

# Consensus on diagnosis and management of Cushing's disease

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1 **Consensus on Diagnosis and Management of Cushing's Disease:**

2 **A Guideline Update**

3

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95 **ABSTRACT**

96

97 **Objective:** Cushing’s disease (CD) requires accurate diagnosis, careful treatment selection, and  
98 long-term management ~~of the disease and its associated comorbidities~~ to optimize patient  
99 outcomes. The Pituitary Society convened a Consensus Workshop comprising more than 50  
100 academic researchers and clinical experts to discuss ~~recent evidence and its~~ the application of  
101 recent evidence to clinical practice.

102 **Participants:** ~~More than fifty academic researchers and clinical experts in pituitary~~  
103 ~~pathophysiology, neurosurgery, endocrinology, and radiation oncology participated. The meeting~~  
104 ~~was supported by unrestricted educational grants to the Pituitary Society.~~

105 **Evidence:** ~~Speakers critically summarized key~~ In advance of the virtual meeting, recent data on  
106 ~~28 discrete topics across areas of screening and diagnosis; optimal use of and outcomes from~~  
107 ~~surgery, medical therapy, and radiation therapy; and identification and management of disease-~~  
108 ~~and treatment-related complications.~~ of CD were critically summarized in recorded lectures  
109 ~~were recorded approximately one month prior to the meeting, and all experts were invited to~~  
110 ~~watch the lectures and offer comments~~ that were reviewed by all participants.

111 **Workshop Process:** ~~During the virtual meeting, speakers provided highlight summaries of their~~  
112 ~~assigned topics, which were discussed by all participants in~~ concise summaries of the recorded  
113 lectures were presented, followed by small group breakout sessions discussions. ~~Summaries and~~  
114 ~~conclusions from group discussions~~ Consensus opinions from each group were collated and an  
115 ~~evidence-based~~ into a draft document ~~was sent to all participants for accuracy review, additional~~  
116 ~~feedback, and approval, which was reviewed and approved by all participants.~~

117 **Conclusions:** Recommendations ~~and key considerations for~~ regarding use of laboratory tests,  
118 imaging, and ~~medical therapy~~ treatment options are presented, along with algorithms for  
119 diagnosis of Cushing's syndrome, ~~monitoring~~, and management of CD. Topics considered that  
120 ~~were rated the most important to address in future research to further improve patient outcomes~~  
121 ~~were~~ also identified.



122 **INTRODUCTION**

123 Cushing’s disease (CD), the most common cause of endogenous Cushing’s syndrome (CS),  
124 is caused by an adrenocorticotropin (ACTH)-secreting pituitary tumor.<sup>1</sup> Optimal patient  
125 outcomes require accurate diagnosis, careful treatment selection, and assessment and  
126 management of the disease and its associated comorbidities to optimize patient outcomes.<sup>2</sup>  
127 Notably, in comparison to patients with adrenal causes of CS, long-term quality of life (QoL) is  
128 worse for patients with CD.<sup>3</sup> Since clinical guidelines published in 2003,<sup>4</sup> 2008,<sup>5,6</sup> and 2015,<sup>7</sup>  
129 novel screening and diagnostic modalities have been identified and new treatments have been  
130 approved for use. These new developments highlight the need for updates to clinical guidelines  
131 on this challenging disorder.

132 The Pituitary Society convened a 2-day virtual workshop in October 2020 to discuss  
133 management of CD, with a goal of critically reviewing the current literature and providing  
134 recommendations for screening and diagnosis; optimal use of and monitoring outcomes from  
135 surgery, medical therapy, and radiation therapy; and identification and management of disease-  
136 and treatment-related complications. The focus was on pituitary, rather than adrenal or ectopic  
137 CS, and overlapping topics that had been recently covered in other consensus statements/reviews  
138 were not included.

139 We briefly review recent evidence and recommendations for clinical practice, grading the  
140 quality of the evidence supporting the recommendations and the strength of the consensus  
141 recommendations. A summary of consensus recommendations, key considerations for use of  
142 different laboratory tests and medical therapies are presented in Tables 1 and 2,  
143 Consensus recommendations for management of CD complications and use of medical therapy  
144 for CD are presented in Panels 1 and 2. and Evidence/recommendations grading schema<sup>8,9</sup> are

145 presented in Tables 1–5 Panel 3. Algorithms for diagnosis, ~~monitoring,~~ of CS and management of  
146 CD are presented in Figures 1 and 2. Topics that were rated the most important to address in  
147 future research to further improve patient outcomes are listed in Table 6 Panel 4.

148 Recommendations for adults with CD are presented here for use in clinical practice but  
149 should be considered alongside patient- and disease-specific factors for personalized care. A  
150 brief section regarding unique considerations in pediatric CD is presented at the end of the  
151 manuscript.

## 153 **METHODS**

154 Workshop co-chairs and steering committee members identified 28 discrete topics related to  
155 CD diagnosis, complications, and treatment to be addressed, and invited experts to summarize  
156 key data on their assigned topics in 15-minute, fully referenced slide-lectures presentations  
157 recorded approximately one month prior to the meeting. Speakers critically reviewed literature  
158 indexed in PubMed and published in English before October 2021. Search terms included  
159 “cushing’s disease,” “ectopic Cushing’s,” and terms associated with each topic: “diagnosis,”  
160 “urinary free cortisol,” “salivary cortisol,” “screening tests,” “confirmatory testing,” “differential  
161 diagnosis,” “localization testing,” “genetics,” “surgery,” “radiation therapy,” “medical therapy,”  
162 “biochemical treatment goals,” “tumor shrinkage,” “clinical outcomes,” “adrenal steroidogenesis  
163 inhibitors,” “glucocorticoid receptor blockers,” “somatostatin receptor ligands,” “dopamine  
164 agonists,” “mortality,” “comorbidities,” “quality of life,” “preoperative treatment,” “combination  
165 therapy,” and “guidelines.” All experts-participants were invited to watch the lectures and offer  
166 comments in advance of the meeting. More than 50 academic researchers and clinical experts  
167 from 13 countries across 5 continents participated in the Workshop.

168 During the 2-day meeting, speakers provided 5-minute highlight summaries of their assigned  
169 topics. Participants were then divided into 4 small groups for extended discussions of each topic  
170 during 6 breakout sessions. Group Session moderators were provided with a set of key questions  
171 to prompt discussion. Brief written reports on the discussion and consensus reached, along with  
172 lecture material and one page summary précis from each speaker, were collated and edited to  
173 develop the recommendations. One person in each group was designated in advance to take notes  
174 and assist in recording key discussion comments and consensus statements based on majority  
175 opinion.

176 After the meeting, speakers prepared detailed précis and literature reviews on their assigned  
177 topics. The fully referenced slide-lecture presentations, précis, and literature reviews were  
178 collated to prepare a draft manuscript, along with more recent data identified in a second  
179 literature review using the same keywords performed by the first and senior author in April 2021.  
180 Consensus recommendations for managing CD complications and use of medical therapy shown  
181 in Panels 1 and 2 were based on written reports from breakout sessions.

182 Speakers were asked to verify for accuracy manuscript sections related to their assigned  
183 topics, and the draft manuscript and consensus recommendations was circulated to all Workshop  
184 participants for review.

185 Speakers were also asked to suggest topics for future research that they consider most  
186 important. The full list of suggestions was sent to all participants, who were ~~invited~~ asked to vote  
187 for those they considered most essential; the most highly ranked topics are listed in Table 6 their  
188 top 5 choices. The senior author tabulated responses; topics with more than 10 votes are shown  
189 in Panel 4. Speakers confirmed the accuracy of the evidence summaries and all authors reviewed

190 ~~and approved the final version of the manuscript. After incorporating edits and comments, the~~  
191 ~~final manuscript was again circulated for review and approval.~~

192

193 **~~Role of the Funding Source~~**

194 ~~Supporters were invited to observe the highlight summaries, but did not observe the small~~  
195 ~~group discussions, had no role in the development of consensus recommendations or topics for~~  
196 ~~future research, and did not review the manuscript prior to publication.~~

197 **DIAGNOSIS OF CS: SCREENING, CONFIRMATORY, AND LOCALIZATION**

198 **MODALITIES**

199

200 **Laboratory Tests (Table 1)**

201 *Background*

202       Diagnosis of CS is often delayed for years, at least in part due to lack of awareness of the  
203 insidious, progressive disease process and the complexity of testing.<sup>10</sup> Screening and diagnostic  
204 tests for CS assess cortisol secretory status: abnormal circadian rhythm with late night salivary  
205 cortisol (LNSC), impaired glucocorticoid feedback with overnight 1-mg dexamethasone  
206 suppression test (DST) or low dose 2-day dexamethasone tes (LDDT), and increased  
207 bioavailable cortisol with 24-hour urinary free cortisol (UFC).<sup>5,6,11,12</sup> In this setting, the  
208 sensitivity of all tests is above 90%, with the highest rates seen with DST and LNSC and the  
209 lowest with UFC; specificity rates are somewhat lower, LNSC being the most specific and DST  
210 and UFC the least specific.<sup>12,13</sup>

211

212 *LNSC*

213       The diagnostic utility of LNSC is based on the assumption that patients with CS lose the  
214 normal circadian nadir of cortisol secretion;<sup>14,15</sup> at least two or three LNSC tests are  
215 recommended.<sup>5,16</sup> Patients with mild CS may have LNSC results just above the upper limit of  
216 normal (ULN). Sampling saliva at usual bedtime rather than at midnight could decrease false  
217 positive results,<sup>17</sup> as cortisol nadir is tightly entrained to the onset of sleep. Although mass  
218 spectrometry can detect both cortisol and cortisone and therefore avoids potential contamination  
219 from topical hydrocortisone preparations, sensitivity is better than with immunoassay, but at the

220 expense of reduced specificity.<sup>18</sup> Multiple, periodic, sequential LNSC are particularly useful for  
221 the longitudinal surveillance needed in distinguishing patients with cyclic CS who exhibit weeks  
222 to months of normal cortisol secretion interspersed with episodes of cortisol excess.<sup>19</sup> By  
223 contrast, this test should not be performed in patients with disruption of the normal day/night  
224 cycle, such as night-shift workers.<sup>14,15</sup>

225

### 226 *Overnight 1-mg DST*

227 In healthy individuals, a supraphysiologic dose of dexamethasone inhibits vasopressin and  
228 ACTH secretion, thereby decreasing cortisol levels. Thus, a serum cortisol value < 1.8 µg/dL (50  
229 nmol/L) at 0800 h in the morning after oral administration of 1 mg dexamethasone between 2300  
230 h and midnight is considered a normal response.<sup>5</sup> Sensitivity at this cut-off is higher than  
231 specificity, and a negative result strongly predicts absence of CS. At higher cutoff points, e.g., 5  
232 µg/dL (138 nmol/L), DST sensitivity is reduced.<sup>12</sup> When cortisol values are less than the lower  
233 cut-off of 1.8 µg/dL, this excludes dysregulated cortisol production from an adrenal  
234 incidentaloma;<sup>20</sup> in this setting, values over 5 µg/dL generally identifies patients with  
235 dysregulated cortisol secretion from an incidentaloma who have overt CS. False positive results  
236 may be seen with rapid absorption/malabsorption of dexamethasone, such as in patients with  
237 increased gut transit time, chronic diarrhea, or celiac disease; concomitant treatment with  
238 CYP3A4 inducers such as phenobarbital, carbamazepine, and St. John's wort (*Hypericum*  
239 *perforatum*); and increased corticosteroid binding globulin (CBG) levels resulting from oral  
240 estrogens, pregnancy, or chronic active hepatitis, as this may increase total cortisol levels.<sup>21-23</sup>  
241 Measuring dexamethasone concomitantly with cortisol, using laboratory-specific ranges of  
242 expected values, can confirm a suppressive concentration and reduce the risk for false-positive

243 results.<sup>24,25</sup> False negative results are less common, and may result from inhibition of  
244 dexamethasone metabolism by concomitant medications, such as fluoxetine, cimetidine, or  
245 diltiazem, which leads to a higher biologically available dose. Decreased CBG and albumin  
246 levels, such as in patients with concurrent nephrotic syndrome, also might produce a falsely low  
247 value.<sup>26</sup> Normative data with modern assays are also needed.

248

#### 249 *UFC*

250 At least two or three 24-hour urine collections are advised to measure UFC to account for  
251 intra-patient variability.<sup>5,27</sup> One advantage with UFC over DST is that overall cortisol production  
252 is independent of changes in CBG, and is not dependent on dexamethasone compliance.  
253 However, although calculating the mean of several collections aids in correct interpretation,  
254 random variability can be as high as 50% between collections.<sup>28</sup> As with LNSC, UFC relies on  
255 accurate collection by the patient.

