free cortisol, overnight dexamethasone suppression test

Adrenocorticotropic hormone (ACTH)-dependent Cushing syndrome (CS) is a rare endocrine disorder in which excessive ACTH drives chronic hypercortisolism, most often from ACTH-secreting pituitary adenomas (Cushing disease [CD]; 80-90% of cases) or ACTH-secreting non-pituitary tumors (ectopic CS; 10-20% of cases) (1). CS is associated with widespread morbidities, including cardiovascular, metabolic, and reproductive dysfunction, as well as muscle weakness, bone loss, and infectious and neuropsychiatric disorders that significantly reduce patient well-being and overall health-related quality of life (2, 3). Although mortality rates have decreased in the past 2 decades, patients with CS still have a significantly higher mortality risk than the general population (4).

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Thorough diagnosis, careful treatment selection, and proactive monitoring are essential to achieving optimal outcomes in patients with CS. However, the presenting symptoms of CS are often nonspecific and vary greatly, leading to diagnostic delays or inaccuracies that adversely impact prognosis and diminish quality of life. Mild disease at presentation is particularly challenging since signs and symptoms may overlap with those of other more common clinical conditions, such as metabolic syndrome, uncontrolled diabetes, psychiatric disorders, alcohol use, and polyendocrine metabolic ovarian syndrome (1-3, 5-9).

The latest expert consensus on the diagnosis of CS and management of CD was published in 2021, offering guidance for the use of novel diagnostic approaches and approved treatments at the time (2). Biochemical testing is central to clinical decision-making throughout the diagnostic process and subsequent treatment and management of CS. Diagnostic tests used to evaluate excess cortisol production include assessment of 24-hour urinary free cortisol (UFC), late-night salivary cortisol (LNSC), and the use of overnight low-dose (mostly 1 mg, 0.5 mg for Japan) dexamethasone suppression tests (ONDST), with varying sensitivity and specificity (2, 6, 10-13). In some patients, dexamethasone-corticotropin-releasing hormone (CRH), desmopressin testing, and midnight serum cortisol have been used to confirm or exclude nonneoplastic hypercortisolism (2, 3, 12, 14, 15). Inferior petrosal sinus sampling (IPSS) using CRH or desmopressin stimulation is used to differentiate between pituitary and ectopic ACTH-secreting tumors, although access to CRH is increasingly limited in many countries (2). Assessment of 24-hour UFC and LNSC is also used to monitor the efficacy of treatment, together with ONDST, for disease recurrence, with varied utility (2, 3, 16). The broad range of available tests and their varying accessibility across countries often leads to uncertainty among clinicians about which biochemical test to select in different clinical contexts.

Challenges encountered in delivering medical therapy to patients with CS vary and include complex dosing schedules, poor adherence, lack of indicators to monitor treatment efficacy, and the need for medication that provides more rapid and longer-lasting control of hypercortisolism (17-19). Previous studies have suggested a need to develop better tolerated and more effective medical therapies for patients with CS (20). Block-and-replace therapeutic approaches with potent medications for hypercortisolemia, along with a glucocorticoid replacement to mitigate the risk of adrenal insufficiency (AI), offer an alternative to traditional approaches of titrating medications (eg, steroidogenesis inhibitors to control hypercortisolism) (21-25). Such block-and-replace regimens are suitable for patients where rapid suppression of cortisol is needed, for example, patients with severe CS, those with cyclic CS, or those ineligible for surgery, especially when biochemical monitoring is less easily available, as well as for those who pose a follow-up challenge for uptitration due to travel distance and those who are more prone to development of acute AI (2, 21-24, 26, 27).

In addition, monitoring for recurrence may be difficult due to discordant clinical manifestations and biomarker test results. Biochemical testing is particularly important for disease monitoring after pituitary surgery, as the development of clinical symptoms often lags behind biochemical evidence of recurrence (7). Moreover, while 24-hour UFC, morning (plasma/serum) cortisol, and LNSC are often used to monitor disease, recent research has emerged on the importance of circadian cortisol rhythm (28), with preliminary evidence suggesting that restoration of circadian rhythm through treatment of CS improves patient outcomes (29-33).

Here, we conducted a modified Delphi panel to update existing and emerging diagnostic and disease monitoring approaches for CS. Delphi panels provide a structured and systematic approach to elicit consensus from a group of experts, and are increasingly used for rare diseases such as CS where evidence is scarce (17, 34, 35). International clinical CS experts were invited by the Pituitary Society to participate in a modified Delphi panel to establish an updated consensus on the utilization of biomarkers in the diagnosis and monitoring of ACTH-dependent CS, address alternative therapeutic approaches (including block-and-replace regimens and circadian rhythm assessments), and identify areas for future research.

Methods

Delphi panelists

The Pituitary Society nominated 2 clinical experts (Maria Fleseriu and Shlomo Melmed) to chair the Steering Committee (SC), which was composed of an additional 6 international experts (Irina Bancos, Jérôme Bertherat, Beverly MK Biller, Hidenori Fukuoka, John Newell-Price, and Martin Reincke) who guided statement development and reviewed the results of the surveys. To avoid bias, the SC did not participate in the consensus-gathering process (ie, they did not answer the survey questions).

Eligible panelists were endocrinology experts who had relevant research about ACTH-dependent CS published in high-ranking peer-reviewed journals; participated in the development of disease-relevant treatment and diagnosis guidelines and had active involvement with peer-reviewed journals and scientific congress committees in the last 5 years; and/or displayed commitment to advancing CS management in clinical practice. Panelists were identified from Pituitary Society members and PubMed searches, and were selected for geographical and gender diversity to ensure a broad and inclusive range of perspectives. Forty-two experts were invited via email, of whom 41 accepted. The SC and panelists were not compensated for their involvement.

Study design

The study utilized a modified Delphi panel approach, characterized by successive iterations of surveys, participant anonymity, and a controlled feedback process. Two survey rounds were conducted for this Delphi panel, as it was deemed by the SC Chairs that further rounds would not add substantial value to the available results and consensus following completion of the second round.

Each round of the survey was delivered through a web-based platform, enforcing key Delphi panel requirements, such as participant anonymity and preventing retrospective changes to the survey once the round had been opened. Question types included Likert-scale, yes/no, single-choice, multiple-choice, ranking, and free-text questions. Likert statements used a 6-point scale: “strongly agree,” “agree,” “slightly agree,” “slightly disagree,” “disagree,” or “strongly disagree.” For all questions except ranking and free-text questions, panelists were also provided with the option to choose “do not wish to answer” or

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"insufficient expertise." An optional free-text box was included for every question to allow panelists the opportunity to contextualize their response.

Round 1 statement development

Round 1 statements were developed by the SC based on their contributions to and knowledge of the literature and clinical guideline reviews, as well as their own extensive clinical experience. Statements were grouped into 4 overarching categories: diagnosis, treatment and monitoring for recurrence, considerations for use of existing biochemical tests, and future opportunities. The treatment and monitoring for recurrence category was further broken down by treatment type: pituitary surgery, medical therapy (presented as separate categories for traditional titration therapies and block-and-replace regimens), and radiation therapy (encompassing conventional radiotherapy such as external-beam radiotherapy and stereotactic radiosurgery, such as Gamma Knife). Due to the lack of novel outcome data, specific questions on monitoring for recurrence after bilateral adrenalectomy were not included. The considerations for existing methods section was further broken down by biomarker test: 24-hour UFC, LNSC, and ONDST. Round 1 also included scoping questions used to gather information and context for statement development in Round 2.

Round 2 statement development

Statements reaching consensus in Round 1 were removed from Round 2. Round 1 statements that were close to reaching consensus or did not reach consensus were evaluated by the SC Chairs for inclusion in Round 2. Statements were either rephrased or expanded based on feedback from the SC and panelists from Round 1. The SC Chairs guided revised statement development and shared the statements with the wider SC for further review.

Where appropriate, Round 2 survey questions were presented to panelists alongside the anonymized group response distribution and their individual response for the related statement from Round 1.

