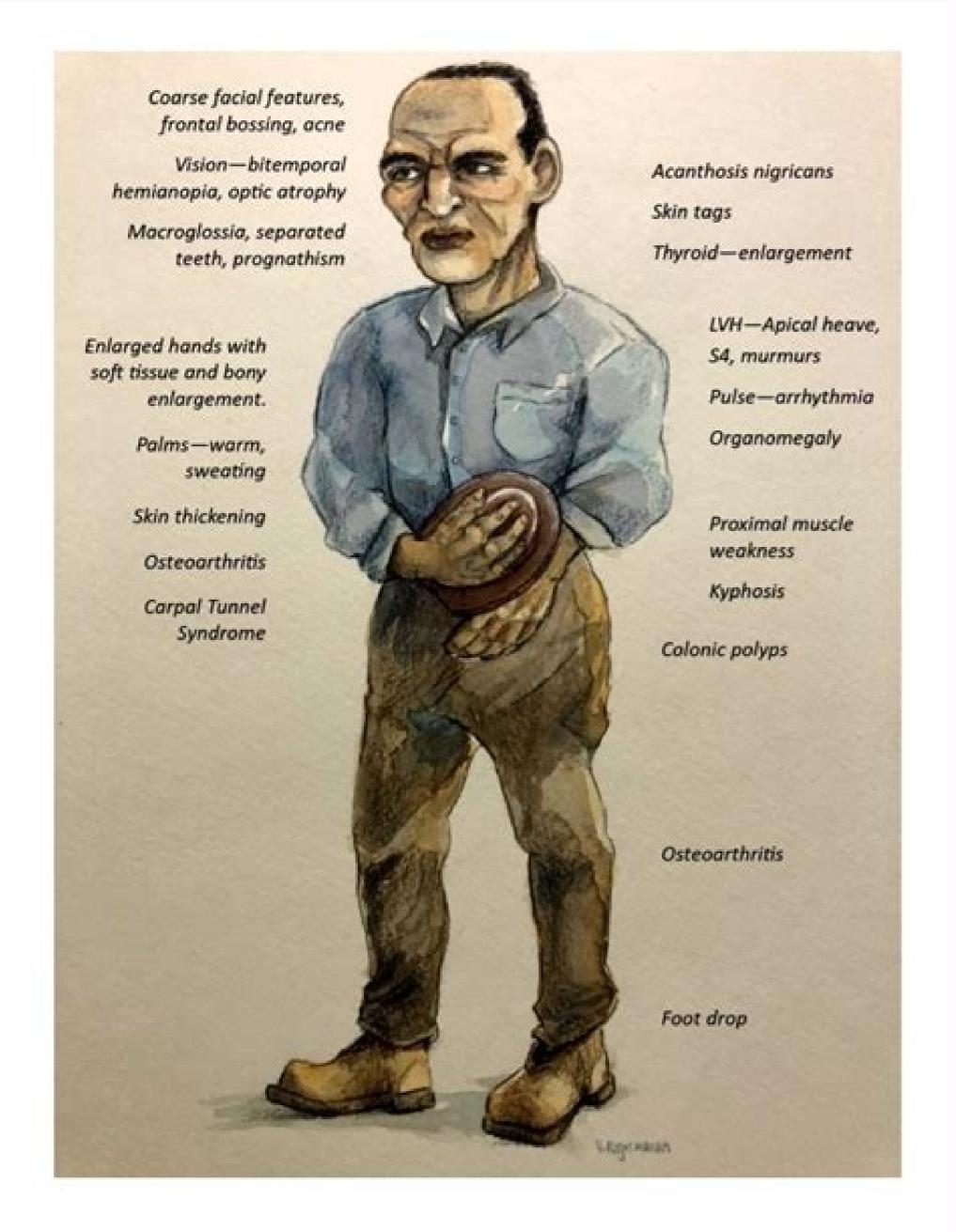
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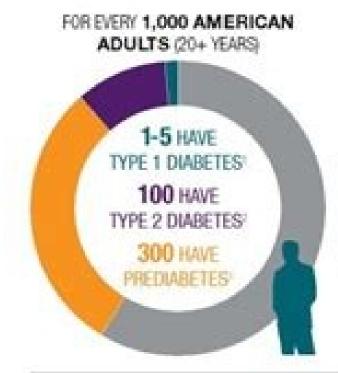




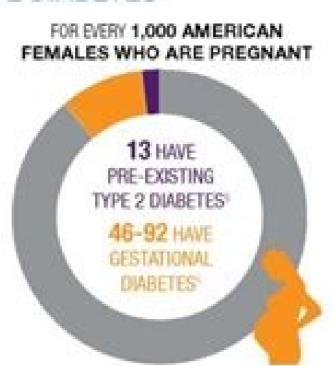


## DIABETES

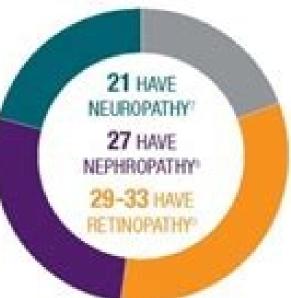
## OVER 29 MILLION AMERICANS HAVE DIABETES



FOR EVERY 1,000 AMERICAN YOUTH (10-19 YEARS)\* 3 HAVE TYPE 1 DIABETES LESS THAN 1 HAS TYPE 2 DIABETES



## FOR EVERY 100 AMERICANS WITH DIAGNOSED DIABETES



IN 2012, DIABETES COST THE US HEALTHCARE SYSTEM BY 2021, IT IS ESTIMATED TO COST AS MUCH AS

\$512 BILLION" \$245 BILLION"

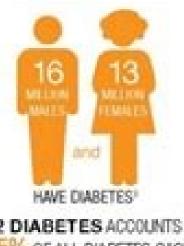
TOTAL ANNUAL HEALTHCARE COSTS (PER CAPITA)

ADULT WITH DIAGNOSED DIABETES

ADULT WITHOUT DIABETES

YOUTH WITH DIAGNOSED DIABETES

YOUTH WITHOUT DIABETES



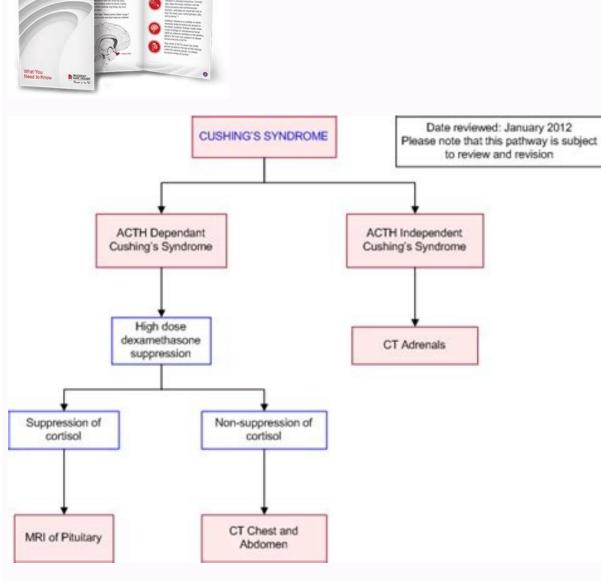
TYPE 2 DIABETES ACCOUNTS FOR 90-95% OF ALL DIABETES CASES.