256 Sex, body mass index (BMI), age, very high or low urinary volume, and sodium intake can  
257 all influence UFC levels and should be taken into account for correct interpretation.<sup>29-33</sup> As urine  
258 volume and glomerular filtration rate strongly predict UFC, other screening tests such as LNSC  
259 may be preferred for patients with renal impairment (CrCl <60mL/min) or significant polyuria  
260 (>5 L/24 h).<sup>34,35</sup>

261

#### 262 *Testing for non-neoplastic hypercortisolism (pseudo-CS)*

263 Psychiatric disorders, alcohol use disorder, polycystic ovary syndrome, and obesity may  
264 activate the hypothalamic-pituitary-adrenal (HPA) axis.<sup>36,37</sup> Such patients also may have  
265 concomitant features of CS that are common in the general population (e.g., weight gain) that

266 lead to biochemical screening. DST, LNSC, and UFC may all show positive (abnormal) results  
267 in these patients with non-neoplastic clinical hypercortisolism, or so-called pseudo-CS.<sup>38</sup>  
268 Furthermore, concomitant medications could result in steroid cross-reactivity or otherwise  
269 interfere with laboratory test results. However, these abnormal results tend to be mildly elevated;  
270 for example, UFC is almost always within 3-fold of normal. The combined LDDT-CRH (Dex-  
271 CRH) test, LDDT, or the desmopressin test may be able to distinguish between ACTH-  
272 dependent CS and pseudo-CS.<sup>39-41</sup> Utility of the Dex-CRH test in this setting is based on the  
273 assumption that only patients with ACTH-dependent CS will show a cortisol response to CRH  
274 after dexamethasone suppression.<sup>42</sup> However, test reliability may differ due to different  
275 protocols, use of various ovine or human CRH doses, characteristics of cortisol and ACTH  
276 assays, and patient characteristics (e.g., degree of hypercortisolism, adrenal versus pituitary CS,  
277 and underlying conditions). Use of the desmopressin test is based on the finding that ACTH-  
278 secreting adenomas express vasopressin V1b (V3) receptors, producing a rise in plasma ACTH  
279 after desmopressin injection.<sup>43</sup> The desmopressin test has a high specificity for CD<sup>44</sup> and is less  
280 complex and expensive than the Dex-CRH test, but both have shown good diagnostic  
281 performance in distinguishing CS from pseudo-CS in some studies; when both tests are done,  
282 they showed excellent agreement.<sup>45,46</sup>

283

## 284 ***Clinical Considerations and Recommendations***

### 285 *Screening and confirmatory testing for CS*

286 There is no single preferred diagnostic test for CS, nor is there consensus on how to decide  
287 whether and when to test, although there have been attempts to develop a score for ease of  
288 diagnosis.<sup>47</sup> Clinical judgment and index of suspicion for CS are very important<sup>48</sup> and underscore



289 the need to individualize decisions about timing and selection for diagnostic testing based on the  
290 clinical scenario (HQ, SR).

291 If CS is suspected, any of the diagnostic tests may be useful. We recommend starting with  
292 DST, UFC, and/or LNSC (HQ, SR) depending on local availability, with the recognition that  
293 multiple LNSCs may be easier for the patient to complete (HQ, SR). If an adrenal tumor is  
294 suspected, we recommend starting with DST (MQ, SR) and only using LNSC if cortisone levels  
295 can be also reported<sup>16,18</sup> (MQ, SR).

296 DST may be the preferred test for shift workers and patients with disrupted circadian rhythm  
297 due to uneven sleep schedules, but may not be reliable in women treated with oral estrogen (HQ,  
298 SR). Measuring dexamethasone level may be useful if a false-positive DST is suspected due to  
299 the clinical scenario (MQ, SR). If UFC is used, two or three collections should be obtained to  
300 evaluate variability (HQ, SR). If LNSC is used, we recommend at least two or three tests (HQ,  
301 SR). Although there were initial concerns about increased risk for infection from SARS-CoV-2  
302 with LNSC,<sup>49</sup> it remains safe for testing for lab personnel when used with proper precautions.<sup>50</sup>  
303 Bilateral inferior petrosal sinus sampling (IPSS) should not be used to diagnose hypercortisolism  
304 because the central-to-peripheral ACTH gradient in healthy controls and pseudo-CS overlaps  
305 that seen in patients with CD<sup>51</sup> (HQ, SR). In cyclic CD, dynamic testing and localization testing,  
306 including IPSS, should be preceded by a confirmatory LNSC, DST, or UFC to document that the  
307 patients are in the active phase.<sup>52</sup>

308 At this time, there is no preference for mass spectrometry over immunoassay in measuring  
309 cortisol level for diagnosis to ensure that patients with mild hypercortisolism are not  
310 excluded.<sup>18,27</sup> However, there remains a need for normative data with modern assays.

311

312 *Ruling out pseudo-CS*

313 Because the etiology of pseudo-CS can vary, there is no single approach to rule it out.<sup>53</sup> We  
314 recommend considering the patient’s clinical history, particularly the duration of symptoms, and  
315 repeating testing to avoid implementing inappropriate treatment if CS is not present (LQ, DR). In  
316 most cases, patients have mild hypercortisolism and can be monitored for 3-6 months to see  
317 whether symptoms resolve; treatment of the underlying condition (such as depression) can  
318 restore normal HPA axis function and cortisol levels (LQ, DR). Standard diagnostic testing is  
319 unreliable in this population. LDDT or serial LNSCs over time correlate with the clinical picture  
320 (LQ, DR). Desmopressin is easy to use and easily administered in an outpatient setting. Dex-  
321 CRH in this setting could be valuable, but published diagnostic accuracy results have varied; use  
322 at an expert center with measurement of dexamethasone levels is advised (MQ, SR),<sup>54</sup> as is  
323 cortisol cut-off adjustments in very obese patients. Note that ovine CRH is not presently  
324 available in the United States, Canada, Brazil, Argentina, Mexico and some other countries.

325

326 **Imaging and Tumor Localization**

327 *Background*

328 MRI is the imaging method of choice for detecting ACTH-secreting pituitary adenomas.  
329 However, as most lesions are very small, using standard 1.5T MRI, only approximately 50% of  
330 microadenomas can be clearly depicted.<sup>55</sup>

331 Technical refinements including spoiled gradient–recalled (SPGR) acquisition echo with 1  
332 mm slice intervals, fluid attenuation inversion recovery (FLAIR)<sup>56</sup> and constructive interference  
333 in the steady state (CISS), may enhance detection, while variants of T1-weighted turbo spin echo  
334 (TSE) sequences and use of ultra high field 3T and 7T magnets allow improved localization of

335 microadenomas.<sup>57-60</sup> Nevertheless, approximately one-third of scans in patients with CD still  
336 remain negative,<sup>61</sup> and higher resolution with 3T or 7T magnets can increase the risk of detecting  
337 incidentalomas that may be unrelated to the disorder.

338 Importantly, tumor size does not necessarily correlate with degree of hypercortisolism in CD.  
339 In fact, patients with larger adenomas frequently present with milder hypercortisolism.<sup>62</sup>

340 Positron emission tomography (PET) has been explored as an alternative to, or in  
341 combination with, MRI for localization of corticotroph adenomas. <sup>18</sup>F-fluoro-deoxy-glucose  
342 (<sup>18</sup>F-FDG) PET/CT was shown to be largely comparable to standard fast spin echo MRI in  
343 detecting pituitary lesions in one series,<sup>63</sup> while a separate study found both standard spin echo  
344 MRI and high resolution <sup>18</sup>F-FDG PET were inferior to SPGR MRI.<sup>64</sup> Prior stimulation with  
345 ovine CRH can increase <sup>18</sup>F-FDG uptake and thus increase detection.<sup>65</sup> PET coregistration with  
346 volumetric MRI (PET/MRCR) combines functional and anatomical imaging. <sup>11</sup>C-methionine  
347 used in this setting may permit more accurate localization of sites of radiotracer uptake.<sup>66</sup> In one  
348 series, this technique correctly localized corticotroph adenomas in patients with *de novo* disease  
349 and persistent/recurrent hypercortisolism following primary surgery, most of whom had negative  
350 or equivocal standard spin echo MRI.<sup>67</sup> However, this approach is not available or approved in  
351 most countries. Alternative strategies (e.g., targeting CRH-R1 expression on corticotroph  
352 tumors) have also recently been proposed, but require further study.<sup>68</sup>

353

#### 354 ***Clinical Considerations and Recommendations***

355 MRI remains the imaging modality of choice for ACTH-secreting pituitary adenomas (HQ,  
356 SR). We suggest 3T over 1.5T MRI where available (LQ, DR). 7T MRI is not widely available

357 and there is currently no justification for re-imaging on 7T MRI if no tumor is detected on  
358 1.5T/3T MRI.

359 It is likely that functional imaging will ultimately prove a better approach than MRI alone.  
360 However, more data are needed to define use of different ligands in various clinical settings.  
361 Although advanced imaging technologies may be available in some centers of excellence, the  
362 benefit of referring all patients for further imaging beyond 3T MRI remains unknown.

363

## 364 **Distinguishing Between CD and Ectopic ACTH-dependent CS**

### 365 *Background*

366 In patients with CD, glucocorticoid (GC) receptors typically retain the ability to inhibit  
367 ACTH secretion in the presence of high doses of dexamethasone, and V2 and V1b (V3R), along  
368 with CRH receptor are all overexpressed. By contrast, most (but not all) ectopic ACTH-secreting  
369 do not express these receptors. Accordingly, desmopressin and CRH stimulation testing have  
370 proven useful in distinguishing between pituitary and ectopic tumors.<sup>69-71</sup> Increased plasma  
371 ACTH and increased cortisol following CRH or desmopressin administration usually indicates  
372 CD.<sup>72-76</sup> Using more than one dynamic test might further improve accuracy.<sup>77</sup> Nevertheless, well-  
373 differentiated neuroendocrine tumors (NETs) may also express any or all of these receptors,  
374 potentially leading to a false positive result. High-dose DST, although it has low accuracy  
375 overall, is still used in some countries. None of the diagnostic tests reach 100% specificity and  
376 results may be discordant in up to one-third of patients;<sup>5,6</sup> differences in type of ectopic tumor, as  
377 well as patient age, sex, and severity of hypercortisolism can all influence outcomes.

378 IPSS, which measures ACTH in pituitary vs peripheral venous drainage, has long been the  
379 gold standard to reliably exclude ectopic ACTH production-<sup>78,79</sup> and should preferably be

380 performed in a specialized center due to the potential risks. A central-to-peripheral ACTH  
381 gradient <2 before or <3 after stimulation suggests an ectopic tumor; however, both false  
382 negatives and false positives have been reported. Prolactin measurement may improve diagnostic  
383 accuracy in such cases and it is essential that patient is hypercortisolemic at the time of IPSS.<sup>80</sup>

384 A non-invasive approach using a combination of three or four tests, specifically CRH and  
385 desmopressin stimulation plus MRI, followed by whole-body CT if diagnosis is equivocal,  
386 correctly diagnosed CD in approximately half of patients in one series, potentially eliminating  
387 the need for IPSS.<sup>81</sup> Interestingly, a positive CT scan despite negative CRH/desmopressin  
388 stimulation and MRI had a negative predictive value of 100%. Currently, this combination of  
389 laboratory and imaging testing as a noninvasive approach to distinguish between pituitary and  
390 ectopic ACTH-secreting tumors is likely limited to specialized centers.<sup>82</sup>

391 <sup>68</sup>Ga-DOTATATE is a modified (Tyr3)-octreotide molecule covalently linked to 1,4,7,10-  
392 tetra-azacyclododecane-1,4,7,10-tetra-acetic acid (DOTA) combined with the radioactive <sup>68</sup>Ga  
393 isotope. The radiopharmaceutical, with a half-life of approximately 1 hour, binds to somatostatin  
394 receptors with an affinity similar to octreotide and can be used as a tracer in PET imaging of  
395 ectopic ACTH-secreting NETs.<sup>83</sup> <sup>68</sup>Ga-DOTATATE localizes about 65% of these tumors,<sup>84</sup>  
396 including those not seen or not definitively identified on cross-sectional imaging, and images are  
397 sharper than with single photon <sup>111</sup>In-DTPA-pentetreotide, with greater sensitivity for small  
398 tumors.<sup>85,86</sup> False positives can occur due to chronic inflammation, and a positive scan does not  
399 definitively prove that the NET is the source of ACTH, but <sup>68</sup>Ga-DOTATATE imaging can be  
400 useful in guiding clinical management.<sup>87</sup>

401 The <sup>68</sup>Ga isotope is typically derived from decaying <sup>68</sup>Ge and the worldwide supply of <sup>68</sup>Ge  
402 is being exhausted. The <sup>68</sup>Ga isotope, if it can be generated locally via a cyclotron, or <sup>64</sup>Cu,

403 which has a longer 12.7-hour half-life and can be centrally produced, may be used as alternative  
404 DOTATATE, DOTATOC, or DOTANOC conjugates.<sup>88</sup>

405

### 406 ***Clinical Considerations and Recommendations***

407 No single laboratory test or combination of tests can absolutely differentiate between  
408 pituitary and ectopic ACTH-secreting tumors (HQ, SR). We recommend using both the clinical  
409 context and test results to guide management (HQ, SR). ~~For example, in a patient with features~~  
410 ~~strongly suggesting an ectopic ACTH syndrome,~~When prompt access to brain MRI is not  
411 available, neck-to-pelvis thin-slice CT scan may be performed prior to pituitary MRI is useful if  
412 suspicion is high for ectopic ACTH syndrome, such as in a male with very high UFC and/or  
413 profound hypokalemia<sup>81</sup> (LQ, DR).