Statistical approach

Consensus was defined as ≥70% of panelists choosing "strongly agree"/"agree" or "strongly disagree"/"disagree" for Likert-scale questions. For yes/no and single-choice consensus-gathering questions/statements, consensus was defined as ≥70% of panelists choosing the same option. Similarly, for scoping questions intended to characterize current clinical practice patterns rather than to elicit consensus, ≥70% of panelists reporting the same approach was used to identify commonly reported practices. For ranking questions, consensus was defined as a Kendall's $W \geq 0.7$. Consensus was not measured for free-text questions; responses were instead used to inform statement development between rounds and provide additional insights. "Slightly agree" or "slightly disagree" were categorized as neutral responses and did not contribute to the consensus calculation; respondents who chose "do not wish to answer" or "insufficient expertise" were considered to have opted out of that question and were not included in the overall calculation. Results were analyzed using the web-based platform and Microsoft Excel.

Results

Delphi rounds

Round 1 was open from October 16, 2025 to November 11, 2025; Round 2 was open from December 17, 2025 to January 14, 2026. All 41 panelists took part in Round 1, with one nonclinical PhD scientist not invited to participate in Round 2 as their expertise was not required for that round.

Seventy-six questions were included in Round 1, of which 45 were clinical practice scoping questions. Of the 31 questions designed to test consensus, 14 reached consensus. Round 2 included 33 questions, of which 8 were designed to collect panelist perspectives but not test consensus. Of the remaining 25 consensus-gathering questions, 11 reached consensus. Key findings based on the consensus achieved in this study as well as guidance and expertise of the SC have been synthesized for diagnosis (Box 1); disease monitoring for pituitary surgery (Box 2), medical therapy (Box 3), and raditation therapy (Box 4); considerations for existing biochemical testing methods (Box 5); and future opportunities (Box 6). The full list of statements/questions with their progression from Round 1 to Round 2, and their corresponding results, are summarized in Table S1 (36).

Diagnosis

In patients with mild symptoms of CS and slightly abnormal results of a single initial screening test, most panelists selected LNSC as

Box 1 Expert consensus and guidance on diagnosis of ACTH-dependent Cushing syndrome

- Screening of patients with *clinical suspicion of CS* should be performed with 1 or more of the 3 tests below:
  - LNSC (at least 2)
  - 24-hour UFC (at least 2)
  - ONDST
- Selection and timing of testing are guided by:
  - Clinical presentation
  - Pretest probability of CS (ie, likelihood of patient having CS before any confirmatory testing, based on clinical judgment) (2, 15)
  - Severity of hypercortisolism
- For patients with *mild* CS symptoms and *mildly abnormal results* of a single initial screening test:
  - *LNSC* (if available) is most commonly used as a confirmatory test
- For patients with *severe symptoms* of CS with *clearly abnormal* screening test *results:*
  - *24-hour UFC* is most commonly used as a confirmatory test
- Once hypercortisolemia is confirmed:
  - *ACTH measurement* is needed to determine if it is ACTH-independent or ACTH-dependent
  - Further localization testing is required for those with ACTH-dependent CS. *Pituitary magnetic resonance imaging (MRI)* followed by either *IPSS* or several other biochemical tests, combined with other imaging, should be performed

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the most frequently used test to confirm a diagnosis of mild CS, with a few panelists noting that they would confirm diagnosis by repeating the initial screening test or conducting additional tests. In patients with severe symptoms and clearly abnormal results, a majority of panelists reported 24-hour UFC as the most frequently used test to confirm severe CS diagnosis. However, there were varied responses on whether biochemical tests are used to exclude CS in a patient with an asymptomatic pituitary incidentaloma, with some panelists noting that they would only do so if there were suggestive clinical CS indicators. For those who indicated that they would use biochemical tests, ONDST was the most frequently selected answer, although this also did not reach consensus.

Presenting symptoms, pretest probability of CS, and severity of hypercortisolism were selected as the top 3 clinical and/or logistical factors influencing choice and timing of biochemical testing when diagnosing CS (Table 1).

Treatment and monitoring for recurrence: pituitary surgery

Most panelists selected IPSS as the most frequently used test to determine the source of ACTH excess in individuals with CS with/without a pituitary mass. Following transsphenoidal surgery (TSS) for resection of ACTH-secreting adenomas, panelists reached consensus that lifelong biomarker monitoring is needed to determine biochemical remission from hypercortisolism as well as to detect later recurrence. In patients with CD in remission with recovered AI following TSS, panelists most frequently selected that they would use LNSC and/or ONDST to monitor for disease recurrence. Although consensus was not reached regarding testing frequency, most panelists agreed that they would test every 6 months or every 12 months.

Following successful surgery with remission and adrenal recovery, panelists most often noted that a change in clinical status, unexpected biomarker test results, and/or inconclusive or ambiguous biomarker test results would cause them to order additional biochemical tests (in addition to those included in the routine schedule/frequency).

Consensus was reached that development of abnormal biochemical markers is the main factor that would prompt treatment after initial TSS. When considering repeat TSS for patients with persistent CD after pituitary surgery, panelists most frequently chose persistently elevated or rising UFC and/or LNSC as the biochemical markers that most commonly influence their decision. Notably, if abnormal biochemical results were accompanied by normal clinical features, most panelists would repeat testing, with some noting that this would also depend on the degree of elevation of the biochemical results. For those with clinical recurrence but normal biochemical test results, panelists reported that they would repeat and/or perform additional testing and treat comorbidities while monitoring cortisol biomarkers as the next step for testing/follow-up (Table 2).

Box 2 Expert consensus and guidance on monitoring after transsphenoidal surgery for Cushing disease

- Monitoring for recurrence:
  - *Lifelong biochemical monitoring* is recommended following resection of ACTH-secreting adenomas to confirm remission and thereafter to detect recurrence
  - *LNSC* (if available) and/or *ONDST* should be used first to monitor for disease recurrence in patients with surgical remission after recovery of hypothalamic-pituitary-adrenal (HPA) function. While there was no consensus on the frequency of testing, most experts agreed they would test every 6 months or 12 months
- If considering treatment after initial TSS:
  - *Persistent cortisol elevation after surgery* or *rising UFC and/or LNSC* should be used to drive clinical decision-making
- In patients with abnormal *biochemical results without corresponding clinical signs*:
  - *Repeating and/or conducting additional tests* is recommended as the next step
- In patients with *normal biochemical results* but *clinical suspicion of recurrence*:
  - *Repeating and/or conducting additional tests* and *treating comorbidities* while *monitoring cortisol biomarkers* is recommended as the next step, choosing the same biochemical markers that were abnormal at the time of diagnosis

Treatment and monitoring for recurrence: medical therapy

Almost all panelists indicated that when considering initiation of medical therapy, 24-hour UFC supported their clinical decision-making, with over two-thirds also selecting that they would use

Box 3 Expert consensus and guidance on monitoring during medical therapy for ACTH-dependent Cushing syndrome

- When initiating medical therapy:
  - *24-hour UFC* should be used to support clinical decision-making
- When monitoring biochemical response to medical therapy:
  - *24-hour UFC and LNSC* values should be used to monitor medical therapy efficacy, but not to diagnose AI
    - In cases where patients have normal UFC but abnormal LNSC at therapy initiation, LNSC should be followed over time
  - *Morning serum cortisol* values should be used to diagnose AI (some immunoassays for cortisol show notable cross-reactivity with 11-deoxycorticosterone when inhibitors of 11β-hydroxylase are used and this may underestimate therapeutic effectiveness with seemingly preserved morning serum cortisol values and risk missing AI based on biochemical grounds alone)
  - *ONDST should not* be *used* to *monitor* the *efficacy* of medical treatment
- Frequency of testing:

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- During *early stages* of *outpatient* medication dose titration for patients with *mild to moderate CS*, testing should be conducted every *2 to 4 weeks*
- For individuals with *severe ectopic CS* on dose titration with a rapidly acting oral medication *in an inpatient setting*, biochemical testing should be carried out *daily*