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- 2014,100(0.517-625) 3 National Diabetus Statistics Report, Gentlers for Disease
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2006;164(9:673-660.

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- 8 Koopman et al. Ansats of Family Medicine.
- 2006,4/6-427-402 9 Zhang et al. The Joseph of the American Modical Assariation 2010;304(0:649-656; Warg et al. American Journal of Ophthalmalogy, 2008;141(3):
- 10. American Diabetes Association: Diabetes Cara. 2013;36(4):1033-1046.
- 11 Vigta et al. Health Athers (Phoject Hopel.) 2012/31/1920-26
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J Clin Endocrinol Metab 75:315-317 [PubMed] [Google Scholar]Meikle AW 1982 Dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone Surgery 142:900-905 [PubMed] [Google Scholar]Meikle AW 1982 Dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethas of simultaneous measurement of simultaneous measuremen 2005 Final adult height and body mass index after cure of paediatric Cushing's disease. Because the test assumes a nadir of cortisol in the late evening, it may not be appropriate for shift workers or those with variable bedtimes, and the timing of the collection should be adjusted to the time of sleeping for those with bedtimes consistently long after midnight. (21) quoted 5-20%, depending on referral bias and diagnostic tests and criteria. Testing for Cushing's syndrome as compared with the general population. This may require patient education using both oral and written instructions. For example, healthy women taking oral estrogen may have increased CBG, and therefore high serum cortisol concentration, but their UFC remains normal. Eur J Endocrinol 157:725-731 [PubMed] [Google Scholar]Krieger DT, Allen W, Rizzo F, Krieger HP 1971 Characterization of the normal temporal pattern of plasma corticosteroid levels. J Clin Endocrinol Metab 92:1326-1333 [PubMed] [Google Scholar] Findling JW, Pinkstaff SM, Shaker JL, Raff H, Nelson JC 1998 Pseudohypercortisoluria: spurious elevation of urinary cortisol due to carbamazepine. Because of this, it is the panel's observation that referral to endocrinology centers with expertise and interest in Cushing's syndrome in patients with abnormal initial testing is likely to be associated with better patient outcomes. The recommendation to perform additional testing is patients with discordant results. Our recommendation is based on high-quality evidence because it derives from the common observation that pursuing the alternative, testing to establish the diagnosis of Cushing's syndrome without first excluding unnecessary testing and the associated consequences) without expectation of benefit. Cushing's syndrome is more likely to be present when a large number of signs and symptoms, especially those with high discriminatory index (e.g. myopathy, plethora, red striae, easy bruising, and thin skin in the young) are present (6,8). Pediatrics 120:e575-e586 [PubMed] [Google Scholar] Bulow B, Jansson S, Juhlin C, Steen L, Thoren M, Wahrenberg H, Valdemarsson S, Wangberg B, Ahren B 2006 Adrenal incidentaloma—follow-up results from a Swedish prospective study. We thank Patricia A. N Engl J Med 350:1629-1638 [PubMed] [Google Scholar]Kyriazopoulou V, Vagenakis AG 1992 Abnormal overnight dexamethasone suppression test in subjects receiving rifampicin therapy. Clin Chem 50:757-759 [PubMed] [Google Scholar]Kidambi S, Raff H, Findling JW 2007 Limitations of mild Cushing's syndrome. Often this evidence comes from the unsystematic observations of the panelists and should therefore be considered suggestions. Cushing's syndrome comprises a large group of signs and symptoms that reflect prolonged and inappropriately high exposure of tissue to glucocorticoids (Table 1). Presentation, diagnosis, and therapy. The loss of circadian rhythm with absence of a late-night cortisol nadir is a consistent biochemical abnormality in patients with Cushing's syndrome (56,57). We encourage caregivers to consider Cushing's syndrome as a secondary cause of these conditions, particularly if additional features of the disorder are present. Appropriately powered and rigorously designed randomized clinical trials to compare diagnostic-treatment strategies should be established to inform clinicians and patients on optimal management. The members of the Clinical Affairs Core Committee, and The Endocrine Society Council for their careful review of earlier versions of this manuscript and their helpful suggestions. J Clin Endocrine Society Council for their careful review of earlier versions of the Clinical Affairs Core Committee, and The Endocrine Society Council for their careful review of earlier versions of the Clinical Affairs Core Committee, and The Endocrine Society Council for their careful review of earlier versions of the Clinical Affairs Core Committee, and The Endocrine Society Council for their careful review of earlier versions of the Clinical Affairs Core Committee, and The Endocrine Society Council for their careful review of earlier versions of the Clinical Affairs Core Committee, and The Endocrine Society Council for their careful review of earlier versions of the Clinical Affairs Core Committee, and The Endocrine Society Council for their careful review of earlier versions of the Clinical Affairs Core Committee, and The Endocrine Society Council for their careful review of earlier versions of the Clinical Affairs Core Committee, and The Endocrine Society Council for their careful review of earlier versions of the Clinical Affairs Core Committee, and the Clinical Affairs Core Committee (and the Clinical Affairs Core Committee) and the Clinical Affairs Core Committee (and the Clinical Affairs Core Committee) and the Clinical Affairs Core Committee (and the Clinical Affairs Core Committee) and the Clinical Affairs Core Committee (and the Clinical Affairs Core Committee) and the Clinical Affairs Core Committee (and the Clinical Affairs Core Committee) and the Clinical Affairs Core Committee (and the Clinical Affairs Core Committee) and the Clinical Affairs Core Committee (and the Clinical Affairs Core Committee) and the Clinical Affairs Core Committee (and the Clinical Affairs [PubMed] [Google Scholar] Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM 2008 A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the GRADE system. Additionally, quality of life improves after surgical treatment but remains below that of age- and gender-matched subjects for up to 15 yr (18). Final stature in patients with endogenous Cushing's syndrome was reported to be disappointing (26), but more recent data showed that most patients with moderate to severe Cushing's syndrome clearly reduces mortality and morbidity. Endocr Rev 19:647-672 [PubMed] [Google Scholar]Cronin C, Igoe D, Duffy MJ, Cunningham SK, McKenna TJ 1990 The overnight dexamethasone test is a worthwhile screening procedure. This easily performed, noninvasive test has been used in children to differentiate patients with Cushing's syndrome from those with simple obesity. National laboratories of excellence might be used as referral centers in difficult cases; approval by the health authorities/insurance companies for such use would be important. Improved clinical outcome data and targeted clinical trials. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. Once the bladder has been emptied into the collection on the second morning, the sample is complete. Patients should be instructed not to drink excessive amounts of fluid and to avoid the use of any glucocorticoid preparations, including steroid-containing skin or hemorrhoid creams, during the collection In another recent report, one of 99 patients with newly diagnosed diabetes mellitus had surgically proven Cushing's disease (34). Switching to nonenzyme-inducing medication may correct this situation, but an alternative and more practical approach is to use another test, such as assessment of midnight salivary or serum cortisol, to exclude Cushing's syndrome in these patients (97). As noted above (see 3.4.1), excreted urine cortisol values decrease below creatinine clearance of 60 ml/min and are quite low, below 20 ml/min (53). For pediatric patients, the adult normal ranges may be used because most pediatric patients are of adult weight (i.e. > 45 kg). At the recommended cutoff point, falsepositive elevations of UFC may be seen in several conditions. We recommend that patients with an abnormal result see an endocrinologist and undergo a second test, either one of the above or, in some cases, a serum midnight cortisol or dexamethasone-CRH test. In general, patients with Cushing's disease show an increase in ACTH, but those with other causes of Cushing's syndrome or those without Cushing's syndrome do not respond (7,22,102). The salivary glands express 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which converts the biologically active cortison (75). J Endocrinol Invest 29:471–482 [PubMed] [Google Scholar] Mitchell IC, Auchus RJ, Juneja K, Chang AY, Holt SA, Snyder WH, 3rd, Nwariaku FE 2007 "Subclinical Cushing's syndrome" is not subclinical: improvement after adrenalectomy in 9 patients. All subsequent voids throughout the day and night should be included in the collection, which is kept refrigerated (but not frozen), up to and including the first morning void on the second day. Circulating
cortisol concentrations are usually normal (or slightly reduced) in obesity, but severe obesity can raise UFC. Other populations may have a high percentage of false-positive results. We thank the European Society of Endocrinology for their co-sponsorship of this guideline. (72) reported that 20% of all participants and 40% of diabetic hypertensive subjects had at least one elevated late-night salivary cortisol measurement. Clin Endocrinol (Oxf) 43:545-550 [PubMed] [Google Scholar]Ma RC, Chan WB, So WY, Tong PC, Chan WB, So WY, Scholar Gold PW, Loriaux DL, Roy A, Kling MA, Calabrese JR, Kellner CH, Nieman LK, Post RM, Pickar D, Gallucci W, et al 1986 Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. High fluid intake (≥5 liters/d) significantly increases UFC (52). J Clin Endocrinol Metab 79:1082-1085 [PubMed] [Google Scholar]Samaras K, Pett S, Gowers A, McMurchie M, Cooper DA 2005 Introgenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. Responses to administration of 3 and 8 mg dexamethasone were normal in some but not all patients (106,108). Therefore, to enhance sensitivity, experts have advocated requiring a lower cutoff for suppression of the postdexamethasone test may give either false-positive or false-positive or false-negative results in conditions that alter the metabolic clearance of the agent; additionally, differences in the performance of cortisol assays may contribute. The dexamethas one-CRH test can be useful in patients with equivocal results for UFC. Therefore, in these conditions a normal result is more reliable than an abnormal one. At the recommended cutoff point, false-negative results of urine cortisol collections also may occur. Conversely, where there is a low clinical index of suspicion, such as in simple obesity, but lack of suppression on dexamethasone testing and mildly elevated UFC, a sleeping midnight serum cortisol less than 1.8 µg/dl effectively excludes Cushing's syndrome at the time of assessment (7). Furthermore, an increase in blood cortisol is reflected by a change in the salivary cortisol concentration within a few minutes (58). However, serum free cortisol values measured over a 24-h period were reported to be elevated (106). J Clin Endocrinol Metab 92:4123-4129 [PubMed] [Google Scholar] Meriod Metab 92:4123-4129 [PubMed] [Google Scholar] Metab 92 Cutler Jr GB 1998 High fluid intake increases urine free cortisol excretion in normal subjects. Clin Endocrinol (Oxf) 40:479-484 [PubMed] [Google Scholar]Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C, Jorgensen JD, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C, Jorgensen J, Kosteljanetz M, Kristensen L, Laurberg P, Schmidt K, Weeke J 2001 Incidence and late prognosis of Cushing's syndrome: a population-based study. Given our objective of using tests with high sensitivity at this stage, we recommend use of the more stringent cutoff of 1.8 µg/dl.Overall, the evidence in adults indicates that in studies with low prevalence of Cushing's syndrome this test has similar performance as the others recommended for initial testing (2). Patients who smoke cigarettes also have been shown to have higher late-night salivary cortisol measurements than do nonsmokers (76). Clin Endocrinol (Oxf) 62:466-472 [PubMed] [Google Scholar]Storr HL, Mitchell H, Swords FM, Main KM, Hindmarsh PC, Betts PR, Shaw NJ, Johnston DI, Clark AJ, Reznek RH, Grossman AB, Savage MO 2004 Clinical features, diagnosis, treatment and molecular studies in paediatric Cushing's syndrome due to primary nodular adrenocortical hyperplasia. 1) (1 @OOO): 3.4.1 Urine free cortisol (UFC; at least two measurements)3.4.2 Late-night salivary cortisol (two measurements)3.4.3 1-mg overnight dexamethasone suppression test (DST)3.4.4 Longer low-dose DST (2 mg/d for 48 h)Algorithm for testing patients suspected of having Cushing's syndrome (CS). These technical comments reflect the best available evidence applied to a typical patient. Thus, the patient can be reassured and no further testing need be done; a recommendation to return in 6 months if symptoms progress ensures that (100%) and specificity (95.2%) for Cushing's syndrome in this setting (68). The influence of gender, age, and coexisting medical conditions on the late-night salivary cortisol concentrations has not been fully characterized. Other tests, such as the loperamide test, have insufficient evidence for their diagnostic accuracy. J Clin Endocrinol Metab 91:2582-2586 [PubMed] [Google Scholar]Nieman L 2007 The dexamethasone-suppressed corticotropin-releasing hormone test for the diagnosis of Cushing's syndrome: what have we learned in 14 years? The subsequent testing, labeling, and treatment of the conditions the sensitivity was 63-75%. J Clin Endocrinol Metab 50:46-51 [PubMed] [Google Scholar]Oguz Y, Oktenli C, Ozata M, Ozgurtas T, Sanisoglu Y, Yenicesu M, Vural A, Bulucu F, Kocar IH 2003 The midnight-to-morning urinary cortisol increment method is not reliable for the assessment of hypothalamic-pituitary-adrenal insufficiency in patients with end stage kidney disease. Cross-filled circles indicate the quality; and adapto, low quality; endocrinologist 8:51-54 [Google Scholar] Meikle AW, Findling J, Kushnir MM, Rockwood AL, Nelson GJ, Terry AH 2003 Pseudo-Cushing syndrome caused by fenofibrate interference with urinary cortisol assayed by high-performance liquid chromatography. It is thought that higher brain centers stimulate CRH release in these conditions, with subsequent activation of the entire HPA axis (10). Endocrinol Metab Clin North Am 29:43-56 [PubMed] [Google Scholar] Terzolo M, Reimondo G, Bovio S, Angeli A 2004 Subclinical Cushing's syndrome. (32) reported 18%; Terzolo et al. J Clin Endocrinol Metab 63:741-746 [PubMed] [Google Scholar] Ann NY Acad Sci 595:260-274 [PubMed] [Google Scholar] Ann NY Acad Sci circadian rhythm and overnight dexamethasone suppression salivary cortisol tests. Program of the Endocrine Society, Washington, DC, 1995, p 99 (Abstract OR39-2) [Google Scholar] Nieman LK, Cutler Jr GB, Oldfield EH, Loriaux DL, Chrousos GP 1989 The ovine corticotropin-releasing hormone (CRH) stimulation test is superior to the human CRH stimulation test for the diagnosis of Cushing's disease. Bone mineral density and cognitive dysfunction improve after successful surgical treatment of Cushing's syndrome but do not normalize in all patients (16,17). Yanovski et al. When the assay upper limit of normal is used as a criterion, the overall evidence supports the diagnostic accuracy of UFC in adults suspected of having Cushing's syndrome (2,51). There is no consensus on the best diagnostic criterion for the 1-mg DST. 1) (1 @OOO): 3.4.1 UFC (at least two measurements)3.4.2 Late-night salivary cortisol (two measurements)3.4.2 Late-night salivary cortisol (two measurements)3.4.3 1-mg overnight DST3.4.4 Longer low-dose DST (2 mg/d for low-dose DST). 