414 If a pituitary tumor  $\geq 10$  mm is detected on MRI and dynamic testing results are consistent  
415 with CD, IPSS is not necessary to confirm the diagnosis (MQ, SR). As it is possible that a  
416 pituitary lesion seen on MRI is an incidental nonfunctioning adenoma or other sellar mass and  
417 the ACTH source is ectopic, clinical presentation should always be considered. Some studies  
418 suggest this is true for lesions  $>6$  mm, but not all expert centers use this lower cutoff. There was  
419 consensus that all patients with lesions  $<6$  mm should have IPSS and those with lesions of  $\geq 10$   
420 mm do not need IPSS (MQ, SR). Expert opinions differ regarding tumors 6-9 mm, but the  
421 majority recommended IPSS to confirm the diagnosis in this circumstance (MQ, DR). Notably,  
422 some of the differences between centers and countries are based on interventional radiology  
423 availability. Prolactin measurement can be useful in ruling out a false negative IPSS (MQ, DR).  
424 While IPSS has high diagnostic accuracy for localization to the pituitary gland, it is not  
425 sufficiently reliable for tumor lateralization to the right or left side of the gland (MQ, SR).

426 A noninvasive alternative using high-dose DST and CRH stimulation test could predict CD if  
427 both tests are positive.<sup>89</sup> However, if tests are discordant, IPSS is necessary (LQ, DR). Emerging  
428 data suggest that CRH/desmopressin testing with pituitary MRI followed by whole-body CT  
429 scan might be a reliable alternative, if assessed by an experienced multidisciplinary team (VLQ,  
430 DR).

431 **COMPLICATIONS OF CD (Table 2 Panel 1)**

432 Strategies for CD management should consider how comorbidities and complications  
433 associated with CD may compromise patient health and QoL. Comorbidities should be addressed  
434 in many cases concomitant with or even before CD-specific treatments to restore normal cortisol  
435 levels.

436

437 **Hypercoagulability**

438 ***Background***

439 Hypercoagulability in CS resulting in an increased risk of thromboembolic events (TE) is  
440 paradoxically coupled with an increased bleeding tendency due to skin atrophy and capillary  
441 fragility.<sup>90,91</sup> Most patients show an activated coagulation cascade, including shortened activated  
442 partial thromboplastin time and increased concentrations of fibrinogen, von Willebrand factor,  
443 and factor VIII, as well as impaired fibrinolysis mediated by elevated levels of plasminogen  
444 activator inhibitor-1 and antiplasmin. Increased thrombin, thromboxane 2, and platelets, with a  
445 compensatory increase in anti-coagulation factors such as protein C and S, have also been  
446 implicated.<sup>92,93</sup>

447 The incidence of venous thromboembolic events (VTE) in patients with endogenous CS is  
448 more than 10-fold higher versus those with nonfunctioning adenomas undergoing surgery<sup>94</sup> and  
449 the odds-ratio is 18-fold higher compared with the healthy population.<sup>92</sup> VTE risk persists in the  
450 first few months after CD surgery, indicating that hypercoagulability is not immediately  
451 reversible with cortisol normalization.<sup>92,95,96</sup> At 30 days, VTE risk post adrenalectomy was 3.4 to  
452 4.75%,<sup>96</sup> and the odds ratio for TE after bilateral adrenalectomy (BLA) in a longer-term study  
453 was 3.74 (95% CI: 1.69-8.27).<sup>95</sup> In a series of 17 patients, biochemical remission following



454 short-term medical therapy (pasireotide ± cabergoline ± ketoconazole) also did not seem to  
455 reverse the risk, as it was not accompanied by changes in pro-anticoagulation factors, and  
456 pulmonary embolism occurred in two patients with a marked UFC decrease.<sup>90,97</sup>

457 Data from retrospective studies<sup>98,99</sup> indicate that thromboprophylaxis can decrease the  
458 incidence of postoperative VTE, particularly when extended to 30 days. Surveys indicate  
459 increased awareness of the need for thromboprophylaxis as well as increased anticoagulation use  
460 in clinical practice,<sup>100</sup> but strategies to identify patients most likely to benefit are still being  
461 developed.<sup>101</sup>

462

### 463 ***Clinical Considerations and Recommendations***

464 There is currently no standard practice for preoperative or postoperative thromboprophylaxis  
465 in patients with CD. Some experts hold estrogen therapy in women who are awaiting surgery,  
466 but care should be taken if it was being used as contraception, because pregnancy also is  
467 associated with increased risk of thrombosis (LQ, DR). In the absence of contraindications, we  
468 recommend prophylactic anticoagulation be considered for all patients at increased VTE risk,  
469 including: a history of embolism or abnormal coagulation testing; severe preoperative  
470 hypercortisolism (e.g., UFC >5 × ULN); current use of estrogen or oral contraceptives; poor  
471 mobility; von Willibrand factor polymorphism; extended preoperative or postoperative hospital  
472 stay; and high postoperative cortisol levels or GC over-replacement for adrenal insufficiency  
473 (MQ, SR). For all patients, early postoperative ambulation and use of compression stockings  
474 should be encouraged<sup>102</sup> (HQ, SR).

475 In cases where perioperative anticoagulant thromboprophylaxis is administered, there was  
476 strong consensus for preference of low molecular weight heparin over oral anticoagulants given

477 the long half life of the latter and the lack of therapy to reverse their effect, which may be  
478 especially concerning in the preoperative setting (LQ, DR).

479 There is also no standard practice for the duration of anticoagulation if administered. Among  
480 meeting participants, recommended treatment duration ranged in the preoperative setting from 2-  
481 4 days to 1-2 weeks, and in the postoperative setting from 1-2 days of the hospital stay up to 2-4  
482 weeks or even longer to 2-3 months (LQ, DR). Anticoagulants may be stopped before surgery  
483 and restarted after surgery to minimize intraoperative bleeding risk, but there was no consensus  
484 on the timing of when to stop and restart prophylaxis.

485

## 486 **Cardiovascular Disease**

### 487 ***Background***

488 Patients with CD show an adverse cardiovascular disease risk profile that may persist even  
489 after successful treatment.<sup>103-106</sup> Visceral, subcutaneous, and total fat may decrease after  
490 remission, although most patients remain overweight or obese.<sup>107</sup> Type 2 diabetes mellitus  
491 (T2DM) is present in up to 30% of patients, and dyslipidemia, with low high-density lipoprotein  
492 (HDL), high low-density lipoprotein (LDL), and high triglycerides, has been reported in 16-64%  
493 of cases at diagnosis. In many patients, but not all, T2DM resolves after remission.<sup>108</sup> Structural  
494 cardiovascular changes improve, including left ventricular hypertrophy, concentric remodelling,  
495 dilated cardiomyopathy, increased intima media thickness, and increased formation of  
496 atherosclerotic plaques, as well as their clinical manifestations, including hypertension and heart  
497 failure, but may not fully resolve despite remission of hypercortisolism.<sup>109</sup>

498 Myocardial infarction, stroke,<sup>110,111</sup> and other vascular events are a primary cause of  
499 increased standardized mortality ratio (SMR; 4.1 to 16) in patients with active/persistent CD.<sup>112</sup>

500 Most studies show these rates do not entirely normalize,<sup>111,113</sup> yet some show rates are lowered  
501 upon remission and one study showed that patients in remission after a single pituitary surgery  
502 have normal SMR at 10 years.<sup>114</sup> Screening and risk assessment for cardiovascular risk factors  
503 before and after surgery is therefore essential.<sup>102</sup>

504

### 505 ***Clinical Considerations and Recommendations***

506 We recommend patients with CD be evaluated, monitored, and treated according to accepted  
507 guidelines for patients at high risk for cardiovascular disease (HQ, SR). The management  
508 approach should be individualized (HQ, SR) based on the complications present, such as  
509 hypertension or hyperlipidemia. Care should be coordinated with the primary care physician and  
510 cardiology consultant, as needed (VLQ, DR).

511

### 512 **Bone Disease**

#### 513 ***Background***

514 Skeletal fragility is a frequent and early complication of hypercortisolism, and fractures may  
515 be the first clinical manifestation of the disease. Vertebral fractures occur in 30-50% of patients,  
516 largely correlating with the severity of hypercortisolism.<sup>115</sup> Suppression of the growth hormone  
517 (GH)/insulin-like growth factor (IGF)-I and hypothalamic-pituitary-gonadal axes as well as  
518 altered parathyroid hormone pulsatility lead to decreased osteoblast number and function, as  
519 evidenced by decreased serum levels of bone formation markers including osteocalcin and  
520 alkaline phosphatase.<sup>116</sup> Dual X-ray absorptiometry (DXA) of the lumbar spine may show low  
521 bone mineral density (BMD), but fractures may occur even in patients with BMD in the normal  
522 or osteopenic range.<sup>117</sup> Although BMD increases were reported after hypercortisolism resolution,

523 some patients show persistently high fracture risk, with men at higher risk compared with  
524 women. Conventional osteoporosis treatments, e.g., bisphosphonates, as well as supportive  
525 treatment with vitamin D and calcium may induce a more rapid improvement in BMD than  
526 cortisol normalization alone, and could be useful in patients with persistent postsurgical  
527 hypercortisolism to prevent further bone loss.<sup>118</sup> Data on the role of specific bone treatments for  
528 patients with osteopenia who are in remission after CD treatment are lacking.

529

### 530 ***Clinical Considerations and Recommendations***

531 We recommend that all patients undergo risk assessment for bone loss and fracture (HQ, SR).  
532 Given the risk for fracture even in patients without osteoporosis, standard DXA alone may not be  
533 sufficiently informative; bone quality assessment (microscanner or trabecular bone score) is  
534 recommended where available (HQ, SR). Morphometric vertebral assessment on x-rays or  
535 vertebral fracture assessments on DXA can be useful in detecting subclinical fractures (HQ, SR)  
536 but might not be practical for all patients. The FRAX tool to assess fracture risk is not validated  
537 for CD.

538 We recommend monitoring and follow-up for all patients with CS who are at high-risk for  
539 osteoporosis and fractures (HQ, SR). Conventional treatment for osteoporosis should be  
540 considered for all patients with persistent CD even in the absence of osteoporosis on BMD  
541 because of the increased fracture risk due to cortisol excess (HQ, SR).