- Identification of under- and overtreatment:
  - *24-hour UFC* values should be used to assess undertreatment
  - *Serum cortisol* levels should be used to assess overtreatment
  - LNSC would be the test to use in patients with persistence or recurrence being managed medically who only had elevation of LNSC when treatment was initiated
- Block-and-replace:
  - *Block-and-replace* can be used rather than traditional dose titration for hypercortisolism alone in patients with *cyclical* or *severe CS*
  - *Hydrocortisone* is the glucocorticoid of choice for most during both the titration phase and long-term treatment for patients on block-and-replace; dexamethasone is also used in the titration phase for ease of cortisol monitoring. Prednisone is used by some clinicians
  - No consensus was reached on the long-term overall risk of developing AI on block-and-replace therapy compared to titration therapy, with most panelists expressing a neutral response; adrenal crises were reported to be infrequent for both approaches
- Circadian rhythm:
  - *Restoration of circadian rhythm* is a treatment goal for patients with CS
  - Assessment of circadian disruption can inform treatment adjustments and be used to predict clinical outcomes

LNSC. While consensus was not reached on the choice of a single biochemical test, almost half indicated that they would assess the results of multiple tests. For the monitoring of biochemical responses to medical therapy, almost all panelists indicated they would use 24-hour UFC, and nearly three-quarters of experts also selected LNSC and/or morning serum cortisol. Notably, panelists agreed that while 24-hour UFC can be used to monitor medical therapy efficacy in CS, it is not an appropriate test for diagnosing AI. All but one of the panelists also indicated they would not use ONDST to monitor the efficacy of medical treatment.

Panelists agreed that biochemical testing should be performed every 2 to 4 weeks during the early stages of medication dose titration in an outpatient setting for the average person with mild to moderate CS in order to achieve the desired level of control. In the inpatient setting for a severely ill patient with ectopic CS, panelists reached consensus that biochemical testing would be performed once a day during dose titration of a rapidly acting oral medication to achieve the desired level of control. The majority of panelists indicated that a change in patient's status, unexpected and inconclusive biomarker test results, planning for pregnancy, and modifications to a medical therapy regimen would warrant additional biochemical testing.

There was consensus that serum cortisol was the most important biomarker for identifying overtreatment, and 24-hour UFC was most important for identifying inadequate treatment (hypercortisolism). Nearly all panelists noted that persistent UFC elevation (reflecting persistent hypercortisolism) would influence decisions when considering individual modifications to medical therapy, and over half of the panelists also indicated that failure to consistently normalize LNSC would affect this decision. There was agreement among panelists that >50% of the time, changes in biomarkers are the primary factor prompting medication dose changes, switching to another medication, or adding another medication.

Panelists agreed that they rarely (1-25% of patients) encounter adrenal crises (acute AI) requiring injectable emergency glucocorticoids and/or hospitalization for individuals receiving medical therapies. Almost all panelists indicated that AI most commonly influences their decision to reduce dosage for a particular medical therapy, followed by assessment of whether radiation therapy (if administered) has been effective and biochemical tests indicating remission. Similarly, nearly all panelists agreed that therapy side effects would influence their decision to discontinue treatment (Table 3).

Summaries of panelist-provided biochemical cutoff values indicative of recurrence, AI, and over- and undertreatment are captured in Tables S2, S3, S4, and S5 (36).

Block-and-replace

Over three-quarters of panelists responded that they had used block-and-replace treatment for CS (including CD) at least once in the past. Most panelists selected that they would use block-and-replace over "traditional" CS medical therapy for hypercortisolism alone in patients with cyclical CS and for those with more severe disease, although a few also selected that this regimen would be considered if monitoring visits were a challenge for patients or if patients were ineligible for surgery. Other scenarios that were noted by panelists include patients who have had bilateral adrenalectomy with later evidence of recurrent endogenous cortisol production (adrenal rests), patients who are not able to identify symptoms of AI, difficulty controlling disease, or if symptoms persist with normal UFC. Most panelists also noted that their approach to biochemical monitoring for patients receiving block-and-replace would differ from those taking solely cortisol-lowering medical therapy. Key themes related to this question indicated that monitoring would be more intensive in the early stages of treatment, and that differences extend beyond the selection of biomarker tests used (eg, more frequent use of morning cortisol compared with 24-hour UFC, for patients on block-and-replace) to include variations in testing considerations (eg, ensuring that serum cortisol is measured prior to a morning hydrocortisone dose as well as tolerating a lower value for cortisol).

Consensus was reached about a preference for using hydrocortisone during the titration phase and for long-term treatment after the full uptitration period for patients being treated with block-and-replace, although dexamethasone and prednisone/prednisolone were also chosen by a few panelists to be used in the titration phase.

Consensus was not reached regarding block-and-replace being safer than medical therapy with titration in the long term. While all panelists reported that their patients on titration medical therapy experienced adrenal crises <50% of the time, slightly fewer panelists reported the same for their patients on block-and-replace (Table 3).

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Table 1 Key results on diagnosis of ACTH-dependent Cushing syndrome

Statement/question	Question type	Outcome	Delphi round
Please rank the following biochemical markers in order of their respective importance when screening an individual presenting with symptoms of Cushing syndrome. • 24-hour UFC • LNSC • Serum cortisol after overnight low-dose DST • Plasma ACTH • Other adrenal steroid hormone biomarkers	Ranking	*N* = 40 *Kendall's W: 0.74*	Round 1
For individuals with mild symptoms of Cushing syndrome and mildly abnormal results of one initial screening test, which biochemical test(s) do you most frequently use to confirm a diagnosis of mild Cushing syndrome?	Multiple-choice	*N* = 40 *LNSC: 80.0%* 24-hour UFC: 62.5% Overnight low-dose DST: 57.5% Desmopressin test: 25.0% Low-dose 2-day dexamethasone test: 20.0% Inpatient midnight serum cortisol: 7.5% Other diagnostic test: 5.0%	Round 1
For those with severe symptoms of Cushing syndrome and clearly abnormal results of one initial screening test, which biochemical test(s) do you most frequently use to further confirm a diagnosis of severe Cushing syndrome?	Multiple-choice	*N* = 40 *24-hour UFC: 77.5%* LNSC: 37.5% Overnight low-dose DST: 25.0% No additional test is required in the context of a concordant abnormal initial test result with clinical features of florid Cushing syndrome: 25.0% Inpatient midnight serum cortisol: 7.5% Desmopressin test: 2.5% Other diagnostic test: 2.5% Low-dose 2-day dexamethasone test: 0%	Round 1
What clinical and/or logistical factors influence your choice and timing of biochemical testing in diagnosing Cushing syndrome?	Multiple-choice	*N* = 40 *Presenting symptoms: 82.5%* *Pretest probability of the individual having Cushing syndrome: 75.0%* *Severity of hypercortisolism: 70.0%* Ability of the patient to complete the test: 67.5% Whether a patient has a normal day/night cycle: 65.0% Patient adherence with testing: 45.0% Patient characteristics: 30.0% Physician or patient access to a reference lab: 25.0% Insurance coverage: 5.0% Other: 0%	Round 1

Abbreviations: ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test; LNSC, late-night salivary cortisol; UFC, urinary free cortisol.

Circadian rhythm

Consensus was achieved for restoring circadian rhythm as a treatment goal for individuals with CS. Consensus was also reached that assessment of circadian rhythm disruption using biomarkers can inform treatment adjustments and predict clinical outcomes for patients receiving titration medical therapy, a question that did not reach consensus in the context of block-and-replace therapy.

Nevertheless, under two-thirds of panelists indicated that measures of circadian rhythm control are routinely checked for their patients receiving titrated therapy; even fewer panelists reported that this is routinely checked for their patients on block-and-replace therapy. Consensus was not reached regarding the frequency of these measures for either scenario.