48 h)3.5 We recommend against the use of the following to test for Cushing's syndrome (e.g. pituitary and adrenal imaging, 8 mg DST).3.6 In individuals with normal test results in whom the pretest probability is high (patients with clinical features suggestive of Cushing's syndrome and adrenal incidentaloma or suspected cyclic hypercortisolism), we recommend further evaluation by an endocrinologist to confirm or exclude the diagnosis (1 @OOO).3.7 In other individuals with normal test results (in whom Cushing's syndrome is very unlikely), we suggest reevaluation in 6 months if signs or symptoms progress ( $2\oplus\bigcirc\bigcirc\bigcirc$ ). In this is syndrome), we recommend further evaluation by an endocrinologist to confirm or exclude the diagnosis ( $1\oplus\bigcirc\bigcirc\bigcirc$ ). In this section, we first discuss the testing strategies and then provide evidence for and remarks about each of the recommended tests that can be used to identify patients with Cushing's syndrome (or refer to an endocrinologist). A suppressed ACTH or dehydroepiandrosterone sulfate concentration supports the diagnosis of Cushing's syndrome in patients with adrenal masses (20,21,22,23). For example, an abnormal UFC may not be accepted if the specimen volume and creatinine suggest overcollection. There is a pressing need to investigate outcomes in patients cured of Cushing's syndrome with modern-day practice. Montori, M.D.—Financial or Business/Organizational Interests: none declared, Significant Financial or Leadership Position: none declared. J Clin Endocrinol Metab 88:3521-3524 [PubMed] [Google Scholar]Lin CL, Wu TJ, Machacek DA, Jiang NS, Kao PC 1997 Urinary free cortison and cortisone determined by high performance liquid chromatography in the diagnosis of Cushing's syndrome. Exp Clin Endocrinol 94:275-280 [PubMed] [Google Scholar]Qureshi AC, Bahri A, Breen LA, Barnes SC, Powrie JK, Thomas SM, Carroll PV 2007 The influence of the route of oestrogen administration on serum levels of cortisol-binding globulin and total cortisol. Authors: A Luger, LHA Broersen, NR Biermasz (ENEA), BMK Biller (ES), M Buchfelder, P Chanson, JOL Jorgensen, F Kelestimur, S Llahana, D Maiter, G Mintziori, F Petraglia, R Verkauskiene (ESPE), SM Webb (Endo-ERN), OM Dekkers Read more Objective: The objective of the study was to develop clinical practice guidelines for the diagnosis of Cushing's syndrome. Participants: The Task Force included a chair, selected by the Clinical Guidelines Subcommittee, members responding syndrome. Participants: The Task Force included a chair, selected by the Clinical Guidelines were reviewed and approved sequentially by The Endocrine Society, five additional experts, a methodologist, and a medical writer. The guidelines were reviewed and approved sequentially by The Endocrine Society five additional experts, a methodologist, and a medical
writer. to a web posting, and The Endocrine Society Council. Higher-quality evidence to support testing should come from studies directly comparing the effect of testing scholar] Reimondo G, Allasino B, Bovio S, Paccotti P, Angeli A, Terzolo M 2005 Evaluation of the effectiveness of midnight serum cortisol in the diagnostic procedures for Cushing's syndrome. In addition, published data, which are often from larger tertiary referral centers, might be biased toward more diagnostically challenging cases, higher pretest probability, and greater disease severity. Unfortunately, there is little information on additionation and distinct procedures for Cushing's syndrome. comorbidities and risk factors in these studies. The few data on the outcome, after surgical remission of hypercortisolism, in patients with familial disease that puts them at risk of Cushing's syndrome (e.g. Carney complex, multiple endocrine neoplasia-1) should be evaluated by an endocrinologist as part of a surveillance screening program. Because of the rarity of Cushing's syndrome, the high prevalence of conditions such as diabetes mellitus, obesity, and depression, and the limitations of the screening tests, the risk of false-positive test results is high. J Clin Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Cerdas S, Fournier C, Guiban D, Guilhaume B, Luton JP 1988 Salivary cortisol measurement: a practical approach to assess pituitary-adrenal function. BMJ 328:1490 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol Metab 84:878-882 [PubMed] [Google Scholar] [Google Scholar] Laudat MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol MH, Mullan R, Erickson D, Harris K, Nadeem S, Endocrinol MH, Mullan R, Erickson D, Harris K, Mallan R, Erickson D, Harris K, Mallan R, Erickson D, Harris K, Ennis R, Erwin PJ, Montori VM 2008 Accuracy of diagnostic tests for Cushing syndrome: a systematic review and meta-analyses. J Clin Endocrinol Metab 90:3077-3083 [PubMed] [Google Scholar]Lindsay JR, Nieman LK 2005 The hypothalamic-pituitary-adrenal axis in pregnancy: challenges in disease detection and treatment. J Clin Endocrinol Metab 69:165-169 [PubMed] [Google Scholar]Newell-Price J, Trainer P, Perry L, Wass J, Grossman A, Besser M 1995 A single sleeping midnight cortisol has 100% sensitivity for the diagnosis of Cushing's syndrome. A falsely low UFC can occur when creatinine clearance falls less than 60 ml/min, and UFC levels fall linearly with more severe renal failure (53). Exp Clin Endocrinol Diabetes 113:225-230 [PubMed] [Google Scholar] Viardot A, Huber P, Puder JJ, Zulewski H, Keller U, Muller B 2005 Reproducibility of nighttime salivary cortisol and overnight dexamethasone suppression test. UFC excretion is normal in the first trimester; however, it increases up to 3-fold by term to overlap values seen in women with Cushing's syndrome (103). Clin Chim Acta 382:15-19 [PubMed] [Google Scholar]Smith RE, Maguire JA, Stein-Oakley AN, Sasano H, Takahashi K, Fukushima K, Krozowski ZS 1996 Localization of 11β-hydroxysteroid dehydrogenase type II in human epithelial tissues. Although there are limited data on the prevalence of the syndrome in these disorders, the diagnosis should be considered. In one study, 2-3.3% of patients with poorly controlled diabetes mellitus had surgically confirmed Cushing's syndrome or mild hypercortisolism. However, given the limited availability outside the United States and cost of the dexamethasone assay, this otherwise desirable approach may not be feasible. As noted above, false-positive rates for the overnight DST are seen in 50% of women taking the oral contraceptive pill because of increased CBG levels (44). The introduction of UFC represented a major advance over measurement of 17-hydroxycorticosteroids for the overnight DST are seen in 50% of women taking the oral contraceptive pill because of increased CBG levels (44). The introduction of UFC represented a major advance over measurement of 17-hydroxycorticosteroids for the overnight DST are seen in 50% of women taking the oral contraceptive pill because of increased CBG levels (44). The introduction of UFC represented a major advance over measurement of 17-hydroxycorticosteroids for the overnight DST are seen in 50% of women taking the oral contraceptive pill because of increased CBG levels (44). The introduction of UFC represented a major advance over measurement of 17-hydroxycorticosteroids for the overnight