542

### 543 **Growth Hormone Deficiency**

#### 544 ***Background***

545 GCs, both endogenous and exogenous, inhibit GH secretion, thereby decreasing IGF-I  
546 production by the liver in patients with CS.<sup>119,120</sup> Although GH production can be fully restored  
547 in most patients after successful therapy and recovery of HPA axis, even years after remission,<sup>121</sup>  
548 persistence of GH deficiency (GHD) can potentially worsen hypercortisolism complications such  
549 as bone loss, myopathy, and memory deficits.<sup>122</sup> Using the insulin tolerance or glucagon  
550 stimulation test, GHD prevalence in adults varies with timing of the diagnosis, ranging from 50-  
551 60% when testing was performed within 2 years after surgery to 8-13% when done more than 2  
552 years after surgery.<sup>121,123</sup> A GHD rate of 65% was observed with the GHRH-arginine test after a  
553 median remission time of 3 years post-surgery,<sup>124</sup> while 36% of patients were diagnosed with  
554 GHD at 99 months after remission post-radiotherapy.<sup>123</sup> Prevalence using the newly approved  
555 macimorelin stimulation test is not known.<sup>120</sup> Notably, IGF-I is an insensitive screening test for  
556 diagnosing GHD in adults.<sup>124</sup>

557 Compared with other GHD etiologies, GHD in patients with CS is more common in women  
558 and younger patients; generally, these patients exhibit higher rates of T2DM, hypertension, low  
559 bone mass, fractures, and worse QoL.<sup>125-127</sup> Myopathy may be partially related to GHD among  
560 patients in remission. While preoperative IGF-I levels during active CS did not predict long-term  
561 myopathy risk, lower 6-month postoperative IGF-I levels strongly predicted more severe long-  
562 term muscle atrophy and weakness after CS remission.<sup>128</sup>

563 GH replacement ameliorates a number of complications associated with metabolic syndrome  
564 and risk for cardiovascular and cerebrovascular disease. Studies show decreased body weight,  
565 waist circumference, and total and LDL-cholesterol, as well as improvement of QoL and BMD.  
566 Conversely, in patients with pre-existing glucose intolerance, it may lead to worsening of  
567 glucose metabolism.<sup>125-127,129-131</sup> GH treatment has not yet been shown in randomized,

568 prospective trials to reverse increased risk for metabolic syndrome and cardiovascular or  
569 cerebrovascular complications.<sup>126</sup>

570

### 571 ***Clinical Considerations and Recommendations***

572 There is currently no standard practice for whether, when, and how to test for GHD in adults  
573 with CD. As postoperative HPA axis recovery is often delayed, we recommend waiting at least  
574 6-12 months after surgery before considering GHD assessment (MQ, SR). Patients with  
575 macroadenomas and more aggressive surgical resection are at higher risk for hypopituitarism.  
576 Patients with 3 or more pituitary hormone deficiencies are more likely to have GHD and do not  
577 need dynamic testing (HQ, SR). Serum IGF-I level alone is not likely to be a reliable indicator,  
578 as levels can be in the lower half of the normal range in patients with GHD on dynamic tests.  
579 Accessibility of GH replacement may be an important factor in determining testing and treatment  
580 considerations. If GH replacement is implemented earlier than 2 years after pituitary surgery, we  
581 recommend retesting periodically to determine whether GH secretion has normalized upon HPA  
582 axis recovery (MQ, SR) .

583 As CS-associated myopathy does not spontaneously resolve during remission,<sup>132</sup> physical  
584 rehabilitation is recommended for all patients (HQ, SR).

585

### 586 **Other Complications**

587 Increased risk for infection,<sup>102</sup> dysfunction of one or more pituitary axes such as central  
588 hypothyroidism,<sup>133</sup> gonadal function impairment, infertility, and other complications may be  
589 seen in patients with CD. Physical and psychological morbidity commonly affects QoL, even  
590 after successful treatment in some patients. Persistence of several features associated with prior

591 hypercortisolism, including affective disorders, cognitive dysfunction, and negative illness  
592 perception can have a sustained impact on well-being.<sup>134</sup> Proximal myopathy, with impaired stair  
593 climbing and straightening up, are characteristic of CS myopathy. The pathology is  
594 multifactorial, including protein degradation through the forkhead box O3 (FOXO3) pathway as  
595 well as accumulation of intramuscular fat and inactivity-associated muscle atrophy.<sup>135</sup>  
596 Furthermore, hypercortisolism remission can induce exacerbation of pre-existing autoimmune  
597 disorders.

598 As these complications have been the subject of recent guidelines<sup>136</sup> and reviews,<sup>102,134</sup> they  
599 were not specifically addressed at the Workshop.

## 600 INITIAL TREATMENT OF CD AND MONITORING FOR RECURRENCE

601

### 602 Pituitary Surgery

#### 603 *Background*

604 Transsphenoidal surgery (TSS) is recommended as first-line therapy for patients with CD.<sup>6,7</sup>  
605 Remission following surgery, typically defined as postoperative serum cortisol <55 nmol/L (<2  
606 µg/dL), is seen in approximately 80% of patients with microadenomas and 60% with  
607 macroadenomas if the procedure is performed by an experienced surgeon.<sup>137-140</sup> Patients in  
608 remission require GC replacement until the HPA axis recovers.<sup>7,136</sup> Some patients may have a  
609 delayed remission; monitoring until cortisol nadir has been reached postoperatively can usually  
610 identify such cases.<sup>141,142</sup> Occasional patients with mild hypercortisolism, cyclic CD, or those  
611 treated medically prior to surgery may achieve remission without demonstrating marked  
612 postoperative hypocortisolism. Treatment at a high-volume center by an experienced surgeon  
613 and tumor characteristics such as detection on MRI, noninvasiveness, and size <1 cm appear to  
614 correlate with higher remission rates;<sup>138,143</sup> whether there is a potential incremental benefit with  
615 an endoscopic approach for macroadenomas remains unclear.<sup>144,145</sup> Overall, complication rates  
616 are low, with more experienced surgeons having even lower rates.<sup>146,147</sup> New-onset pituitary  
617 insufficiency, seen in approximately 10% of patients, as well as permanent diabetes insipidus  
618 (DI), cerebrospinal fluid (CSF) leak, and VTE seen in <5% of patients, are the most common  
619 complications; peri-operative mortality is <1%.<sup>143,144</sup>

620 How to measure surgical expertise for CD remains unclear. Hospitals that limit the number  
621 of neurosurgeons performing TSS show better outcomes and reduced complication rates, shorter  
622 postoperative length of stay, and lower costs, and survey data demonstrate that neurosurgeons



623 who have performed more than 200 TSS in their careers have the lowest complication rates.<sup>148-</sup>  
624 <sup>151</sup> It has been suggested that regionalized neurosurgery teams of 4-5 experts per 2.5-5 million  
625 inhabitants could allow for optimal outcomes, reduced costs, and increased quality of care  
626 overall.<sup>149,152</sup>

627

### 628 ***Clinical Considerations and Recommendations***

629 We recommend patients with CD undergo surgery in specialized Pituitary Tumor Centers of  
630 Excellence (PTCOE) wherever possible (HQ, SR).<sup>152</sup> Surgery should be performed by an  
631 experienced pituitary neurosurgeon and follow-up conducted by a multidisciplinary team that  
632 includes a pituitary endocrinologist (HQ, SR). Outcomes of pituitary surgery and cost  
633 effectiveness (LQ, DR) should be reported and be made available in the public domain.

634

### 635 **Monitoring for Recurrence (Table 1)**

#### 636 ***Background***

637 Recurrence after successful pituitary surgery is characterized as the reappearance of clinical  
638 and biochemical features of hypercortisolism following initial remission. Low or undetectable  
639 cortisol in the immediate postoperative period is a defining criterion of remission, but does not  
640 necessarily predict lack of recurrence;<sup>153</sup> some patients who show early remission with very low  
641 postoperative cortisol levels may experience later recurrence.<sup>154</sup> Published recurrence rates vary  
642 between 5% and 35%, with half appearing within the first 5 years after surgery and half after up  
643 to 10 years or more.<sup>137,155-157</sup>

644 Lifelong monitoring for recurrence is required.<sup>158</sup> In patients who responded preoperatively  
645 to desmopressin, early postoperative loss of response to desmopressin with/without

646 dexamethasone or CRH may offer a more precise prediction of recurrence risk,<sup>70,159-165</sup> but is not  
647 consistently used or recommended by most experts.

648 Compared to their use in the initial diagnosis of CS, LNSC, 1-mg DST, UFC, and  
649 desmopressin tests have a lower sensitivity for recurrence, but specificity is high, up to 95% or  
650 more.<sup>158</sup> LNSC can detect postoperative elevated cortisol levels earlier than 1-mg DST, while  
651 UFC is usually the last test to become abnormal in patients who recur.<sup>166,167</sup> Thus, LNSC may  
652 allow for earlier intervention, but serial tests are advised due to wide variability in results.<sup>167-170</sup>

653 Evaluation for recurrence should begin when the HPA axis recovers, and then annually or  
654 sooner if clinical suspicion.<sup>171,172</sup> In practice, however, clinical manifestations and biomarkers  
655 may be discordant. Moreover, diagnosis of early recurrence presents the additional challenge  
656 about when and how to intervene with treatment in these patients.<sup>171,172</sup>

657

### 658 ***Clinical Considerations and Recommendations***

659 We recommend lifelong monitoring for recurrence of CD (MQ, SR). Postoperative dynamic  
660 testing can potentially predict recurrence (LQ, DR), but its utility in clinical practice remains to  
661 be established as some patients with low predicted likelihood of recurrence may recur many  
662 years later.

663 Among the tests available, LNSC is the most sensitive for detecting recurrence and should be  
664 done annually after the HPA axis has recovered postoperatively (MQ, SR). LNSC usually  
665 becomes abnormal before DST and UFC, although monitoring for recurrence should also take  
666 into consideration which specific tests were abnormal for an individual patient at initial diagnosis  
667 (MQ, SR). If only slight biochemical abnormalities are seen without clinical features of

668 hypercortisolism, close monitoring with repeat testing and treatment of comorbidities rather than  
669 treatment of the underlying disorder per se can be considered (LQ, DR).

670

## 671 **Repeat Pituitary Surgery**

### 672 ***Background***

673 Repeat TSS can be considered in patients with biochemical evidence of recurrent CD if  
674 tumor is evident on MRI.<sup>139,173-176</sup> At select expert centers where successful reoperation has been  
675 reported despite a lack of detectable adenoma on MRI, either ACTH-staining adenoma on  
676 pathology or a central ACTH gradient on IPSS at initial operation was often present.<sup>174,175</sup>

677 Tumor factors including size and presence of extra-sellar extension should be considered in  
678 determining eligibility for reoperation, and neurosurgeon experience likely plays a role in  
679 achieving good results.<sup>155,156,177</sup> Remission rates after reoperation vary widely in the literature,  
680 ranging from a low of 37% to a high of 88%, at least in part due to different remission criteria  
681 and durations of follow-up.<sup>174</sup> Although some have reported a significantly higher incidence of  
682 both surgical complications (e.g., CSF leak, meningitis) and endocrinological complications  
683 (e.g., DI and hypopituitarism) with repeat than with initial surgery, significant deterioration of  
684 pituitary function or serious morbidity is less likely in experienced hands.<sup>155,156</sup>

685

### 686 ***Clinical Considerations and Recommendations***

687 If there are no contraindications for surgery, we suggest repeat TSS in patients with  
688 biochemical evidence of recurrent CD if tumor is evident on MRI, especially if the first surgery  
689 was not done in a PTCOE (LQ, DR). If MRI does not show tumor presence, reoperation may be

690 appropriate if an experienced surgeon at a high-volume center considers it feasible and positive

691 pathology or a central gradient on IPSS was seen before initial operation (LQ, DR).

692 **MEDICAL THERAPY FOR CD**

693 Drugs used for treatment of CD target adrenal steroidogenesis, somatostatin and dopamine  
694 receptors in the pituitary, and GC receptors.<sup>6,7,178</sup> They may be used to treat hypercortisolism in  
695 patients with persistent or recurrent CD and those who are not candidates or refuse surgery, and  
696 to control cortisol levels in patients undergoing radiation therapy (RT).<sup>139,179,180</sup> Available  
697 medications and investigational drugs that reported phase 3 trial results are described in **Table**  
698 23.