Panelists agreed that monitoring diurnal cortisol patterns with LNSC or morning serum cortisol values provides helpful

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Table 2 Key results on pituitary surgery for Cushing disease

Statement/question	Question type	Outcome	Delphi round
Which of the following tests do you most frequently use to determine the source of ACTH excess in individuals with Cushing syndrome with/without a pituitary mass?	Multiple-choice	$N = 40$ *Inferior petrosal sinus sampling (IPSS): 85.0%* Desmopressin (DDAVP) stimulation test: 45.0% High-dose 8-mg DST (serum cortisol): 42.5% Pretest probability: 35.0% Corticotropin-releasing hormone (CRH) stimulation test: 22.5% Other: 22.5%	Round 1
When considering repeat transsphenoidal surgery (TSS) for persistent Cushing after pituitary surgery, which biochemical markers most commonly influence your decision?	Multiple-choice	$N = 40$ *Persistently elevated UFC: 77.5%* Persistently elevated LNSC: 67.5% Persistent failure to suppress cortisol after low-dose DST: 55.0% Trend of rising cortisol values: 27.5% Discrepancies between biochemical markers and clinical presentation: 12.5% Other: 10.0%	Round 1
For postoperative individuals with Cushing disease in remission with recovered adrenal insufficiency, which of the following biochemical tests do you use to monitor for disease recurrence following TSS?	Multiple-choice	$N = 40$ *LNSC: 85.0%* *Overnight low-dose DST: 70.0%* 24-hour UFC: 55.0% Whichever test was most abnormal preoperatively: 30.0% Other: 5.0%	Round 1
Which of the following would cause you to order additional biochemical tests in addition to routine schedule/frequency following successful surgery with remission and adrenal recovery?	Multiple-choice	$N = 40$ *Change in clinical status: 100.0%* *Unexpected biomarker test results: 95.0%* *Inconclusive or ambiguous biomarker test results: 87.5%* When a patient starts planning for pregnancy: 67.5% Abnormal MRI findings: 60.0% Significant change in serum potassium levels: 57.5% Rate at which patient recovered from adrenal insufficiency: 57.5% Perceived risk of recurrence: 40.0% Patient characteristics: 25.0% Other: 2.5%	Round 1
Lifelong biomarker monitoring is needed for individuals with Cushing disease following TSS to determine whether they are in biochemical remission from hypercortisolism as well as to detect later recurrence.	Likert	$N = 40$ *Agree: 82.5%* Neutral: 12.5% Disagree: 5.0%	Round 1
Which factor is the main consideration that would prompt treatment after initial TSS (repeat TSS or medical therapy)?	Single-choice	$N = 40$ *Biochemical markers becoming abnormal: 82.5%* Clinical features: 17.5% Change in pituitary adenoma size on MRI: 0% Other: 0%	Round 1
What is your next step for testing/follow-up if there are abnormal biochemical results but normal clinical features?	Multiple-choice	$N = 40$ *Repeat testing: 82.5%* Treat comorbidities and follow cortisol biomarkers: 57.5% Observe patient: 47.5% Treat hypercortisolism: 45.0% Other: 0%	Round 1

(*continued*)

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Table 2 Continued

Statement/question	Question type	Outcome	Delphi round
What is your next step for testing/follow-up if there is clinical recurrence but normal results from biochemical tests?	Multiple-choice	$N = 40$ *Repeat and/or perform additional testing: 92.5%* *Treat comorbidities and follow cortisol biomarkers: 77.5%* Observe patient: 52.5% Treatment of hypercortisolism: 15.0% Other: 0%	Round 1
When considering repeat TSS for persistent Cushing disease after pituitary surgery, which biochemical markers most commonly influence your decision?	Multiple-choice	$N = 40$ *Persistently elevated or rising UFC: 85.0%* *Persistently elevated or rising LNSC: 75.0%* Persistent failure to suppress cortisol after low-dose DST: 62.5% Discrepancies between biochemical markers and clinical presentation: 17.5%	Round 2

Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; DDAVP, 1-deamino-8-D-arginine vasopressin; DST, dexamethasone suppression test; IPSS, inferior petrosal sinus sampling; LNSC, late-night salivary cortisol; MRI, magnetic resonance imaging; TSS, transsphenoidal surgery; UFC, urinary free cortisol.

information about restoration of circadian rhythm and treatment efficacy for patients with titrated medical therapy (consensus was not reached for the same question within the context of block-and-replace therapy) (Table 3). While consensus was not reached on which circadian assessment was most important for monitoring patients with CS and mild symptoms of hypercortisolemia while receiving medical therapy, the majority of panelists chose LNSC as most important for patients on titration therapy and block-and-replace therapy.

Treatment and monitoring for recurrence: radiation therapy

The majority of panelists reported that they would use 24-hour UFC and/or LNSC to monitor for hypercortisolism resolution following radiation therapy. Most panelists indicated that morning 8:00-9:00 serum cortisol measurements and provocative cortisol tests would be used to monitor for AI after radiation therapy has controlled hypercortisolism in CD. Consensus was reached that biochemistry should be routinely assessed every 6 months in the first 5 years after radiation therapy for patients controlled on medical therapy (Table 4).

Box 4 Expert consensus and guidance on monitoring after radiation therapy for ACTH-dependent Cushing syndrome

- Monitoring following radiation therapy:
  - *24-hour UFC* and *LNSC* values should be used to monitor for hypercortisolism remission
  - *Results of morning serum cortisol* and *provocative testing* should be used to assess for development of *AI* after biochemical control is achieved

Considerations for existing biochemical testing methods

Overall, panelists reported a mostly equal use of mass spectrometry and immunoassay for assaying 24-hour UFC and LNSC, though a majority reported the use of immunoassay for ONDST.

Nearly all panelists reported that they would request additional biochemical tests as the next step when recurrence of CS is clinically suspected with borderline or mildly abnormal 24-hour UFC or LNSC values (Table 5). For both tests, most panelists indicated that they would typically require 2 samples for each patient (Table S6) (36).

The majority of panelists responded that 2 abnormal tests for 24-hour UFC and LNSC would be needed to indicate recurrent CS. For ONDST, most panelists noted that one abnormal test would

Box 5 Considerations for existing biochemical testing methods

- *Additional biochemical testing* is warranted when *clinical recurrence of CS is suspected* despite *borderline* or *mildly* abnormal *UFC or LNSC values*
- Number of tests required to confirm recurrence:
  - *Two* abnormal *UFC* or *LNSC* results are required to *confirm recurrence*
  - *Recurrence* could be determined by a *single abnormal ONDST,* after carefully excluding false positive results, in the presence of *suggestive symptoms*
- No consensus was reached regarding routine measurement of dexamethasone levels for ONDST, with most experts agreeing they would less often/rarely (<50% of the time) do this routinely; dexamethasone measurements were considered important in selected cases where a false positive test is suspected, as well as in patients on concomitant medications that could influence dexamethasone metabolism

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Table 3 Key results on medical therapy for ACTH-dependent Cushing syndrome