DST are seen in 50% of women taking the oral contraceptive pill because of increased CBG levels (44). The introduction of UFC represented a major advance over measurement of 17-hydroxycorticosteroids for the overnight DST are seen in 50% of women taking the oral contraceptive pill because of the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% of women taking the overnight DST are seen in 50% (170HCS), which reflects both urine metabolites and cortisol. (28) measured bedtime salivary cortisol levels in a large number of obese subjects and found a specificity of 92% when they used a RIA technique, but a better specificity of 92% when they used a RIA technique, but a better specificity of 92% when tandem mass spectrometry was used. Most clinicians using the late-night salivary cortisol test ask patients to collect a saliva sample on two separate evenings between 2300 and 2400 h. N Engl J Med 314:1329-1335 [PubMed] [Google Scholar]Cushing H 1932 The basophil adenomas of the pituitary body and their clinical manifestations. In particular, there are conflicting data on the need to treat mild or so-called subclinical Cushing's syndrome. notably in patients with adrenal incidentalomas. As a result, a normal (low) midnight cortisol value probably excludes Cushing's syndrome, but the diagnostic threshold for either serum or salivary cortisol is not known. The reasons for this apparent decrease in specificity are unknown. J Clin Endocrinol Metab 66:343–348 [PubMed] [Google Scholar]Luthold WW, Marcondes JA, Wajchenberg BL 1985 Salivary cortisol for the evaluation of Cushing's syndrome. Various methods have been used to measure cortisol in the saliva, resulting in difference ranges and yielding differences in sensitivity and specificity (59,60,61,62,63,64,65,66,67). Arch Intern Med 142:1448-1452 [PubMed] [Google Scholar]Workman RJ, Vaughn WK, Stone WJ 1986 Dexamethasone and demonstration of a normal hypothalamic-pituitary-adrenal axis. It is likely that similar values for awake measurements would have similar utility, but this has not been tested directly. Overall in 92 patients without Cushing's syndrome, the specificity of the LDDST was 70% (95% confidence interval 59-87%), compared with a 60% specificity for the dexamethasone-CRH test (95% confidence interval 59-87%). However, there are also drugs (carbamazepine and fenofibrate) that may interfere with some of these chromatographic methods (Table 3), thereby causing falsely elevated values (40,41). 88%) (30). When used in patients with a high clinical index of suspicion of Cushing's syndrome and who had normal UFC and full suppression on dexamethasone testing, a sleeping midnight serum cortisol of greater than 1.8 μg/dl or an awake value of greater than 7.5 μg/dl increases the probability of Cushing's syndrome (96). (9) proposed a different protocol: administering 48 h of dexamethasone at 6-h intervals but beginning at 1200 h and obtaining serum cortisol at 0800 h, exactly 2 h (rather than 6 h as in the usual protocol) after the last dexamethasone dose. For pediatric patients weighing more than 40 kg, the initial adult protocol described above and the adult threshold for normal suppression [50 nmol/liter) had high sensitivity (100%) for the diagnosis of Cushing's syndrome (96). Given a weak recommendation, careful consideration of the patient's circumstances, values, and preferences is appropriate to determine the best
course of action. Linked to each recommendation is a description of the evidence, values that panelists considered in making the recommendation (when making these explicit was necessary), and remarks, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. J Clin Endocrinol Metab 84:440-448 [PubMed] [Google Scholar] Findling JW Raff H, Aron DC 2004 The low-dose dexamethasone suppression test: a reevaluation in patients with Cushing's syndrome. Dexamethasone is given in doses of 0.5 mg for 48 h, beginning at 0900 h on d 1, at 6-h intervals, i.e. at 0900, 1500, 2100, and 0300 h. Although the probability of Cushing's syndrome has not been evaluated in a large number of children, clinical experience suggests that the specificity of these clinical features for the diagnosis is also very high (30). Initial testing for hypercortisolism may be desirable to the extent that its results will favorably affect outcomes that matter to patients. Br Med J (Clin Res Ed) 289:1188-1191 [PMC free article] [PubMed] [Google Scholar] Magiakou MA, Mastorakos G, Oldfield EH, Gomez MT, Doppman JL, Cutler Jr GB, Nieman LK, Chrousos GP 1994 Cushing's syndrome in children and adolescents. UFC provides an integrated assessment of cortisol secretion over a 24-h period. Whereas the most common cause is iatrogenic from medically prescribed corticosteroids, endogenous Cushing's syndrome is an uncommon disorder. Metabolism 28:955-977 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby JC 1971 Assessment of adrenocortical function. Arch Gen Psychiatry 42:897-903 [PubMed] [Google Scholar] Melby Melb glucose and cortisol in intensive care patients. Overall, the evidence in adults suggests that the accuracy of this test is similar to that of UFC (2). Eur J Endocrinol 153:803-809 [PubMed] [Google Scholar]Moro M, Putignano P, Losa M, Invitti C, Maraschini C, Cavagnini F 2000 The desmopressin test in the differential diagnosis between Cushing's disease and pseudo-Cushing states. If a sleeping value is desired, the blood sample must be drawn within 5-10 min of waking the patient, or through an indwelling line, to avoid false-positive results (96). Young children may have their cortisol nadir earlier than midnight. J Clin Endocrinol Metab 93:666-673 [PubMed] [Google Scholar] Etxabe J, Vazquez JA 1994 Morbidity and mortality in Cushing's disease: an epidemiological approach. N Engl J Med 331:629-636 [PubMed] [Google Scholar]Erickson D, Natt N, Nippoldt T, Young Jr WF, Carpenter PC, Petterson T, Christianson T 2007 Dexamethasone-suppressed corticotropin-releasing hormone stimulation test for diagnosis of mild hypercortisolism Because Cushing's syndrome tends to progress and severe hypercortisolism is probably associated with a worse outcome, it is likely that early recognition and treatment of mild disease would reduce the risk of residual morbidity. (see Who should be tested below.) If Cushing's syndrome is not considered, the diagnosis is all too often delayed. In addition, overactivity of the hypothalamic-pituitary-adrenal (HPA) axis occurs without true Cushing's syndrome, so that there is an overlap between physiological and pathophysiological and pathophysiologica study (9). Subsequent reports showed lower diagnostic accuracy of the LDDST (7,88,89,90). In particular, the expected salivary and serum concentrations in these tests are close to the functional limit of detection of the assays. Because Cushing's syndrome tends to progress, accumulation of new features increases the probability that the syndrome is present. In an effort to improve on specificity, higher cutoff points have been advocated, inevitably at the cost of sensitivity: values of serum midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity: values of serum midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The sleeping midnight cortisol greater than 8.3-12 µg/dl had 90-92% sensitivity with specificity of 96% (63,101). The s responses due to the stress of hospitalization; this approach may not be possible in some practice settings. J Clin Endocrinol Metab 83:348-352 [PMC free article] [PubMed] [Google Scholar] Meinardi JR, Wolffenbuttel BH, Dullaart RP 2007 Cyclic Cushing's syndrome: a clinical challenge. This approach also seeks to use more convenient and less expensive tests. 