699

700 **Medical Therapy: Targeting Adrenal Steroidogenesis**

701 ***Background***

702 Adrenal steroidogenesis inhibitors that have been available for many years, including  
703 ketoconazole, metyrapone, mitotane, and etomidate, as well as the recently approved  
704 osilodrostat, block one or more adrenal enzymes, decreasing GC synthesis and/or adrenal  
705 androgen production and secretion.<sup>181</sup> They are effective in controlling cortisol excess, but do not  
706 directly target the pituitary ACTH-secreting adenoma, nor restore HPA axis circadian rhythm.<sup>182</sup>

707 When treatment is dose-titrated to achieve cortisol normalization, there is a risk of adrenal  
708 insufficiency (AI) with overtreatment. Alternatively, for patients treated with a block-and-replace  
709 regimen, there is a risk of inappropriate GC over-replacement if complete blockade is not  
710 achieved.<sup>180</sup> Some adverse events (AEs) relate to the increase in ACTH seen in CD patients.  
711 Buildup of adrenal hormones proximal to the blockade with mineralocorticoid or androgenic  
712 activity may result in edema, alkalosis, and hypokalemia, or hyperandrogenic symptoms such as  
713 acne and hirsutism in women. Potential AEs related to drug-drug interactions are a key factor in  
714 treatment selection and use.<sup>183</sup>

715

716 *Ketoconazole*

717 Ketoconazole blocks multiple adrenal enzymes, including those involved early in the steroid  
718 biosynthetic pathway. This avoids excess circulation of androgen and mineralocorticoid  
719 precursors, but it may also decrease gonadal steroid synthesis; men may experience  
720 hypogonadism and gynecomastia, which can limit prolonged treatment.<sup>184</sup> Review of 310 CS  
721 patients treated in 5 studies with a mean dose of 673.9 mg/d and followed for a mean of 12.6  
722 months showed UFC normalization in 64.3% (median 50%; range 44.7-92.9%), but up to 23% of  
723 initially responsive patients lost biochemical control and escaped.<sup>179</sup> Similarly, data derived from  
724 the largest retrospective study of 200 patients with CD who took ketoconazole showed that  
725 64.7% of 51 patients treated for more than 24 months with a mean dose of 600 mg/d normalized  
726 UFC levels, but 15.4% escaped.<sup>185</sup> Improvement in clinical features of CS has also been seen,  
727 including decreased body weight and blood pressure, improved glucose metabolism, and  
728 decreased muscle weakness.<sup>179</sup>

729 Hepatotoxicity, seen in 10-20% of patients, is mostly asymptomatic with mild or moderate  
730 increases in liver enzymes ( $\leq 5 \times \text{ULN}$ )<sup>186</sup> and typically appears within the first 6 months of  
731 treatment initiation; these seem not to be dose-dependent and are reversible within 2-12 weeks  
732 after dose decrease or discontinuation. However, as serious hepatotoxicity has been reported, in  
733 patients with no obvious risk factors, the United States Food and Drug Administration (FDA)  
734 introduced a black-box warning and recommends weekly monitoring of liver function tests  
735 (LFTs) in patients with fungal infections treated with ketoconazole. Of note, the use of  
736 ketoconazole for CS is off-label in the US. Gastrointestinal disturbances and AI are also common,  
737 seen in 5-20% of patients, and skin rash is observed in approximately 5%.<sup>179</sup> It is important to

738 note that there are a number of drug-drug interactions with ketoconazole; careful review of the  
739 patient's medication list for potentially problematic interactions is essential.

740

#### 741 *Metyrapone*

742 Review of treatment experience with the 11 $\beta$ -hydroxylase inhibitor metyrapone in 120 CS  
743 patients in 5 studies with a mean dose of 2127.5 mg/d and followed for a mean of 8.7 months  
744 showed normalization of UFC in 71% (median 75.5%; range 45.4-100%), with up to 18%  
745 escaping after initial response.<sup>179</sup> A subsequent retrospective multicenter study of 164 CS  
746 patients reported that 43% of patients achieved biochemical control with monotherapy given for  
747 a mean duration of 8 months at a mean starting dose of 1040 mg/d and escalating to 1425  
748 mg/d.<sup>187</sup> An observational study of 31 CS patients, including 20 with CD, demonstrated that  
749 treatment with metyrapone at a median dose of 1000 mg/d for 9 months induced a rapid decrease  
750 in both UFC and LNSC after the first month of treatment (-67 and -57%, respectively, from  
751 baseline), with sustained normalization at the last visit in 70% and 37% of patients,  
752 respectively.<sup>188</sup> Three patients exhibited loss of control at the 9-month visit despite normal UFC  
753 levels at 6 months and 2 patients also showed normal LNSC. Notably, 11-deoxycortisol may  
754 produce clinically relevant cross-reactivity with cortisol in both blood and urine  
755 immunoassays.<sup>189</sup> A recently presented multicenter prospective study of 50 patients with CS  
756 showed 47% had UFC normalization at 12 weeks; median metyrapone dose was 1500 mg/day  
757 (250; 5750) and AI was reported in 12% of patients.<sup>190</sup>

758 Patients treated with metyrapone typically show a general improvement in clinical features of  
759 CS (66% in the prospective study), such as blood pressure, glucose metabolism, psychiatric  
760 disturbances, and muscle weakness.<sup>179</sup>

761 Hirsutism, dizziness, arthralgia, fatigue, hypokalemia, and nausea are the most commonly  
762 reported AEs with metyrapone; AI, abdominal pain, and atopic dermatitis are less frequently  
763 reported.<sup>179</sup> AEs secondary to hyperandrogenism can limit prolonged treatment, especially in  
764 females.

765

#### 766 *Osilodrostat*

767 Proof-of-concept and phase 2 prospective studies showed that osilodrostat, an 11 $\beta$ -  
768 hydroxylase and aldosterone synthase inhibitor, was effective in reducing cortisol and was well-  
769 tolerated.<sup>191-193</sup> This was further evaluated in 137 CD patients enrolled in a phase 3, prospective,  
770 multicenter, double-blind randomized withdrawal study.<sup>194</sup> After 12 weeks of open-label dose-  
771 titrated treatment and another 12 weeks of open-label dose-optimized treatment, 72 patients  
772 (53%) had maintained normal UFC and were eligible for randomization. By week 34, at the end  
773 of the randomized treatment period, 86% of those randomized to osilodrostat maintained normal  
774 UFC versus 29% of those randomized to placebo (OR 13.7 [95% CI: 3.7, 53.4]; p<0.0001).

775 Treatment with osilodrostat also yielded clinical improvements. By week 48, patients  
776 demonstrated significant decreases in body weight, blood pressure, and total and LDL  
777 cholesterol, as well as decreased fasting serum glucose and HbA1c levels. QoL and depression  
778 scores also improved.<sup>194</sup>

779 Nausea, anemia, and headache were reported in 8-11% of patients, while AEs related to  
780 hypocortisolism were reported in about half of patients, mostly during the open-label dose-  
781 titration period. These were generally manageable with dose reductions or interruptions,  
782 although GC replacement was required in 25 of 70 (36%) patients with one or more  
783 hypocortisolism-related AE. In addition, 42% of treated patients in the phase 3 study showed



784 effects from increased levels of adrenal steroid precursors, including hypokalemia and  
785 hypertension; 11% of women reported hirsutism.<sup>194</sup> In another large prospective phase 3 study, a  
786 significantly greater proportion of patients receiving osilodrostat (77.1%) achieved mean UFC ≤  
787 ULN after 12 weeks of treatment versus placebo (8.0%), with improvements seen in clinical  
788 features, cardiovascular disease markers, and QoL. Interestingly, hypocortisolism-related AEs  
789 occurred in 27.4% of patients, far fewer than in the prior study.<sup>195</sup>

790

### 791 *Mitotane*

792 Mitotane inhibits several steroidogenic enzymes and has a long-lasting adrenolytic action in  
793 steroid-secreting adrenocortical cells. It suppresses hypercortisolism in 80% of cases, but with a  
794 slow onset of action and highly variable bioavailability.<sup>180</sup> Induction of CYP3A4-mediated rapid  
795 inactivation of cortisol leads to a requirement for a 2- to 3-fold increased GC replacement dose  
796 when treatment of AI is needed or with a block-and-replace strategy.<sup>196</sup> It is rarely used for  
797 CD;<sup>179</sup> in the largest study, a mean dose of 2.6 g/d controlled hypercortisolism in 71.6% of  
798 patients after a median of 6.7 months.<sup>197</sup>

799 Gastrointestinal disturbances are common, dose-dependent, and reversible; neurological  
800 toxicity, seen in up to half of patients in some studies, can limit long-term use. Increases in liver  
801 enzymes are often observed and treatment should be stopped if elevations are  $> 5 \times$  ULN.

802 Mitotane is teratogenic and an abortifacient. Because of its long terminal half-life, this may  
803 limit its use in women who desire future pregnancy. Most participants considered that use of  
804 mitotane should be limited to patients with adrenal carcinoma.

805

806 *Etomidate*

807 Originally developed as an anesthetic, etomidate was shown to rapidly normalize cortisol  
808 levels in almost all cases, leading to its use in the acute control of severe hypercortisolism in  
809 hospitalized patients.<sup>198</sup> Low-dose etomidate (0.04–0.05 mg/kg/h) is used for partial blockade,  
810 with a high-dose (0.5–1 mg/kg/h) regimen for complete blockade. In such cases, IV  
811 hydrocortisone is required to avoid etomidate-induced AI.<sup>199</sup> Very low doses (0.025 mg/kg/h)  
812 may be used in hospitalized patients outside ICU,<sup>200</sup> although this may depend on local practice.

813 Myoclonus, nausea, vomiting, and dystonic reactions are seen in up to one-third of patients at  
814 higher anesthetic doses. Compared with the lipid formulation, the propylene glycol preparation is  
815 more frequently associated with thrombophlebitis and pain on injection, and also with additional  
816 AEs, such as hemolysis and renal tubular injury, as well as lactic acidosis at high doses.<sup>199</sup>

817

## 818 **Medical Therapy: Targeting Pituitary Somatostatin and Dopamine Receptors**

### 819 ***Background***

820 Both the dopamine agonist cabergoline and the somatostatin receptor ligand pasireotide are  
821 used in CD patients with persistent or recurrent hypercortisolism,<sup>7,139,179</sup> although only  
822 pasireotide is approved for use in this population.<sup>7,201,202</sup> Pasireotide and cabergoline normalize  
823 UFC in 25-50% of patients and can lead to adenoma shrinkage in some patients with a detectable  
824 adenoma. This tumor effect is clinically important for patients with a large residual tumor as well  
825 as for patients with corticotroph tumor progression, or Nelson's syndrome.

826

827 *Pasireotide*

828 In a phase 3 study of 162 CD patients treated with SC pasireotide, UFC normalized at month  
829 6 in 26% of those treated with 900 µg BID and 15% of those treated with 600 µg BID without  
830 dose increases. Higher rates of UFC normalization were seen in those with baseline UFC <5 ×  
831 ULN<sup>201</sup> and significant clinical improvement was noted in most patients.<sup>202</sup>

832 A second phase 3 study treated 150 CD patients with 10 mg or 30 mg monthly IM  
833 pasireotide LAR. At month 7, 40% of patients in both groups showed normalized UFC  
834 regardless of dose titration, with higher response rates in those with baseline UFC <2 × ULN.<sup>203</sup>  
835 At month 12, improvements in blood pressure were greater in those with normalized UFC; BMI,  
836 weight, waist circumference, and QoL were all improved regardless of UFC control.<sup>204</sup> Long-  
837 term extension studies showed that biochemical and clinical improvements could be maintained  
838 for up to five years in select patients who continued the study.<sup>205,206</sup> Of note, in real-life settings,  
839 limited data are available on long-term treatment compliance, and several studies show a high  
840 rate of treatment discontinuation. Treatment with pasireotide LAR also led to a decreased median  
841 tumor volume of 17.8% in those treated with the 10 mg dose and 16.3% in those treated with 30  
842 mg dose, with 43% and 47% of patients, respectively, showing ≥20% reduction.<sup>203</sup>

843 Of note, a separate longitudinal study in CD patients with Nelson's syndrome after BLA  
844 showed that pasireotide LAR rapidly suppressed ACTH levels and yielded sustained reductions  
845 over 24 weeks.<sup>207</sup>

846 Between one- and two-thirds of CD tumors harbor a mutation in *USP8*,<sup>208,209</sup> and these  
847 mutated tumors may show higher SST5 expression compared with wild-type tumors.<sup>210,211</sup> As  
848 pasireotide has a high affinity for this receptor, *USP8* mutational status may prove a useful  
849 marker for predicting treatment response.

850 The risk for hyperglycemia is high with pasireotide.<sup>201,203,212</sup> In the two phase 3 studies,  
851 approximately 70% of patients reported hyperglycemia-related AEs, with new antidiabetic  
852 medication initiation or dose adjustments required in approximately half of patients.<sup>201,203</sup> The  
853 high rates of hyperglycemia are thought to result from inhibition of insulin and incretin secretion  
854 combined with a lesser degree of glucagon inhibition.<sup>213</sup> Management with GLP-1 receptor  
855 agonists or DDP-4 inhibitors are therefore thought to be particularly useful.<sup>214,215</sup>

856

### 857 *Cabergoline*

858 Available data on cabergoline use in patients with CD are derived mostly from small  
859 retrospective studies demonstrating biochemical normalization in 25-40% of patients, with loss  
860 of control observed in 20-40% of patients initially controlled.<sup>216,217</sup>

861 A retrospective, multicenter cohort study of 53 patients treated with a median cabergoline  
862 dose of 2.3 mg/wk (range, 0.5-6.0) yielded normal UFC levels in 40% of patients during the first  
863 year, but only 23% of those showed sustained UFC normalization after a median 32.5 months of  
864 follow-up.<sup>218</sup> The lower control rate may be due to under-titration, as a smaller study of 20  
865 patients treated with cabergoline titrated to a maximum of 7 mg/wk (median 3.5 mg/wk) showed  
866 normalized UFC in 40% of patients at 24 months.<sup>219</sup> Weight, glycemic control, and hypertension  
867 improved in 25-40% of complete responders,<sup>218</sup> and tumor shrinkage was reported in 50%.<sup>219</sup>  
868 Patients with Nelson's syndrome may also respond to cabergoline treatment, and both ACTH  
869 normalization and tumor shrinkage have been reported.<sup>220</sup> Although not approved in this setting,  
870 cabergoline has been used in pregnant patients with prolactinomas and other pituitary adenomas,  
871 including CD.