Statement/question	Question type	Outcome	Delphi round
Medical therapy (titration therapy)			
When considering initiation of medical therapy, which of the following biochemical tests do you use to support your clinical decision-making?	Multiple-choice	$N = 40$ *24-hour UFC: 95.0%* LNSC: 67.5% Overnight low-dose overnight DST: 30.0% Other: 10.0%	Round 1
Which of the following biochemical tests do you use to monitor biochemical response to medical therapy?	Multiple-choice	$N = 40$ *24-hour UFC: 97.5%* *LNSC: 72.5%* *Morning cortisol: 72.5%* Serum cortisol day curves: 20.0% Salivary cortisol/cortisone: 12.5% Overnight low-dose DST: 5.0% Whichever test was most abnormal preoperatively: 5.0% Other: 7.5%	Round 1
Which of the following scenarios would prompt you to order additional biochemical tests in addition to your routine schedule or frequency after medical therapy?	Multiple-choice	$N = 40$ *Change in patient's status: 100.0%* *Unexpected biomarker test results: 100.0%* *Inconclusive or ambiguous biomarker test results: 87.5%* *When a patient starts planning for pregnancy: 75.0%* *Changes in medical therapy regimen: 72.5%* Significant change in serum potassium levels: 57.5% Patient characteristics: 35.0% Other: 2.5%	Round 1
Although 24-hour UFC can be used to monitor medical therapy efficacy in Cushing syndrome, it is not appropriate for diagnosing adrenal insufficiency.	Likert	$N = 40$ *Agree: 92.5%* Neutral: 5.0% Disagree: 2.5%	Round 1
During routine follow-up of individuals with Cushing syndrome, which biochemical test do you consider most important for assessing overtreatment?	Single-choice	$N = 40$ *Serum cortisol: 87.5%* 24-hour UFC: 7.5% LNSC: 0% Whichever test was most abnormal preoperatively: 2.5% Other: 2.5%	Round 1
During routine follow-up of individuals with Cushing syndrome, which biochemical test do you consider most important for assessing whether the patient is being undertreated?	Single-choice	$N = 40$ *24-hour UFC: 70.0%* LNSC: 10.0% Serum cortisol: 15.0% Whichever test was most abnormal preoperatively: 5.0% Other: 0%	Round 1
When considering modifications to an individual's medical therapy (eg, change in dose, changing to a different medical therapy, adding a different medical therapy), which biochemical markers most commonly influence your decision?	Multiple-choice	$N = 40$ *Persistent elevation of UFC indicating ongoing hypercortisolism: 97.5%* Changes in biochemical results trends over serial measurements: 62.5% Failure to consistently normalize LNSC: 60.0% Discrepancies between biochemical markers and clinical presentation: 47.5% Other: 5.0%	Round 1
When considering reducing dosage for a particular medical therapy, which factors most commonly influence your decision?	Multiple-choice	$N = 40$ *Adrenal insufficiency: 95.0%* *To assess whether radiation therapy has taken effect yet: 77.5%* *Biochemical tests indicating remission: 70.0%* Glucocorticoid withdrawal syndrome: 67.5% Other: 5.0%	Round 1

(*continued*)

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Table 3 Continued

Statement/question	Question type	Outcome	Delphi round
How frequently have you encountered adrenal crises (acute adrenal insufficiency) requiring injectable emergency glucocorticoids and/or hospitalization for individuals on medical therapy regimens?	Single-choice	$N = 39$ *Rarely (1-25% of patients): 87.2%* Sometimes (26-50% of patients): 12.8% Often (51-75% of patients): 0% Very often (76-99% of patients): 0%	Round 1
Which of the following would influence your decision to discontinue treatment?	Multiple-choice	$N = 39$ *Decided on another treatment: 97.4%* *Side effects of the medical therapy: 92.3%* *In patients who have received radiation therapy, and in whom a trial of medication did not result in rising cortisol biomarkers: 82.1%* Patient's insurance no longer covers the medication: 25.6% Other: 5.1%	Round 1
Assessing circadian rhythm disruption using biomarkers can inform treatment adjustments and predict clinical outcomes for patients receiving medical therapy.	Likert	$N = 41$ *Agree: 75.6%* Neutral: 19.5% Disagree: 4.9%	Round 1
Monitoring diurnal cortisol patterns, such as with LNSC or morning cortisol, provides valuable information about restoration of circadian rhythm and treatment efficacy for patients treated with medical therapy.	Likert	$N = 40$ *Agree: 80.0%* Neutral: 20.0% Disagree: 0%	Round 1
Assessment of circadian rhythm through single diurnal measurements is sufficient (ie, no additional tests, such as UFC or LNSC, need to be performed) for patients on medical therapy.	Likert	$N = 39$ Agree: 5.1% Neutral: 15.4% *Disagree: 79.5%*	Round 1
Biochemical testing should be performed every 2-4 weeks during the early stages of dose titration of the medication in an outpatient setting for your average individual with mild to moderate Cushing syndrome in order to achieve the desired level of control.	Likert	$N = 40$ *Agree: 97.5%* Neutral: 0% Disagree: 2.5%	Round 2
How often do you typically perform biochemical testing initially during dose titration of a rapidly acting oral medication in an inpatient setting for a severely ill individual with ectopic Cushing syndrome to achieve the desired level of control?	Single-choice	$N = 39$ Every 4 hours: 7.7% Every 12 hours: 10.3% *Once a day: 82.1%*	Round 2
In your clinical practice, in what proportion of patients are changes in biomarkers the primary factor (as compared to other factors, like drug safety and tolerability, clinical status, etc.) prompting medication dose changes, switching to another medication, or adding another medication?	Single-choice	$N = 40$ *Very often/Often (≥50% of the time): 75.0%* Less often/Rarely (<50% of the time): 25.0%	Round 2
How often do your patients receiving medical therapy with titration (not block-and-replace regimen) experience adrenal crises?	Single-choice	$N = 40$ Very often/Often (≥50% of the time): 0% *Less often/Rarely (<50% of the time): 100.0%*	Round 2
How frequently do you have to discontinue treatment for individuals on medical therapy regimens for various reasons?	Single-choice	$N = 40$ Very often/Often (≥50% of the time): 10.0% *Less often/Rarely (<50% of the time): 90.0%*	Round 2

(*continued*)

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Table 3 Continued

Statement/question	Question type	Outcome	Delphi round
Restoring circadian rhythm is a treatment goal for individuals with Cushing syndrome.	Single-choice	$N = 24$[a] *Agree: 95.8%* Neutral: 4.2% Disagree: 0%	Round 2
Circadian assessment should only be used as an adjunct when monitoring for disease activity (should not be used as a sole test to titrate medical therapy).	Single-choice	$N = 24$[a] *Agree: 70.8%* Neutral: 8.3% Disagree: 20.8%	Round 2
Medical therapy (block-and-replace)			
In which of the following scenarios would you be likely to consider using block-and-replace rather than medical therapy for hypercortisolism alone?	Multiple-choice	$N = 32$[b] *Cyclical Cushing syndrome: 87.5%* *Severe disease: 81.3%* If monitoring visits are a challenge for patients: 46.9% Patient is ineligible for surgery: 21.9% Other: 12.5%	Round 1
For individuals being treated with block-and-replace regimens, which glucocorticoid do you prefer to use during the titration phase?	Single-choice	$N = 32$[b] *Hydrocortisone: 71.9%* Prednisone or prednisolone: 9.4% Dexamethasone: 12.5% Other: 6.3%	Round 1
For individuals on block-and-replace regimens, which glucocorticoid do you prefer to use for long-term treatment after the full uptitration period has been completed?	Single-choice	$N = 31$[b] *Hydrocortisone: 87.1%* Prednisone or prednisolone: 9.7% Dexamethasone: 0% Other: 3.2%	Round 1
How often do your patients on block-and-replace therapy experience adrenal crises?	Single-choice	$N = 33$[c] Very often/Often (≥50% of the time): 6.1% *Less often/Rarely (<50% of the time): 93.9%*	Round 2
In your practice, are measures of circadian rhythm control routinely checked for patients on block-and-replace therapy?	Single-choice	$N = 34$[c] Yes: 20.6% *No: 79.4%*	Round 2

[a]Question asked among those who responded "Yes" ($n/N = 24/40$) to "In your practice, are measures of circadian rhythm control routinely checked for patients receiving medical therapy using titration (not block-and-replace regimen)?" in Round 2.
[b]Question asked among those who responded "Yes" ($n/N = 32/41$) to "Have you ever used block-and-replace treatment for Cushing syndrome, including Cushing disease?" in Round 1.
[c]Question asked among those who responded "Yes" ($n/N = 34/40$) to "Have you ever used block-and-replace treatment for Cushing syndrome, including Cushing disease?" in Round 2.
Abbreviations: ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test; LNSC, late-night salivary cortisol; UFC, urinary free cortisol.

be needed to indicate recurrent CS in the presence of suggestive symptoms with no other abnormal biochemical tests (Table S7) (36). No consensus was reached regarding routine dexamethasone level measurement when ordering an ONDST.