3.4 For the initial testing for Cushing's syndrome, we recommend one of the following tests based on its suitability for a given patient (Fig. In particular, glucocorticoid components of skin creams (including bleaching agents), herbal medications, "tonics," and joint or nerve injections may be overlooked. J Endocrinol Invest 22:241-249 [PubMed] [Google Scholar]Wood PJ, Barth JH, Freedman DB, Perry L, Sheridan B 1997 Evidence for the low dose dexamethasone suppression test to screen for Cushing's syndrome-recommendations for a protocol for biochemistry laboratories. Dexamethasone levels show interindividual variation, however, even in healthy individuals on no medication. To evaluate for false-positive and negative responses, some experts have advocated simultaneous measurement of both cortisol and dexamethasone for these tests to ensure adequate plasma dexamethasone for the examethasone for the examethas adequate plasma devamental for the exame care providers and each patient's individual circumstances. The Endocrine Society makes no warranties of merchantability and fitness for a particular use or purpose. European population-based studies reported an incidence of two to three cases per 1 million inhabitants per year (4,5). Finally, stress immediately before the collection also may increase salivary cortisol physiologically; therefore, ideally, samples should be collected on a quiet evening at home (64). Theoretically, contamination with blood might increase salivary cortisol levels. J Clin Endocrinol Metab 92:4290-4293 [PubMed] [Google Scholar]Martin NM, Dhillo WS, Banerjee A, Abdulali A, Jayasena CN, Donaldson M, Todd JF, Meeran K 2006 Comparison of the dexamethasone suppression test in the diagnosis of Cushing's syndrome. Various doses of dexamethasone have been used, but 1 mg dexamethasone is usually given between 2300 and 2400 h, and cortisol is measured between 0800 and 0900 h the following morning. Eur J Endocrinol 154:419-423 [PubMed] [Google Scholar]Libe R, Dall'Asta C, Barbetta L, Baccarelli A, Beck-Peccoz P, Ambrosi B 2002 Long-term follow-up study of patients with adrenal incidentalomas. At each stage the Task Force incorporated needed changes in response to written comments. Conclusions: After excluding exogenous
glucocorticoid use, we recommend testing for Cushing's syndrome in patients with multiple and progressive features compatible with the syndrome, particularly those with a high discriminatory value, and patients with adrenal incidentaloma. Ann Clin Biochem 34(Pt 3):222-229 [PubMed] [Google Scholar]Khan A, Ciraulo DA, Nelson WH, Becker JT, Nies A, Jaffe JH 1984 Dexamethasone suppression test in recently detoxified alcoholics: clinical implications. This difference in physiology forms the basis for measurement of a midnight serum or late-night salivary cortisol. Biologically active free cortisol in the blood is in equilibrium with cortisol in the salivary cortisol does not appear to be affected by the rate of salivary cortisol does not appear to be affected by the rate of salivary cortisol does not appear to be affected by the rate of salivary cortisol does not appear to be affected by the rate of salivary cortisol does not appear to be affected by the rate of salivary cortisol does not appear to be affected by the rate of salivary cortisol does not appear to be affected by the rate of salivary cortisol in the salivary cortisol does not appear to be affected by the rate of saliv Grinspoon S, Klibanski A, Zervas NT 1999 Long-term mortality after transsphenoidal surgery for Cushing disease. Clin Endocrinol (Oxf) 61:553-559 [PubMed] [Google Scholar] Magiakou MA, Mastorakos G, Chrousos GP 1994 Final stature in patients with endogenous Cushing's syndrome. Serum cortisol is measured at 0900 h, 6 h after the last dose of dexamethasone. Clinicians need a greater appreciation of the recommendations use the phrase "we recommendations use the phrase from published cutoff data. In terms of the strength of the recommendations use the phrase "we suggest" and the number 2. Additionally, it is possible that the 2-h time interval between dexamethasone and CRH administration is critical so that compliance must be assured. In the United States, ovine-sequence CRH is available commercially (ACTHREL; Ferring Corp., Malmo, Sweden) with Food and Drug Administration-approved labeling for the differential diagnosis of Cushing's syndrome. In the absence of additional data, a normal response to 1 mg dexamethasone is likely to exclude Cushing's syndrome, but an abnormal response is not diagnostic. Rarely patients have been described with episodic secretion of cortisol excess in a cyclical pattern with peaks occurring at intervals of several days to many months (93). In Europe, the human-sequence CRH (95). As noted above, the nocturnal nadir of serum cortisol values is lost in patients with Cushing's syndrome, forming the basis of this test. Reports show good correlation between salivary and simultaneous serum cortisol values in healthy volunteers (73,74). J Clin Endocrinol Metab 92:2972-2976 [PubMed] [Google Scholar] Gatta B, Chabre O, Cortet C, Martinie M, Corcuff JB, Roger P, Tabarin A 2007 Reevaluation of the combined dexamethasone suppression-corticotropin-releasing hormone test for differentiation of mild Cushing's disease and the combined dexamethasone suppression-corticotropin-releasing hormone test for differentiation of mild Cushing's disease and the combined dexamethasone suppression-corticotropin-releasing hormone test for differentiation of mild Cushing's disease and the combined dexamethasone suppression-corticotropin-releasing hormone test for differentiation of mild Cushing's disease and the combined dexamethasone suppression-corticotropin-releasing hormone test for differentiation of mild Cushing's disease and the combined dexamethasone suppression-corticotropin-releasing hormone test for differentiation of mild Cushing's disease and the combined dexamethas and the from pseudo-Cushing's syndrome. For example, in a study of men aged 60 yr or older, Liu et al. Patients with concordant normal results should not undergo further evaluation. A thorough drug history noting current or recent use of these medications, oral, rectal, inhaled, topical, or injected, should be obtained before embarking on any biochemical testing (28). This strategy increases confidence in the test results if consistently normal or abnormal results are obtained. Variable absorption and metabolism of dexamethasone may influence the result of both the overnight 1-mg DST and the 48-h, 2 mg/d test. J Clin Endocrinol Metab 87:1949-1954 [PubMed] [Google Scholar]Hermus AR, Smals AG, Swinkels LM, Huysmans DA, Pieters GF, Sweep CF, Corstens FH, Kloppenborg PW 1995 Bone mineral density and bone turnover before and after surgical cure of Cushing's syndrome. As with all hormone assays, the physician must be aware that several collection and assay methods are available for the measurement of cortisol, and results for a single sample measured in various assays may be quite different (39). 