872 Cabergoline-induced impulse-control disorder is likely under-reported, and can manifest as  
873 hypersexuality, pathological gambling, excessive alcohol consumption, overeating, and  
874 uncontrolled shopping.<sup>221</sup> This behavior may occur within months of initiating cabergoline  
875 therapy, or may manifest later, and improves or resolves on treatment discontinuation.<sup>222,223</sup>

876 High cumulative doses of ergotamine-derived dopamine agonists used in patients with  
877 Parkinson's disease were associated with risk for cardiac valve regurgitation.<sup>224</sup> Although one  
878 retrospective review of 50 prolactinoma patients found that moderate tricuspid regurgitation was  
879 more frequent in those treated with higher doses,<sup>225</sup> a large multicenter study found no  
880 association between the cumulative cabergoline dose and age-corrected prevalence of any  
881 valvular abnormality.<sup>226</sup> Furthermore, a meta-analysis showed that it remains an open question  
882 whether such echocardiographic findings are clinically significant.<sup>227</sup>

883

## 884 **Medical Therapy: Targeting the Peripheral Tissue Glucocorticoid Receptor**

### 885 *Mifepristone*

886 The glucocorticoid receptor blocker mifepristone is effective in controlling some effects of  
887 hypercortisolism regardless of etiology. As endogenous cortisol is not decreased, the efficacy of  
888 mifepristone can only be evaluated clinically. Close monitoring for AI is required, and the anti-  
889 progesterone action in women can cause endometrial hyperplasia and vaginal bleeding.

890 An open-label study of 50 patients with uncontrolled endogenous CS, including 43 with CD,  
891 showed that after 24 weeks of treatment, 60% with a concurrent diagnosis of T2DM or impaired  
892 glucose tolerance had a significant reduction of  $\geq 25\%$  from baseline in area under the curve for  
893 glucose during an oral glucose tolerance test; 38% of those with hypertension showed a

894 significant reduction of  $\geq 5$  mm Hg from baseline in diastolic blood pressure. Insulin resistance,  
895 weight, waist circumference, and QoL also improved.<sup>228</sup>

896 Twelve patients showed increased blood pressure, including 9 with hypokalemia who  
897 required spironolactone, consistent with activation of the mineralocorticoid receptor.

898 Endometrial hypertrophy and irregular menstrual bleeding were also reported, consistent with the  
899 anti-progesterone activity of this medication. Dexamethasone was administered in 7 patients with  
900 signs and symptoms of AI, underscoring the need for careful monitoring.<sup>228</sup> Importantly, cortisol  
901 levels remain high, and measures of low cortisol typically used to confirm AI due to  
902 overtreatment with other medical therapies cannot be used with mifepristone. Rather, only  
903 clinical features can be used.<sup>229</sup>

904 Continued mifepristone treatment of 27 patients with CD included in a long-term extension  
905 study showed sustained  $\geq 2$ -fold ACTH elevations, but tumor volume progression, seen in 3  
906 patients with macroadenomas up to 25 months from baseline, did not correlate with ACTH  
907 increases.<sup>230</sup> Thyroid function should be closely monitored and thyroid hormone replacement  
908 adjusted as needed.<sup>231</sup> All medications taken by the patient should be carefully reviewed given  
909 the potential for drug-drug interactions with mifepristone.

910

### 911 **Medical Therapy: Clinical Considerations and Recommendations**

912 We recommend individualizing medical therapy for all patients with CD based on the clinical  
913 scenario, including severity of hypercortisolism. Regulatory approvals, treatment availability,  
914 and drug costs vary between countries and determine treatment selection. However, where  
915 possible, it is important to consider balancing cost of treatment with the cost and significant  
916 adverse consequences of ineffective or insufficient treatment. In patients with severe disease, the

917 primary goal is to treat aggressively to normalize cortisol levels (or cortisol action if using  
918 mifepristone). Multiple serial tests of both UFC and LNSC are used to monitor treatment  
919 outcomes.<sup>158,232,233</sup>

920 A brief summary of Workshop discussions about how to best incorporate each of the  
921 different treatment options is presented below and in [Table 4Panel 2](#).

922

### 923 *Initial treatment selection for medical therapy*

924 Adrenal steroidogenesis inhibitors are usually used first given their reliable effectiveness. For  
925 patients with mild disease and no visible tumor on MRI, ketoconazole, osilodrostat, or  
926 metyrapone are typically preferred. Cabergoline also may be used for mild CD; it is less effective  
927 and has a slower onset of action, but requires less frequent dosing. For patients with mild-to-  
928 moderate disease and some residual tumor, there may be a preference for cabergoline or  
929 pasireotide because of the potential for tumor shrinkage. However, the high rate of  
930 hyperglycemia with pasireotide would make patient selection critical.

931 For patients with severe disease, rapid normalization of cortisol is the most important goal.  
932 With osilodrostat and metyrapone, response will typically be seen within hours, and with  
933 ketoconazole within a few days. Etomidate also works rapidly and could be used if the patient is  
934 hospitalized and cannot take oral medications. For patients with severe hypercortisolism,  
935 combinations of steroidogenesis inhibitors may be necessary. However, if hypercortisolism is  
936 very severe and not responsive to optimized medical therapy, including combinations, BLA  
937 should be considered to avoid worsening outcomes.

938 Other patient factors can be important for initial treatment selection. For example,  
939 cabergoline should not be used in patients with a history of bipolar or impulse control disorder,

940 but may be a preferred first choice in a young woman desiring pregnancy. Although none of  
941 these drugs is specifically approved for use in pregnancy, metyrapone may be also considered  
942 with precautions in selected women who are pregnant. In such cases, given the higher normal  
943 cortisol levels during pregnancy, a higher cut-off target for cortisol, such as  $1.5 \times \text{ULN}$ , is used.

944 Mifepristone improves key clinical features associated with hypercortisolism, specifically  
945 hyperglycemia and weight gain. However, it could be challenging to use in standard clinical  
946 practice, and often worsens hypokalemia. There are no biochemical markers that can be reliably  
947 used to follow to monitor cortisol levels, increasing the risk for AI due to overtreatment, and its  
948 long half-life requires several days of stress-dose GC replacement, preferably dexamethasone, if  
949 AI ensues. Because cortisol measurements cannot be used for dosing or safety monitoring, this  
950 should be used only by clinicians with extensive experience in CD; counseling patients that  
951 cortisol levels monitoring is not reliable, especially for adrenal insufficiency, is also important.

952 There are few rigorous data supporting specific regimens for combination therapy, but  
953 several have been described<sup>234-236</sup>. Many experts consider combining ketoconazole with  
954 metyrapone to maximize adrenal blockade when monotherapy is not effective or to allow lower  
955 doses of both drugs, although a steroidogenesis inhibitor plus a tumor-targeting agent, such as  
956 ketoconazole plus cabergoline, is also a rational combination, especially if there is visible tumor  
957 present. Other combinations that may be used include triplets of cabergoline, pasireotide, plus  
958 ketoconazole, and metyrapone, ketoconazole, plus mitotane. Risk for potentiating adverse effects  
959 with combination therapy, such as QTc prolongation, should also be considered.

960



961 *Selecting an adrenal steroidogenesis inhibitor*

962 The longest clinical experience for adrenal steroidogenesis inhibitors is with ketoconazole  
963 and metyrapone. These agents are approved for use in CD in Europe, but not in the United States  
964 (where only osilodrostat is approved in this category), and they may not be available in some  
965 countries. Ketoconazole may be favored for ease of dose titration, but it is often under-dosed for  
966 fear of inducing hepatotoxicity. LFTs should be regularly monitored, but treatment does not  
967 necessarily have to be discontinued if LFTs are mildly elevated, yet stable.<sup>237</sup> Osilodrostat and  
968 metyrapone can induce rapid control in the majority of patients. They are not limited by  
969 monitoring of LFTs and hypogonadism does not occur in men. It is expected that osilodrostat  
970 will be increasingly used as it becomes widely available given its high efficacy and twice-daily  
971 dosing. It is necessary to monitor for AI and osilodrostat effects on androgens, but whether  
972 treatment selection should be based on patient sex in long-term treatment is not yet known.  
973 Mitotane, rarely used for patients with CD in most centers, has a slower onset of action.

974 A block-and-replace regimen may be considered for patients with severe disease, cyclical  
975 CS, and patients ineligible for surgery. This may be a particularly useful approach if monitoring  
976 visits are infrequent due to external factors such as pandemic, lack of transportation or other  
977 issues. Caution is needed to avoid GC over-replacement and inducing iatrogenic CS.

978

979 *Monitoring response to medical therapy*

980 For all patients, regular monitoring for treatment efficacy is required, including measures of  
981 cortisol and patient symptoms and comorbidities, especially weight, glycemia, and blood  
982 pressure. In addition, QoL is important to take into account, preferably through patient-reported  
983 outcomes. Cortisol levels are often measured by UFC; notably, this test is not useful when there

984 are concerns for AI. Morning cortisol and/or LNSC may be used as an alternative, but because of  
985 the loss of circadian rhythm, it is unclear whether targeting diurnal secretion alone is meaningful.  
986 Nevertheless, morning cortisol values may be especially pertinent in patients taking higher  
987 medication doses in the evening than in the morning.<sup>182</sup>

988 As designs, medication up-titration schemes, comparator arms, inclusion/exclusion criteria,  
989 and primary endpoints differ even among prospective studies, it is difficult to directly compare  
990 treatment outcomes, either for efficacy or for adverse effects. Furthermore, some drugs have not  
991 been prospectively studied for CS. When using UFC normalization as a target, osilodrostat has  
992 the highest efficacy based on data from several prospective clinical trials, followed by  
993 metyrapone (retrospective and prospective data), ketoconazole (retrospective data), pasireotide  
994 (prospective), and cabergoline (retrospective and prospective). As improvement in clinical  
995 features of CS and diabetes are used as markers of mifepristone efficacy, it cannot be directly  
996 compared for biochemical efficacy with other available treatments. Patients who normalized both  
997 UFC and LNSC with pasireotide LAR showed better clinical outcomes than those who  
998 normalized UFC alone,<sup>232</sup> and a higher treatment dose at bedtime may help restore circadian  
999 rhythm patterns, but there is no rigorous evidence to support the latter approach.

1000 Change in treatment should be considered if cortisol levels are persistently elevated after 2-3  
1001 months on maximum tolerated doses. If cortisol does not normalize but is reduced and/or there is  
1002 some clinical improvement, combination therapy can be considered. If there is clear resistance to  
1003 treatment, we suggest switching to a different therapy. However, it is important to ensure that  
1004 insufficient disease control due to under-dosing is not misinterpreted as treatment resistance.

1005 With adrenal-targeting agents, there may be concern for tumor growth due to ACTH-cortisol  
1006 feedback interruption. However, it can be difficult to determine whether such tumor progression

1007 is due to this loss of feedback or reflects the underlying behavior of aggressive, recurrent disease.  
1008 We suggest monitoring ACTH levels, as significant elevations may be a sign of new tumor  
1009 growth and a need for MRI, with the important caveats that ACTH has a short half-life and levels  
1010 fluctuate and do not necessarily reflect tumor growth. If progressive increase in tumor size is  
1011 seen,<sup>238</sup> treatment should be suspended and the management plan reassessed. MRI is typically  
1012 done 6-12 months after initiating treatment and repeated every few years depending on the  
1013 clinical scenario.

1014 With combination therapies, it is also important to monitor for potential overlapping  
1015 toxicities, particularly QTc prolongation, as well as drug-drug interactions.

1016

#### 1017 **Primary and Preoperative Medical Therapy for *De Novo* CD**

1018 Primary medical therapy is used when successful resection of an adenoma is unlikely due to  
1019 unfavorable localization, significant invasiveness, or lack of visualization on MRI. Recent  
1020 double-blind randomized phase 3 studies evaluating the efficacy of several novel drugs included  
1021 only a small percentage of patients with *de novo* CD, ranging from 0% to 28%.<sup>196</sup> Further studies  
1022 are needed to demonstrate utility of the different medical therapies in this setting, either as  
1023 monotherapy or in combination, while also taking into account the potential effects of such  
1024 treatment on adenoma size.