Future opportunities

The need for improved diagnostic accuracy was the main theme that emerged as an unmet need in the management of CS. Consensus was reached regarding the need to develop newer and more reliable biomarkers to accurately monitor cortisol production and optimize diagnosis and treatment of CS, and that priority should be placed on circadian rhythm biomarkers for further research (Table 6). Steroid metabolomics were also

Box 6 Future opportunities

- Primary unmet needs identified:
  - *Improved diagnostic accuracy* in the initial diagnosis of CS and for identifying recurrence and determining management
  - *Development of more reliable biomarkers* to better assess cortisol production and circadian rhythm disruption
- Potential tools identified for monitoring disease progression and treatment response include:
  - Steroid metabolomics
  - Additional markers including: dehydroepiandrosterone sulfate (DHEAS) and FK506 Binding Protein 5 (FKBP5) methylation

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Table 4 Key results on radiation therapy for ACTH-dependent Cushing syndrome

Statement/question	Question type	Outcome	Delphi round
Which of the following biochemical tests do you use to monitor hypercortisolism resolution following radiation therapy?	Multiple-choice	*N* = 38 *24-hour UFC: 94.7%* *LNSC: 71.1%* Overnight low-dose DST: 55.3% Whichever test was most normal: 21.1% Other: 10.5%	Round 1
After the efficacy of radiation therapy has been established, which of the following biochemical tests do you use to monitor for adrenal insufficiency?	Multiple-choice	*N* = 40 *08:00-09:00 serum cortisol: 97.5%* *Short Synacthen Test/Cortrosyn Stimulation Test or other provocative cortisol tests with specific cortisol sampling time points: 75.0%* Salivary cortisol or cortisone: 7.5% Other: 5.0%	Round 1
Which of the following scenarios would prompt you to order additional biochemical tests in addition to your routine schedule or frequency after radiation therapy?	Multiple-choice	*N* = 39 *Change in patient's status: 100.0%* *Unexpected biomarker test results: 92.3%* *Inconclusive or ambiguous biomarker test results: 89.7%* *When a patient starts planning for pregnancy: 74.4%* Significant change in serum potassium levels: 38.5% Patient characteristics: 30.8% Other: 2.6%	Round 1
In a patient controlled on medical therapy who underwent radiation therapy, how often do you routinely assess biochemistry afterwards during the first 5 years?	Single-choice	*N* = 40 *Every 6 months: 87.5%* Every 12 months: 12.5%	Round 2

Abbreviations: ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test; LNSC, late-night salivary cortisol; UFC, urinary free cortisol.

noted as a possible opportunity for clinical application; additional biomarkers that were raised by panelists included the use of DHEAS for diagnosis and FKBP5 methylation and markers for cortisol action for monitoring disease progression and treatment response.

Discussion

Diagnosis

For diagnosing CS, a patient's presenting symptoms was the most frequently selected clinical and/or logistical factor influencing panelists' choice and timing of biochemical testing. Although presenting symptoms may lead to clinical suspicion of CS, these symptoms are often nonspecific and overlap with many common conditions (1-3, 5-9). In addition, biochemical tests can yield false positives in patients with nonneoplastic hypercortisolism (also known as pseudo-CS) (2, 3, 12, 14, 15, 37), suggesting that symptoms and abnormal biochemical results alone may not be sufficient to confirm a diagnosis of CS. Tests are often expensive, cumbersome to conduct, or limited in availability (38); the sensitivity, specificity, and precision of tests vary and can be affected by intra-patient variability (2, 10, 13). As such, it is important that all differential diagnoses are excluded and tests are performed only if there is a high suspicion of CS based on clinical features or concomitant pathologies (eg, adrenal adenoma). Indeed, most panelists chose pretest probability of CS as a factor that influences the choice and timing of biochemical testing for CS diagnosis.

Incorrect diagnoses of CS can lead to the misuse of medical therapy and unnecessary surgical intervention (7); to ensure an accurate diagnosis, all diagnostic tests may need to be repeated due to laboratory errors or heterogenous results, unless severe disease is manifested. Delays in diagnosis have been noted as a challenge for CS (2, 39, 40), which may be attributed in part to the complexity of biochemical testing. Panelists noted several barriers to employing biochemical tests, including lack of standardization of testing assays/reference ranges; intra-individual variability; patient-related factors (eg, ability to perform the test, adherence, medication, comorbidities, and pregnancy); insurance coverage and reimbursement challenges; and availability of the test (ie, lab capacity and availability in specific regions).

While 24-hour UFC has long been considered the first-line diagnostic test for CS (9, 15), results from this panel show that LNSC was more frequently selected to diagnose mild CS. The use of LNSC as a diagnostic test is increasing (9), with a growing body of evidence defining reference ranges and sensitivity and

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Table 5 Key results on the use of 24-hour UFC, LNSC, and ONDST (serum cortisol)

Statement/question	Question type	Outcome	Delphi round
24-hour UFC			
What are the main challenges you face when using 24-hour UFC to monitor disease activity in Cushing syndrome?	Multiple-choice	$N = 40$ *Collection can be burdensome and decrease patient adherence: 92.5%* *Results may be normal with early recurrence because UFC is typically the last biomarker to become abnormal: 87.5%* *Many patient characteristics can affect results: 72.5%* Interpreting intra-patient variability: 60.0% Laboratory turnaround times: 40.0% Insurance company requirement to use a specific laboratory: 2.5% Other: 5.0%	Round 1
What is your next step if 24-hour UFC results are borderline or mildly abnormal in the context of monitoring disease activity for Cushing syndrome when recurrence is clinically suspected?	Multiple-choice	$N = 40$ *Request additional biochemical tests: 95.0%* Correlate with clinical features: 65.0% Repeat testing with UFC: 62.5% Other: 2.5%	Round 1
LNSC			
What is your next step if borderline or mildly abnormal LNSC results are obtained when monitoring disease activity for Cushing syndrome when recurrence is clinically suspected?	Multiple-choice	$N = 34$[a] *Request additional biochemical tests: 97.1%* *Repeat testing with LNSC: 79.4%* *Correlate with clinical features: 76.5%* Other: 2.9%	Round 1
What are the main challenges you face when using LNSC to monitor disease activity in Cushing syndrome?	Multiple-choice	$N = 34$[a] *Working schedule (eg, night-shift workers, etc.): 85.3%* *Interpretation of borderline results: 73.5%* *Intra-patient variability due to factors like stress or sleep disturbance: 70.6%* Results may be normal despite recurrence: 50.0% Sample collection adherence: 44.1% Variability introduced by different laboratory assay methods: 38.2% Laboratory turnaround times: 35.3% Pregnancy: 29.4% Insurance company requirement to use a specific laboratory: 2.9% Other: 2.9% Not available in my country: 0%	Round 1
ONDST (serum cortisol)			
Which analytical method(s) do you, or your laboratory, currently use for assaying cortisol post-overnight DST when monitoring disease activity in Cushing syndrome?	Multiple-choice	$N = 40$ *Immunoassay: 80.0%* Mass spectrometry: 25.0% I am unable to choose (dictated by local availability): 10.0% I am unable to choose (dictated by health insurance): 0% Other: 0%	Round 1
What are the main challenges you face when using overnight low-dose DST to monitor disease activity in Cushing syndrome?	Multiple-choice	$N = 40$ *Use of oral estrogen, including oral contraceptives that increases corticosteroid-binding globulin (CBG): 90.0%*	Round 1

(*continued*)

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Table 5 Continued

Statement/question	Question type	Outcome	Delphi round
		Pregnancy: 67.5% Interpretation of borderline results: 62.5% There is limited evidence specifically assessing utility for recurrence: 45.0% Serum dexamethasone cannot be measured in the laboratory I use: 30.0% Timing of blood collection (between 08:00-09:00) affecting accuracy and reproducibility: 27.5% Variability introduced by different laboratory assay methods: 25.0% Fluctuations due to time of day or stress: 20.0% Other: 2.5%	
Do you use overnight low-dose DST to monitor the efficacy of medical treatment?	Single-choice	$N = 40$ Yes: 2.5% *No: 97.5%*	Round 2

[a]Question asked among those who responded "Yes" ($n/N = 34/41$) to "Is LNSC used as standard practice in your country/region?" in Round 1.
Abbreviations: CBG, corticosteroid-binding globulin; DST, dexamethasone suppression test; LNSC, late-night salivary cortisol; UFC, urinary free cortisol.