1, 10000.3.9.2 We suggest against the use of the desmopressin test, except in research studies, until additional data validate its utility (2000).3.9.3 We recommend against any further testing for Cushing's syndrome in individuals with concordantly negative results on two different tests (except in patients suspected of having the very rare case of cyclical disease) (1 @OOO).3.9.4 We recommend tests to establish the cause of Cushing's syndrome in patients with concordantly positive results from two different tests, provided there is no concern regarding possible non-Cushing's syndromeaConditions associated with hypercortisolism in the absence of Cushing's syndromeaConditions associated with hypercortisolism in the absence of Cushing's syndromeaConditions. Glucocorticoid resistance Morbid obesity Poorly controlled diabetes mellitusUnlikely to have any clinical features of Cushing's syndrome Physical stress (hospitalization, surgery, pain) Malnutrition, anorexia nervosa Intense chronic exercise Hypothalamic amenorrhea CBG excess (increased serum but not urine cortisol)3.9.5 We suggest further evaluation and follow-up for the few patients with concordantly negative results who are suspected of having cyclical disease and also for patients with discordant results, especially if the pretest probability of Cushing's syndrome is high (2000).4.1 Pregnancy: We recommend the use of UFC and against the use of dexamethasone testing in the initial evaluation of pregnant women ( $1 \oplus \Phi \oplus \bigcirc$ ).4.2 Epilepsy: We recommend against the use of dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone testing in patients and the second devament and the sec mg overnight DST rather than UFC for initial testing for Cushing's syndrome in patients with severe renal failure (2000).4.5 Adrenal incidentaloma: We suggest use of the 1-mg DST or late-night cortisol test, rather than UFC, in patients suspected of having mild Cushing's syndrome (2000). The Clinical Guidelines Subcommittee of The Endocrine Society deemed detection and diagnosis of patients with Cushing's syndrome a priority area in need of practice guidelines and appointed a six-member Task Force to formulate evidence-based recommendations. Clin Chim Acta 151:33-39 [PubMed] [Google Scholar] Papanicolaou DA, Mullen N, Kyrou I, Nieman LK 2002 Nighttime salivary cortisol: a useful test for the diagnosis of Cushing's syndrome. This focus may be due to the rarity of the disease and the availability of diverse diagnostic methods. Initial studies suggested that an awake midnight serum cortisol greater than 7.5 µg/dl (>207 nmol/liter) had a sensitivity and specificity greater than 96% (98,99). Ann Clin Biochem 44:281-284 [PubMed] [Google Scholar]Poll EM, Kreitschmann-Andermahr I, Langejuergen Y, Stanzel S, Gilsbach JM, Gressner A, Yagmur E 2007 Saliva collection method affects mostic strategy. The test is done by administering
the 48-h 2 mg/d DST, followed by administration of CRH (1 μg/kg, iv) 2 h after the last dose of dexamethasone. Diagn the normal range for the assay, serum cortisol greater than 1.8 µg/dl (50 nmol/liter) after 1 mg dexamethasone (1-mg DST), and late-night salivary cortisol greater than 1.8 µg/dl (4 nmol/liter). 3.5 We recommend against the use of the following to test for Cushing's syndrome (1-mg DST), and late-night salivary cortisol greater than 1.8 µg/dl (50 nmol/liter). 3.5 We recommend against the use of the following to test for Cushing's syndrome (1-mg DST), and late-night salivary cortisol greater than 1.8 µg/dl (50 nmol/liter). 3.5 We recommend against the use of the following to test for Cushing's syndrome (1-mg DST), and late-night salivary cortisol greater than 1.8 µg/dl (4 nmol/liter). 3.5 We recommend against the use of the following to test for Cushing's syndrome (1-mg DST), and late-night salivary cortisol greater than 1.8 µg/dl (50 nmol/liter). 3.5 We recommend against the use of the following to test for Cushing's syndrome (1-mg DST), and late-night salivary cortisol greater than 1.8 µg/dl (50 nmol/liter). 3.5 We recommend against the use of the following to test for Cushing's syndrome (1-mg DST), and late-night salivary cortisol greater than 1.8 µg/dl (50 nmol/liter). 3.5 We recommend against the use of the following to test for Cushing's syndrome (1-mg DST), and late-night salivary cortisol greater than 1.8 µg/dl (50 nmol/liter). 3.5 We recommend against the use of the following the use of th ketosteroidsInsulin tolerance testLoperamide testTests designed to determine the cause of Cushing's syndrome (e.g. pituitary and adrenal imaging, 8 mg DST).3.6 In individuals with normal test results in whom the pretest probability is high (patients with clinical features suggestive of Cushing's syndrome and adrenal incidentaloma or suspected cyclic hypercortisolism), we recommend further evaluation by an endocrinologist to confirm or exclude the diagnosis (1000).3.7 In other individuals with normal test results (in whom Cushing's syndrome is very unlikely), we suggest reevaluation in 6 months if signs or symptoms progress (2000).3.8 In individuals with at least one abnormal test result (for whom the results could be falsely positive or indicate Cushing's syndrome), we recommend further evaluation of abnormal initial test results, we recommend performing another recommended test (Fig. All statements are recommendations except for those prefaced by suggest. The response to those tests used specifically to establish the cause of Cushing's syndrome (e.g. pituitary, adrenal or thoracic imaging, plasma ACTH concentration, CRH stimulation test, 8 mg dexamethasone suppression test) may be both abnormal in healthy people and normal in patients with Cushing's syndrome and therefore are not helpful in establishing the diagnosis (78). Our recommendations for retesting patients with initially normal test results who develop new or progressive signs or symptoms of Cushing's syndrome comes from the panel's clinical observations and relate to the recognition that the patient's pretest probability of Cushing's syndrome would be higher on retesting and that hypercortisolism may have evolved concomitantly with the progression of the clinical syndrome, enhancing the likelihood that repeat tests would be positive. Similarly, the recommendation to retest patients with suspected cyclic Cushing's syndrome comes from the recognition that these individuals may have normal test results when the disorder is quiescent (93). The performance and interpretation of subsequent testing for Cushing's syndrome requires considerable expertise (both in the clinic and in the laboratory) and may be followed by either complex testing to establish its cause and surgical treatments or expert reassurance of patients that they do not have this condition. J Endocrinol Invest 26:609-615 [PubMed] [Google Scholar]Ramirez G, Gomez-Sanchez C, Meikle WA, Jubiz W 1982 Evaluation of the hypothalamic hypophyseal adrenal axis in patients receiving long-term hemodialysis. However, no data addressing this assumption have been reported. Our recommendations for testing for Cushing's syndrome are based on direct evidence from observational studies indicating a large treatment effect (which we have rated as low to moderate quality evidence) on morbidity and mortality in patients diagnosed with the condition. Newell-Price, M.D., F.R.C.P., Ph.D.—Financial or Business/Organizational Interests: Society for Endocrinology, United Kingdom, Clinical Endocrinology, Trustee to Pituitary Foundation, United Kingdom, Significant Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; Martin Savage, M.D.—Financial Interest or Leadership Position: none declared; M.D.—Financial Interest or Leadership Position: n Position: Hormone Reproduction, Ipsen; Paul Michael Stewart, M.D., F.R.C.P.