1025 Published evidence supporting the role of preoperative medical therapy in patients with CD  
1026 is sparse, and it is not used in the majority of patients, although there are regional variations. A  
1027 meta-analysis showed no differences in cortisol normalization rate between those who received  
1028 cortisol-lowering medications in the preoperative setting versus use as adjuvant treatment.<sup>239</sup> It  
1029 may be an option in severely ill patients for whom surgery is contraindicated or if waiting time

1030 for surgery is long<sup>139</sup> or in patients with life-threatening complications of hypercortisolism  
1031 requiring rapid control of cortisol excess.<sup>230,240</sup> Physician surveys show that preoperative therapy,  
1032 mostly with ketoconazole and/or metyrapone, is used in up to 20% of CD patients, especially  
1033 those with more severe clinical features or nonvisible adenoma.<sup>241</sup>

1034 Retrospective studies show preoperative steroidogenesis inhibitor therapy for a mean of 4  
1035 months yields cortisol normalization rates of 50% to 72%, although subjective symptom  
1036 improvement was observed in only one-third of cases.<sup>185,187</sup> Lower rates of postoperative  
1037 hypoadrenalism from preoperative medical therapy could, in theory, protect against the  
1038 occurrence of a proinflammatory and procoagulant state,<sup>94,241</sup> but the prevalence of postsurgical  
1039 complications, including VTE, are similar regardless of its use.<sup>241</sup> If the HPA axis recovers  
1040 during preoperative treatment, AI may not be seen postoperatively, so it may be more difficult to  
1041 determine whether remission is present.

1042 Preoperative cabergoline likely has limited value, as a significant decrease in cortisol was  
1043 seen in only one-fourth of patients in a cohort treated prospectively for 6 weeks.<sup>242</sup>

1044

#### 1045 ***Clinical Considerations and Recommendations***

1046 There are no rigorous data supporting use of primary or preoperative medical therapy. Most  
1047 experts would consider such an approach with adrenal steroidogenesis inhibitors if surgery is  
1048 delayed, either because of scheduling or due to outside factors such as a pandemic (VLQ, DR).

1049 Patients with severe CD who have potentially life-threatening metabolic, psychiatric,  
1050 infectious, or cardiovascular/thromboembolic complications also may benefit from preoperative  
1051 medical therapy in select cases (LQ, DR). Although this has not been clearly confirmed, some  
1052 experts consider it may have a potentially favorable effect on glucose, cardiovascular, and

1053 coagulation parameters (VLQ, DR). Few use it to decrease the extent of postoperative cortisol  
1054 withdrawal manifestations.

1055 Monitoring and follow-up of patients treated with preoperative therapy can be challenging as  
1056 postoperative cortisol assessments for surgical cure are not reliable. The patient's perspective  
1057 regarding this approach would be valuable to incorporate into future research studies (VLQ,  
1058 DR).

1059 **RADIATION THERAPY**

1060 ***Background***

1061 RT is primarily used as adjuvant therapy for patients with persistent or recurrent disease after  
1062 TSS <sup>7,243</sup> or in the setting of aggressive tumor growth. Approximately two-thirds of patients  
1063 achieve biochemical remission during the years after treatment with conventional external-beam  
1064 RT, typically 45-50 Gy administered in <2 Gy fractions, or stereotactic radiosurgery (SRS),  
1065 which is administered as single dose or a few fractions of approximately 20 Gy.<sup>244</sup> However,  
1066 more recent series with SRS, including whole sellar RT,<sup>245</sup> show higher biochemical remission  
1067 rates. In a multicenter study of GammaKnife SRS in 278 subjects followed for a mean of 5.6  
1068 years, biochemical control was attained in 80% and durable control of hypercortisolism was  
1069 maintained in 57%.<sup>246</sup> Tumor control rates are typically higher, with approximately 95% of  
1070 patients treated with SRS showing decreased or stable tumor volume on MRI.<sup>244</sup> A small single-  
1071 center study of proton beam RT showed complete response (either cortisol or ACTH  
1072 normalization) in patients with persistent corticotroph adenomas due to CD or Nelson's  
1073 syndrome, with low morbidity after a median follow-up of 62 months.<sup>247</sup>

1074 SRS may also be used as primary therapy in patients with high surgical risk or who refuse  
1075 surgery. In this setting, endocrine remission was attained in 81% of 46 patients at 5 years of  
1076 follow-up.<sup>248</sup> Long-term follow-up is needed as recurrence and tumor growth have been  
1077 described post-RT.

1078 Given the latency until remission is achieved with RT, adjuvant medical therapy is needed to  
1079 control hypercortisolism, and periodic withdrawal of medication to allow measurement of  
1080 cortisol secretion is performed to assess treatment effect.<sup>7</sup> Although data are mixed on whether

1081 ketoconazole<sup>246,249</sup> or cabergoline<sup>250</sup> treatment at the time of SRS limits efficacy, these  
1082 medications are often withheld temporarily at the time of RT.

1083 Hypopituitarism is the most common side effect of both conventional RT and SRS, seen in  
1084 25-50% of patients, and generally increases over time. Risk of secondary malignancy, cranial  
1085 nerve damage, and stroke are low with SRS.<sup>251</sup> In patients treated with SRS, distance of at least  
1086 3-5 mm between the tumor and the optic chiasm and a chiasm dose <8 Gy is recommended to  
1087 limit treatment damage.<sup>251</sup> Longer term data will help address whether use of different SRS  
1088 modalities (GammaKnife, LINAC, proton beam) confers lower rates of stroke and  
1089 hypopituitarism compared with conventional RT.

1090

#### 1091 ***Clinical Considerations and Recommendations***

1092 RT is most commonly used in cases of persistent hypercortisolism after incomplete  
1093 corticotroph tumor resection, particularly if the tumor is aggressive or invasive and/or considered  
1094 unresectable (HQ, SR). SRS is likely more convenient as few treatment sessions are required, but  
1095 avoiding optic chiasm exposure is critical (HQ, SR). Lifelong monitoring for pituitary hormone  
1096 deficiencies and recurrence is required in all patients undergoing RT (HQ, SR). Imaging for  
1097 secondary neoplasia in the radiation field also should be considered (HQ, SR).

1098 **ADRENALECTOMY**

1099 ***Background***

1100 BLA offers immediate control of cortisol excess in patients with persistent or recurrent CD  
1101 not responsive to medical therapy,<sup>7,139,252</sup> but is only considered for select patients due to the  
1102 resultant AI and need for life-long GC and mineralocorticoid replacement therapy.<sup>253</sup>  
1103 Laparoscopic BLA using either a transperitoneal or posterior retroperitoneal approach is  
1104 associated with a complication rate between 10% and 18% in the largest series, and a mortality  
1105 rate of <1%.<sup>254,255</sup> Long-term clinical relapse of hypercortisolism due to adrenal rest stimulation  
1106 by high ACTH is uncommon (<10%), while clinical improvement in BMI, T2DM, hypertension,  
1107 and muscle weakness is reported in more than 80%.<sup>256</sup>

1108 Corticotroph tumor progression after BLA is a long-term concern in 25% to 40% of patients  
1109 after 5 to 10 years.<sup>256-258</sup> Most cases can be managed with surgery, RT, or medical therapy.  
1110 However, as a subset of patients with aggressive tumors will show clinical consequences from  
1111 the tumor mass despite treatment, long-term monitoring is required. A European consensus  
1112 focused on management of these patients was recently published.<sup>259</sup>

1113 Corticotroph tumor progression after BLA does not seem to be influenced by pregnancy.<sup>260</sup>  
1114 This may make BLA a preferred option in female patients with an immediate pregnancy plan. In  
1115 most cases, however, BLA is rarely performed as the first-line treatment after failure of initial  
1116 pituitary surgery, and duration of disease before adrenal surgery is typically 3 to 4 years or  
1117 more.<sup>255</sup> Whether and how this might impact long-term treatment outcomes remains unknown.

1118



1119 *Clinical Considerations and Recommendations*

1120 In patients with CD, BLA is often considered a treatment of last resort in most centers after  
1121 all other options have failed (MQ, SR). However, BLA may be warranted earlier in patients with  
1122 severe hypercortisolism in whom a rapid, definitive effect on cortisol is needed to avoid  
1123 prolonged systemic effects of uncontrolled disease (MQ, SR). Many expert centers recommend  
1124 BLA earlier in the course of the disease for females with CD desiring pregnancy (MQ, SR).

1125 After BLA, plasma ACTH and serial imaging of the pituitary gland are used for monitoring  
1126 at intervals dictated by the clinical scenario, usually starting 6 months after surgery (HQ, SR).  
1127 More frequent evaluation may be necessary if there is a clinical suspicion of corticotroph tumor  
1128 progression (HQ, SR).

1129 ~~Unilateral adrenalectomy has been suggested for patients with primary bilateral~~  
1130 ~~macronodular adrenal hyperplasia with mild to moderate hypercortisolism and/or overt CS with~~  
1131 ~~asymmetric glands; in such cases, the larger adrenal gland is usually removed (LQ, DR).~~  
1132 ~~Importantly, if hypercortisolism persists or recurs, BLA and/or medical therapy is required.~~  
1133 ~~Unilateral adrenalectomy is not recommended for patients with very severe bilateral hyperplasia~~  
1134 ~~and symmetrical glands (HQ, SR).~~

1135 **ADDITIONAL CONSIDERATIONS**

1136 **Genetics of CD**

1137 Corticotroph adenomas are predominantly of sporadic origin, based on a monoclonal  
1138 expansion of a singular mutated cell.<sup>261</sup> These adenomas abundantly express EGFR, which  
1139 signals to induce ACTH production.<sup>262</sup> Somatic activating driver mutations in *USP8* are present  
1140 in 36-60% of corticotroph adenomas.<sup>209</sup> These mutations lead to persistent overexpression of  
1141 EGFR, thereby perpetuating the hyper-synthesis of ACTH. Rarely, mutations in the  
1142 glucocorticoid receptor *NR3C1*, the *BRAF* oncogene, the deubiquitinase *USP48*, and *TP53* are  
1143 encountered.<sup>261</sup> Patients with familial tumor syndromes, such as *MEN1*, *FIPA*, and *DICER1*  
1144 rarely develop corticotroph adenomas. It has been proposed that corticotroph tumors may be sub-  
1145 classified based on *USP8* driver mutations and clinical behavior.<sup>263</sup> As *USP8* mutational status  
1146 may predict recurrence after TSS,<sup>264</sup> such genomic classifications may open new avenues for  
1147 more targeted, personalized treatment modalities in the future.

1148

1149 **Diagnosis and Management of CS in Children**

1150 Endogenous CS is extraordinarily rare before age 18. Germline mutations in *MEN1*, *RET*,  
1151 *AIP*, *PRKARIA*, *CDKN1B*, *DICER1*, *SDHx*, and *CABLES1* may all predispose children to CD,  
1152 although screening is usually reserved for cases in which there is either family history or other  
1153 signs suggestive of a genetic syndrome.<sup>265</sup>

1154 Lack of height gain concomitant with weight gain is the most common presentation of CS in  
1155 children, making the disorder somewhat easier to detect in children than in post-pubertal  
1156 adolescents or adults. Using the insulin tolerance test or the glucagon stimulation test, the

1157 estimated prevalence of severe GHD (< 9 mU/L) and partial GHD (< 30 mU/L) is 31% and 54%,  
1158 respectively.<sup>266</sup>

1159 Documentation of hypercortisolism with 24-hour UFC, LNSC, or overnight 1 mg DST are all  
1160 used to confirm diagnosis. The diagnostic approach and test performances are slightly different  
1161 from adults, as recently extensively reviewed.<sup>267</sup> The Dex-CRH test is not useful in children. In  
1162 children over age 6, CD is the most common cause of CS; in children under age 6, adrenal causes  
1163 are more common. Algorithms for testing to distinguish ACTH-dependent disease from ACTH-  
1164 independent syndromes are available. Notably IPSS role in children is more limited compared  
1165 with adults.<sup>268</sup>

1166 As in adults, surgical resection of the ACTH-secreting tumor is the first-line treatment  
1167 intervention. However, unlike in adults, thromboprophylaxis should not be routinely used due to  
1168 bleeding risk, but reserved for selected pediatric patients. With successful treatment, adrenal  
1169 function typically recovers within approximately 12 months.<sup>269</sup> Evaluation for GHD should be  
1170 done by 3-6 months after surgery and immediate GH replacement given if needed to ensure  
1171 proper growth. Use of GH replacement is associated with adequate final height, but obesity is not  
1172 fully reversible.<sup>270</sup> For those who require medical therapy, ketoconazole or metyrapone is  
1173 typically used and morning cortisol is used to monitor response. Pasireotide is not recommended  
1174 and clinical trials of osilodrostat in children are underway. Block-and-replace regimens with  
1175 metyrapone also may be considered.