Table 6 Key results on future opportunities for ACTH-dependent Cushing syndrome

Statement/question	Question type	Outcome	Delphi round
Biomarkers are valuable to support clinicians in making treatment decisions and managing individuals with Cushing syndrome.	Likert	$N = 41$ *Agree: 97.6%* Neutral: 0% Disagree: 2.4%	Round 1
There is a need for the development of newer and more reliable biomarkers to accurately monitor cortisol production and optimize diagnosis and treatment of Cushing syndrome.	Likert	$N = 41$ *Agree: 90.2%* Neutral: 4.9% Disagree: 4.9%	Round 1
Which of the following emerging biomarker(s) do you believe warrants further research and investigation to improve monitoring of disease progression and treatment response in Cushing syndrome?	Multiple-choice	$N = 39$ *Circadian rhythm biomarkers: 84.6%* Measuring hair cortisol levels: 61.5% Measuring salivary cortisone: 59.0% Interstitial and/or soft tissue fluid profiling: 53.8% Other: 10.3%	Round 1
Which of the following biomarkers would you consider to be the highest priority for further research and investigation to improve monitoring of disease progression in Cushing syndrome?	Single-choice	$N = 38$ *Circadian rhythm biomarkers, including cortisol and cortisone: 76.3%* Measuring hair cortisol levels: 15.8% Other: 7.9%	Round 2
Which of the following biomarkers would you consider to be the highest priority for further research and investigation to improve monitoring of treatment response in Cushing syndrome?	Single-choice	$N = 39$ *Circadian rhythm biomarkers, including cortisol and cortisone: 82.1%* Measuring hair cortisol levels: 7.7% Other: 10.3%	Round 2

Abbreviations: ACTH, adrenocorticotropic hormone.

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specificity (2, 41, 42) and demonstrating greater sensitivity of LNSC than 24-hour UFC for detecting mild or recurrent CS (2, 42-45). Research has also demonstrated the potential role of late-night salivary cortisone, which has shown a minor but significant improvement in diagnostic accuracy compared with LNSC (41).

Few panelists also selected the use of the desmopressin test in the diagnosis of mild and severe CS, suggesting a lower usage of this test for confirmatory testing despite its availability. Additionally, there was no consistent approach to using biochemical testing to exclude CS in patients with an asymptomatic pituitary incidentaloma. However, several panelists noted that they would only test if there were suggestive clinical indicators, and that further evaluation would be required, in line with published guidelines (46).

Interestingly, only about 50% of the panelists indicated they frequently used desmopressin stimulation tests as a localization test to determine the source of ACTH excess (pituitary or ectopic), with even fewer electing to use CRH stimulation tests, which may in part be explained by the lack of availability of CRH in most countries.

Treatment and monitoring for recurrence: pituitary surgery

While IPSS was selected as the most commonly used test to determine the source of ACTH excess in CS patients, it should be noted that previous guidance states that IPSS is not recommended if the adenoma is >6 to 10 mm (1-3, 7). For IPSS, there is growing evidence to show that desmopressin has a similar robust stimulation response to CRH at 5-minutes poststimulation (47). Although the role of IPSS in tumor lateralization for preoperative planning is limited, it remains a valuable tool for confirming a pituitary source of ACTH excess (48).

Despite initial remission after successful surgical resection of a corticotroph adenoma, recurrence can occur frequently (1-3). For monitoring of recurrence following TSS, most panelists responded that LNSC and/or ONDST would be used; only around half of panelists reported that they would also use 24-hour UFC. LNSC is accurate for identifying remission and recurrence in postoperative patients with CD (10), suggesting a pivot away from the use of 24-hour UFC as a first-choice test to monitor remission and recurrence (9, 38). However, consensus was not reached regarding the frequency of testing, suggesting that this is an area for further investigation. The diagnosis of CD recurrence, which occurs in 5% to 35% of patients after transient remission following surgical resection of ACTH-secreting adenomas (2, 3, 38, 49), is often difficult to establish at an early stage as cortisol secretion is usually moderate and intermittent (38).

Symptoms of hypercortisolism may take up to a year to resolve after surgery (50), and achieving remission within 2 years may lower cancer risk among patients with CD (51) and reduce mortality risk in patients with CS (4), thereby suggesting a remission timeframe for optimal patient outcomes. Remission is currently seen in approximately 80% of patients with microadenomas and 60% with macroadenomas if the procedure is performed by an experienced surgeon (2). Patients in remission require glucocorticoid replacement until HPA axis recovery; as remission could be delayed, patients should be monitored until achieving postoperative cortisol nadir (2). In this study, panelists reached consensus that lifelong biomarker monitoring is needed to determine whether patients are in biochemical remission from hypercortisolism and to detect later recurrence, which aligns with published guidance (2, 3, 16, 52).

Treatment and monitoring for recurrence: medical and radiation therapy

As with diagnosis and monitoring for recurrence following pituitary surgery, panelists indicated that they would use 24-hour UFC, LNSC, and/or morning serum cortisol to monitor biochemical response to medical therapy. This aligns with the literature that LNSC may be a superior choice to 24-hour UFC in monitoring treatment efficacy (44). Research also supports serial measurements of saliva cortisol or cortisone, particularly for chronotherapy (30, 31, 53-55), though its use for block-and-replace regimens could also be envisioned. While nearly all panelists indicated that persistent UFC elevation would most commonly influence their decision to modify a patient's medical therapy, over half also selected that failure to consistently normalize LNSC would affect this decision. These are particularly important considerations in the monitoring of patients receiving medical therapy who do not have elevated 24-hour UFC when treatment was initiated; previous guidance has also indicated that monitoring should be performed with LNSC if it was the only abnormal biochemical result upon the start of medical therapy (2).

A pooled analysis of patients treated with osilodrostat using titration therapy reported hypocortisolism-related events (including AI) in 46.3% of patients, mostly within 12 weeks but also much later in the course of the treatment, with AI (3.5%) also being the most common investigator-reported adverse event leading to permanent osilodrostat discontinuation (24). In this Delphi panel, panelists indicated that their patients rarely experience adrenal crises with titration therapy or block-and-replace therapy, although these findings may be influenced by selection bias for patients undergoing titration and the inclusion of patients who receive hydrocortisone on an as-needed basis. Studies on other adrenal steroidogenesis inhibitors and AI vary in design and drug potency (55-58), but the available evidence demonstrates a need for frequent biochemical assessments to monitor for AI (55-59).

Block-and-replace

With advances in medical therapy, the block-and-replace approach has seen broader adaptation because it offers cortisol control with low risk of AI (2, 21, 23, 27, 60). However, the ideal patient population and monitoring approach for this regimen have not been defined.

In alignment with the literature, the majority of panelists indicated in this study that they would consider block-and-replace regimens for those with cyclic (26, 27, 61) or more severe CS (37). In such scenarios that necessitate a rapid suppression of cortisol, the block-and-replace approach may be warranted to minimize the risk of adrenal crises (26, 60). Some panelists agreed that this approach would also be considered for patients ineligible for surgery or when monitoring visits are a challenge for patients, which has also been previously reported (2, 23, 26, 60). The use of block-and-replace treatments minimizes the risk of AI (2, 21, 23, 27, 60), reducing the need for constant monitoring, which is enabled in an inpatient setting.

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However, caution is needed to avoid glucocorticoid overreplacement and inducing iatrogenic CS (2). Although there are no standard guidelines for monitoring block-and-replace therapy, it is recommended that serum cortisol concentrations are monitored at 8:00-9:00 following the achievement of AI to obtain an accurate reading of daily cortisol production, depending on the type of glucocorticoid regimen used (21, 62). Updated morning serum cortisol thresholds, which may vary depending on the assay used, may better predict and rule out central AI, further supporting the use of morning serum cortisol as a reliable cost-effective test to diagnose medication-induced AI (63, 64).