1176 Early diagnosis and expert management is critical given the potential for long-term adverse  
1177 health outcomes from prolonged hypercortisolism as well as from morbidity associated with TSS  
1178 or RT. Children with CS should be referred to multidisciplinary centers of excellence with  
1179 pediatric endocrinologists expert in managing disorders of the pituitary, and with specialized

1180 neurosurgery units. If an underlying genetic syndrome is present, genetic counseling for the child  
1181 and family members as well as investigations into other disorders associated with the syndrome  
1182 are necessary.<sup>267,271,272</sup>

1183

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1191

#### 1192 **Data Availability**

1193 Data sharing is not applicable to this article as no datasets were generated or analyzed.

1194

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1336

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**Table 2 Panel 1. Complications of CD: Summary of Recommendations**

<p><i>Hypercoagulation</i></p> <ul style="list-style-type: none"> <li>• Prophylactic anticoagulation should be considered for patients at risk for VTE, including history of embolism or abnormal coagulation testing; severe preoperative hypercortisolism; current use of estrogen or oral contraceptives; poor mobility; extended preoperative or postoperative hospital stay; and high postoperative cortisol levels or cortisol over-replacement in patients with AI (MQ, SR)</li> <li>• Early postoperative ambulation and use of compression stockings should be encouraged for all patients (HQ, SR)</li> <li>• If thromboprophylaxis is administered, low-molecular weight heparin is preferred over oral anticoagulants (LQ, DR)</li> <li>• Anticoagulants may be discontinued before surgery to minimize intraoperative bleeding risk, but the timing of when to stop and when to reinstate after surgery is unclear (LQ, DR)</li> <li>• Optimal duration of anticoagulation after surgery is still unclear (LQ, DR)</li> <li>• Thromboprophylaxis should not be <u>routinely</u> used in pediatric patients <u>due to bleeding risk but reserved for selected patients</u></li> </ul>
<p><i>Cardiovascular Disease</i></p> <ul style="list-style-type: none"> <li>• Evaluate, monitor, and treat according to current guidelines for patients at high risk for cardiovascular disease (HQ, SR)</li> <li>• Management approach should be individualized (HQ, SR) based on the complications present and care should be coordinated with primary care and cardiology physicians as needed (VLQ, DR)</li> </ul>
<p><i>Bone Disease</i></p> <ul style="list-style-type: none"> <li>• Risk assessment for bone loss and fracture recommended in all patients (HQ, SR)</li> <li>• Standard DXA alone may not be sufficiently informative; bone quality (microscanner or trabecular bone score) or morphometric assessment is recommended where available (HQ, SR)</li> <li>• Monitor and follow-up as for all adults high-risk populations (HQ, SR)</li> <li>• Consider conventional osteoporosis treatments, <u>e.g., bisphosphonates</u>, for patients with persistent CD even if BMD is normal because of increased fracture risk due to cortisol excess (HQ, SR)</li> </ul>
<p><i>GH Deficiency</i></p> <ul style="list-style-type: none"> <li>• In adults, wait at least 6-12 months after surgery to allow HPA axis recovery before considering GHD assessment (MQ, SR)</li> <li>• If GH is replaced earlier than 2 years after surgical remission, retest periodically off treatment as the axis may recover (MQ, SR)</li> <li>• In children, evaluate for GHD 3-6 months after surgery and immediately initiate GH replacement if needed to ensure proper growth</li> </ul>

Abbreviations: AI, adrenal insufficiency; BMD, bone mineral density; CD, Cushing’s disease; DXA, dual x-ray absorptiometry; GHD, growth hormone deficiency; HPA, hypothalamus-pituitary-adrenal; VTE, venous thromboembolism.

**Table 4 Panel 2. Medical Therapy for CD: Summary of Recommendations**

<p><i>Which factors are helpful in selection of a medical therapy?</i></p> <ul style="list-style-type: none"> <li>• If there is a need for rapid normalization of cortisol, we recommend an adrenal steroidogenesis inhibitor; osilodrostat and metyrapone have the fastest action and are orally available, while etomidate can be used intravenously in very severe cases (HQ, SR)</li> <li>• In mild disease, if residual tumor is present and there is a potential for tumor shrinkage, consider pasireotide or cabergoline (MQ, SR)</li> <li>• If there is a history of bipolar or impulse control disorder, consider avoiding cabergoline (MQ, SR)</li> <li>• If an expert pituitary endocrinologist is not available to monitor treatment response, use mifepristone cautiously (LQ, DR); we recommend counseling patients that cortisol cannot be used to monitor treatment response or AI (SQ, SR). Drug-drug interactions must be considered when this medication is used.</li> <li>• In pregnant women or those desiring pregnancy, consider cabergoline or metyrapone, although no CD medications are approved for use in pregnancy (LQ, DR)</li> <li>• Drug intolerance or side effects as well as concomitant comorbidities such as T2DM and hypertension should further guide type of medication used (MQ, SR)</li> <li>• Consider cost and estimated therapy duration, especially if definitive treatment (i.e., pituitary and adrenal surgery) is planned or while awaiting effects of radiotherapy (LQ, DR)</li> </ul>
<p><i>Which factors are used in selecting an adrenal steroidogenesis inhibitor?</i></p> <ul style="list-style-type: none"> <li>• Rapidity of action, tolerability, ease-of-use, degree of likely biochemical normalization, and specific clinical improvement as well as local availability and cost of each drug should be considered at therapy start (MQ, SR)</li> <li>• Ketoconazole may be favored for ease of dose titration; concern about inducing hepatotoxicity and the need to monitor liver enzymes may lead to under-dosing (MQ, SR). Drug-drug interactions must be considered and hypogonadism may occur in men</li> <li>• Osilodrostat achieves high rates of cortisol normalization. Dosing schedule may be more convenient for patients compared with metyrapone, but neither metyrapone nor osilodrostat is limited by hypogonadism in men (HQ, SR)</li> <li>• Mitotane is rarely used as monotherapy in CD in most centers (LQ, DR)</li> </ul>
<p><i>How is tumor growth monitored when using an adrenal steroidogenesis inhibitor or glucocorticoid receptor blocker?</i></p> <ul style="list-style-type: none"> <li>• MRI is typically obtained 6-12 months after initiating treatment and repeated every few years depending on the clinical scenario (MQ, SR)</li> <li>• It can be difficult to determine whether tumor progression is due to loss of cortisol feedback or reflects the underlying behavior of aggressive, recurrent disease (LQ, DR)</li> <li>• We suggest monitoring ACTH levels, as progressive elevations in ACTH may be a sign of tumor growth and a need for MRI, although the half-life of ACTH is short, levels fluctuate and do not necessarily reflect tumor growth (LQ, DR)</li> <li>• If progressive tumor growth is seen, medical treatment should be suspended and the management plan reassessed (MQ, SR)</li> </ul>

<i>When is preoperative medical therapy used?</i>
<ul style="list-style-type: none"> <li>• There are no rigorous data supporting use of preoperative medical therapy (MQ, SR)</li> <li>• Most experts would consider use of adrenal steroidogenesis inhibitors if surgery is delayed, either because of scheduling or due to external factors (LQ, DR)</li> <li>• Patients with severe CD who have potentially life-threatening metabolic, psychiatric, infectious, or cardiovascular/thromboembolic complications may benefit in select cases (LQ, DR)</li> </ul>
<i>How is treatment response monitored? Which factors are considered in deciding whether to use combination therapy or to switch to another therapy?</i>
<ul style="list-style-type: none"> <li>• Response should be defined based on a combination of clinical (improved phenotype, weight, hypertension, glucose metabolism, QoL) and biochemical endpoints or only clinical endpoints when glucocorticoid receptor blockers are used (MQ, SR)</li> <li>• Cortisol levels are often measured by UFC (except when using mifepristone); UFC is not useful if AI is a concern (HQ, SR)</li> <li>• Because of the loss of biologic circadian rhythm, it is unclear whether targeting diurnal secretion alone with morning cortisol and/or LNSC is meaningful (LQ, DR)</li> <li>• Change in treatment should be considered if cortisol levels are persistently elevated after 2-3 months on maximum tolerated doses (MQ, SR)</li> <li>• If cortisol does not normalize but is reduced and/or there is some clinical improvement, combination therapy can be considered (LQ, DR)</li> <li>• If there is clear resistance to treatment despite dose escalation, we suggest switching to a different therapy (LQ, DR)</li> </ul>
<i>Which agents are used for optimal combination therapy?</i>
<ul style="list-style-type: none"> <li>• There are few rigorous data supporting specific regimens for combination therapy (HQ, SR)</li> <li>• Many experts consider combining ketoconazole with metyrapone or potentially ketoconazole with osilodrostat to maximize adrenal blockade when monotherapy is not effective or to allow lower doses of both drugs (LQ, DR)</li> <li>• Ketoconazole plus cabergoline or pasireotide, and pasireotide plus cabergoline may be rational combinations if there is visible tumor present (LQ, DR)</li> <li>• Other combinations that may be used include triplets of cabergoline, pasireotide, plus ketoconazole, and ketoconazole, metyrapone, plus mitotane (LQ, DR)</li> </ul>

Abbreviations: ACTH, adrenocorticotropin; AI, adrenal insufficiency; CD, Cushing's disease; LNSC, late-night salivary cortisol; MRI, magnetic resonance imaging; QoL, quality of life; UFC, urinary free cortisol.

**Table 5 Panel 3. Grading of Evidence and Recommendations**

<b>Evidence</b>	<ul style="list-style-type: none"><li>• Very low quality (VLQ): expert opinion supported by one or few small uncontrolled studies</li><li>• Low quality (LQ): supported by large series of small uncontrolled studies</li><li>• Moderate quality (MQ): supported by one or few large uncontrolled studies or meta-analyses</li><li>• High quality (HQ): supported by controlled studies or large series of large uncontrolled studies with sufficiently long follow-up</li></ul>
<b>Recommendations</b>	<ul style="list-style-type: none"><li>• Discretionary recommendation (DR): based on VLQ or LQ evidence</li><li>• Strong recommendation (SR): based on MQ or HQ evidence</li></ul>

Based on Guyatt et al *BMJ* 2008 and *Giustina et al Nat Rev Endocrinol* 2014.

**Table 6 Panel 4. Topics for Future Research Topics Ranked of Highest Importance**

<i>Screening and diagnosis of CS</i>
<ul style="list-style-type: none"> <li>• Optimize pituitary MR and PET imaging using improved data acquisition and processing to improve microadenoma detection</li> <li>• Compare diagnostic algorithms for the differential diagnosis using invasive versus non-invasive strategies</li> <li>• Identify additional corticotroph adenoma mutations and development of a comprehensive panel of genomic/proteomic tests for CD diagnosis</li> </ul>
<i>Complications of CD</i>
<ul style="list-style-type: none"> <li>• Define use of anticoagulant prophylaxis and therapy in different populations and settings</li> <li>• Optimize the approach in managing long-term complications</li> </ul>
<i>Treatment of CD</i>
<ul style="list-style-type: none"> <li>• Determine clinical benefit of restoring the circadian rhythm, potentially with a higher nighttime medication dose</li> <li>• Identify better markers of disease activity and control</li> <li>• Develop new, better tolerated, more effective medical therapies</li> <li>• Define populations that might benefit from preoperative medical treatment</li> </ul>

Abbreviations: CD, Cushing’s disease; CS, Cushing’s syndrome; MR, magnetic resonance; PET, positron emission tomography.



## **Figure Legends**

### **Figure 1. Algorithm for diagnosis of Cushing's syndrome**

Abbreviations: ACTH, adrenocorticotropin; CBG, corticosteroid binding globulin; CD, Cushing's disease; CRH, corticotropin stimulating hormone; CS, Cushing's syndrome; CT, computed tomography; Dex, dexamethasone; DM, diabetes mellitus; DST, dexamethasone suppression test; GC, glucocorticoid; IPSS, inferior petrosal sinus sampling; MRI, magnetic resonance imaging; PCOS, polycystic ovary syndrome; UFC, urinary free cortisol.

### **Figure 2. Algorithm for management of Cushing's disease.**

Abbreviations: ACTH, adrenocorticotropin; DST, dexamethasone suppression test; IPSS, inferior petrosal sinus sampling.