Although most panelists selected LNSC as the most important circadian assessment for monitoring patients with CS and mild symptoms of hypercortisolemia while receiving block-and-replace therapy, it is important to note that this should be withheld for 24 hours if the patient is on hydrocortisone to avoid interference with test results (53, 65). Saliva cortisone could be used to avoid contamination, although it is not currently readily available for clinical use.

As block-and-replace is a relatively new approach for ambulatory patients (ie, outside of intensive care, in critically ill patients who need immediate control of very high cortisol), there was less consensus on this topic among panelists. Nevertheless, given the increasing interest in block-and-replace regimens, the findings of this study represent an initial step toward achieving expert consensus on the use of this therapy; further research is needed to define and standardize patient-monitoring strategies.

Circadian rhythm

The loss of circadian rhythm in patients with CS underscores the increasing importance placed on the use of circadian rhythm biomarkers for monitoring disease activity at diagnosis and after treatment. In this study, panelists agreed that restoring circadian rhythm should be a treatment goal for individuals with CS. Even when patients receive cortisol-lowering therapy and have a normalized UFC, mild hypercortisolism can persist (29). There is evidence that restoring the physiological early morning rise in cortisol among patients with AI improves outcomes, including fatigue and quality of life (33). Conversely, persistently elevated cortisol levels, especially during the night, have been associated with more adverse outcomes, such as hypertension, diabetes, and poorer clinical scores (27, 29, 31, 32, 49, 66). Loss of rhythmicity in clock genes during active CS may persist for certain genes even after remission of CS (67), further emphasizing the importance of monitoring and restoring circadian rhythm.

While panelists agreed that assessing circadian rhythm disruption using biomarkers can inform treatment adjustments and predict clinical outcomes for patients receiving titrated medical therapy, only 60.0% reported that measures of circadian rhythm control are routinely checked for these patients. Interestingly, the panelists did not reply similarly in the context of block-and-replace therapy, with only 20.6% of panelists reporting that measures of circadian rhythm control are routinely checked. These conflicting results and the lack of consensus on how frequently to measure these biomarkers in both scenarios suggest that, although clinicians see value in restoring circadian rhythm, it may not yet be standard practice for many. This may be especially true for therapeutic strategies such as block-and-replace, pointing to an area for further investigation. In addition, future research should investigate whether circadian rhythm control, as assessed through biomarkers, differs between the acute phase after medication initiation and longer-term chronic management.

Radiation therapy

Consistent with the findings on diagnosis and other therapies, most panelists selected that they would use 24-hour UFC and LNSC to monitor hypercortisolism following radiation therapy. Past research has noted inconsistent definitions of biochemical remission as a barrier in disease monitoring after radiotherapy, and has suggested that testing for LNSC in addition to 24-hour UFC may theoretically allow for a greater number of recurrences to be detected (68). Indeed, evidence also exists to show that LNSC may be as accurate as 24-hour UFC in identifying remission in patients after radiation therapy (69). As radiation can lead to delayed hypopituitarism with central AI, monitoring morning serum cortisol and provocative testing is essential (70). More information is needed regarding the frequency of monitoring for remission beyond the 5 years that were addressed in the current Delphi panel survey.

Considerations for existing methods

Although the results of this study show that in practice the use of mass spectrometry and immunoassay for 24-hour UFC and LNSC was comparable among panelists, previous guidance has recommended the use of liquid chromatography tandem mass spectrometry when testing for LNSC due to its higher specificity for CS (2).

The majority of panelists responded that 2 abnormal test results for 24-hour UFC and LNSC would be needed to indicate recurrent CS. This aligns with previously published recommendations on confirming hypercortisolism to mitigate the risk of misdiagnosis (1, 2, 6, 11).

Altered absorption or metabolism of dexamethasone can influence ONDST outcomes (71, 72). While measuring dexamethasone serum concentration can improve the reliability of test interpretation (71-74), a 2022 study demonstrated adequate dexamethasone concentrations among a majority of patients, suggesting that routine measurement may be unnecessary and only required when nonadherence or abnormal dexamethasone absorption or metabolism is suspected (71). No consensus was reached in this study regarding routine dexamethasone level measurement when ordering an ONDST, but the high risk of false positive results for ONDST should always be considered (2, 3, 6-9).

Future opportunities

Panelists agreed that further investigation is required to elucidate circadian rhythm biomarkers, aligning with the literature (67). Measuring cortisol concentrations in blood, saliva, urine, or hair plays a fundamental role in the clinical course of patients with CS by highlighting qualitative or quantitative abnormalities in cortisol production. Hair cortisol and cortisone perhaps hold most promise in reflecting long-term elevated cortisol exposure (1, 3, 29, 38, 75); steroid metabolomics were also noted as a possible opportunity for clinical application (3, 38). Previous literature has considered validation of a multiomic approach,

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combining genomics, transcriptomics, proteomics, and metabolomics to provide innovative molecular tests for CS (38). Panelists also noted the difficulty in accurately distinguishing between pituitary and ectopic sources of ACTH excess as a challenge for diagnosis (76), with recent research exploring the use of a 4-mg intravenous dexamethasone suppression test (77), as well as machine-learning and UFC-based diagnostic algorithms to address this (78, 79).

Strengths and limitations

The Delphi panel method offers a robust methodology to gather expert consensus, with key methodological considerations enforced by using a customized web-based Delphi survey platform. The panel comprised a range of experts representing a wide geographical diversity, with no panelist attrition occurring across rounds. One nonclinical PhD scientist was included in Round 1 to provide additional expertise on the use and interpretation of biochemical tests; for Round 2, their expertise was deemed not to be necessary by the SC as questions pertained to clinical scenarios.

The SC drafted and reviewed statements to ensure clinical relevance and medical accuracy. Due to the international scope of the Delphi panel, not all nuances related to differing regional practices and healthcare structures could be included. Accordingly, some variation in responses was expected and may have limited the extent of consensus among this diverse group of panelists. While areas that did reach consensus have been highlighted, it is important to note that areas of nonconsensus also serve as informative and meaningful outcomes that not only showcase differences in regional practices but also identify areas where further evidence generation, education, or alignment may be warranted. It would be beneficial for future research to explore how considerations and guidance included here may be applied in practice in specific countries and/or regions. Furthermore, due to the heterogenous nature of CS clinical presentations and the individualized care needed, not all patient scenarios could be uniformly captured. Nevertheless, the robustness of this initiative lies in the diverse geographic backgrounds and experiences of the international panelist group. While most statements were drafted to be as applicable to as many panelists as possible, an “opt-out” option was provided if they did not wish to answer or did not feel that they had the relevant experience to ensure that responses reflected the specific expertise required.

While the questions related to diagnosis in this study were applicable to all patients with CS, many others regarding recurrence after TSS and monitoring post-radiation pertained exclusively to CD, which is the most frequent cause of CS. Furthermore, questions related to severe CS addressed mostly patients with ectopic CS. Aspects of ACTH-dependent CS that were not comprehensively evaluated per the scope of this Delphi panel present an opportunity for further research and discussion.

Conclusion

This modified Delphi panel gathered updated expert consensus on the use of biomarkers in existing and emerging diagnostic and disease monitoring approaches for ACTH-dependent CS. Notably, a majority of panelists reported the use of LNSC for the diagnosis of mild CS, monitoring of recurrence following TSS for CD, monitoring of biochemical response to medical therapy, and monitoring of hypercortisolism after radiation therapy for CD, suggesting a shift from conventional approaches. Alternative therapeutic strategies such as block-and-replace as well as treatment algorithms to improve circadian rhythm control are emerging for longer-term chronic management and warrant broader evaluation and possible adoption. Research priorities should be aimed at advancing diagnostic accuracy and establishing reliable biomarkers to assess cortisol production and circadian disruption.

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Data availability

Original data generated and analyzed during this study are included in this published article or in the supplementary information.

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