—Financial or Business/Organizational Interests: International Society for Endocrinology, Significant Financial or Leadership Position: none declared; \* Victor M. 1, 1 @OOO).3.8.2 We suggest against the use of the desmopressin test, except in research studies, until additional data validate its utility (2 $\oplus$ OOO).3.8.3 We recommend against any further testing for Cushing's syndrome in individuals with concordantly negative results on two different tests (except in patients suspected of having the very rare case of cyclical disease) (1 $\oplus$ OOO).3.8.4 We recommend tests to establish the cause of Cushing's syndrome in individuals with concordantly negative results on two different tests (except in patients suspected of having the very rare case of cyclical disease) (1 $\oplus$ OOO).3.8.4 We recommend tests to establish the cause of Cushing's syndrome in individuals with concordantly negative results on two different tests (except in patients suspected of having the very rare case of cyclical disease) (1 $\oplus$ OOO).3.8.4 We recommend tests to establish the cause of Cushing's syndrome in individuals with concordantly negative results on two different tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests to establish the cause of Cushing's syndrome in individuals with concordantly negative results on two different tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOO).3.8.4 We recommend tests (except in patients) (1 $\oplus$ OOOO).3.8 We recommend tests (except in patients) (1 $\oplus$ OOOO). patients with concordantly positive results from two different tests, provided there is no concern regarding possible non-Cushing's hypercortisolism (Table 2) (1 • • ○ ○).3.8.5 We suggest further evaluation and follow-up for the few patients with discordant results, especially if the pretest probability of Cushing's syndrome is high (2000). If the initial test result is abnormal, further evaluation by an endocrinologist will be considered. Conversely, in cases in which there is a high pretest probability of Cushing's syndrome but a normal initial test, use of an additional alternative test has the potential benefit of disclosing those with milder disease. In an effort to improve the sensitivity of the 48-h, 2 mg/d test, researchers developed a combined CRH stimulation test. J Clin Psychopharmacol 4:94-97 [PubMed] [Google Scholar]Liddle GW 1960 Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. Assays differ widely in their accuracy; results near the cutoff value on a single measurement often can be explained by assay variability. Therefore, unlike serum cortisol, which measures both CBG-bound and free hormone, UFC is not affected by conditions and medications that alter CBG. Conversely, once the clinical scenario suggests a high pretest probability of the disorder, sensitivity needs to be high so that cases are not recommended for patients suspected of having cyclic disease. When these two assay techniques are used, normal subjects usually have salivary cortisol
levels at bedtime, or between 2300 and 2400 h, of less than 145 ng/dl (4 nmol/liter). Underlying disorders that may cause mild hypercortisolism (Table 2) should be considered and testing repeated when these are treated or resolved. Upper limits of normal are much lower with HPLC or LC-MS/MS than in antibody-based assays. If the initial testing results are normal, assuming that there is no reason to mistrust the result (see remarks below), then the patient is very unlikely to have Cushing's syndrome. 1, 1 @OOO).3.8.1 We suggest the additional use of the dexamethasone-CRH test or the midnight serum cortisol test in specific situations (Fig. The research in this area yields data on the likelihood of Cushing's syndrome in certain populations and on the accuracy of currently available tests in these populations and on the accuracy of currently available tests in these populations. Megestrol acetate (medroxyprogesterone acetate) is a synthetic progesterone acetate) is a synthetic progesterone acetate (medroxyprogesterone acetate) is a synthetic progesterone acetate. cause Cushing's syndrome (29). To date such evidence is not available in this field. These guidelines focus on the more common clinical scenarios, with brief mention of conditions and situations that are rare or more common clinical scenarios, with brief mention of conditions and situations that are rare or more common clinical scenarios, with brief mention of conditions and situations that are rare or more common clinical scenarios, with brief mention of conditions and situations and situations and situations are common clinical scenarios. drug history to exclude exogenous glucocorticoid exposure leading to iatrogenic Cushing's syndrome before conducting biochemical testing (1 + 40). (1 + 40). (1 + 40). (1 + 40). progressive features, particularly those that are more predictive of Cushing's syndrome (Table 1) (10000). As We recommend against widespread testing for Cushing's syndrome in any other patient group (1 $\oplus$ OOO). Features of Cushing's syndrome may occur as a result of exogenous glucocorticoid use. Arch Intern Med 157:1651-1656 [PubMed] [Google Scholar]Batista DL, Riar J, Keil M, Stratakis CA 2007 Diagnostic tests for children who are referred for the investigation of Cushing syndrome. Until additional data validate the utility of the test in a larger population of patients with all causes of Cushing's syndrome, it seems prudent to restrict this test to research studies. 4.1 Pregnancy: We recommend the use of dexamethasone testing in the initial evaluation of pregnant women (1000). 4.2 Epilepsy: We recommend against the use of dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone clearance and recommend instead measurements of nonsuppressed cortisol in blood, saliva, or urine (1 • • • ○).4.3 Renal failure: We suggest using the 1-mg overnight DST rather than UFC for initial testing for Cushing's syndrome in patients with severe renal failure (2000).4.4 Cyclic Cushing's syndrome: We suggest use of UFC or midnight salivary cortisol tests rather than UFC in patients suspected of having mild Cushing's syndrome (2000).4.5 Adrenal incidentaloma: We suggest use of the 1-mg DST or late-night cortisol test, rather than UFC in patients suspected of having mild Cushing's syndrome (200). Screening for hypercortisolism is more difficult in pregnancy, particularly in the second and third trimesters. The guidelines are not intended to dictate the treatment of a particular patient. The Endocrine Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.Lynnette K. Using a variety of assays and diagnostic criteria, investigators from different countries have reported that late-night salivary cortisol levels yield a 92-100% sensitivity and a 93-100% sensitivit Scholar]Hamrahian AH, Oseni TS, Arafah BM 2004 Measurements of serum free cortisol in critically ill patients. The optimal test is the LDDST. Lancet 1:1234-1236 [PubMed] [Google Scholar]Pfohl B, Sherman B, Schlechte J, Stone R 1985 Pituitary-adrenal axis rhythm disturbances in psychiatric depression. Previous studies using various doses of dexamethasone and differing criteria for suppression suggest that at least 2 wk of abstinence from alcohol are needed to reduce the false-positive rate (84). First described by Liddle (85) in 1960, the LDDST initially evaluated urinary 170HCS as an indicator of cortisol suppression. J Clin Endocrinol Metab 87:4515-4521 [PubMed] [Google Scholar]Putignano P, Toja P, Dubini A, Pecori Giraldi F, Corsello SM, Cavagnini F 2003 Midnight salivary cortisol versus urinary free and midnight serum cortisol as screening tests for Cushing's syndrome. J Clin Endocrinol Metab 24:621-627 [PubMed] [Google Scholar]Pecori Giraldi F, Pivonello R, Ambrogio AG, De Martino MC, De Martin M, Scacchi M, Colao A, Toja PM, Lombardi G, Cavagnini F 2007 The dexamethasone-suppressed corticotropin-releasing hormone stimulation test and the desmopressin test to distinguish Cushing's syndrome from pseudo-Cushing's states. We recommend additional testing in patients with discordant results, normal responses suspected of cyclic hypercortisolism, or initially normal responses who accumulate additional features over time. 3.1 We recommend obtaining a thorough drug history to exclude excessive exogenous glucocorticoid exposure leading to iatrogenic Cushing's syndrome in the following groups: Patients with unusual features for age (e.g. osteoporosis, hypertension) (Table 1) (1 • • ○ ○) Overlapping conditions Features that best discriminate Cushing's syndrome; most do not have a high sensitivity Easy bruising Facial plethora Proximal myopathy (or proximal muscle weakness)Striae (especially if reddish purple and > 1 cm wide)In children, weight gain with decreasing growth velocityCushing's syndrome features in the general population that are common and/or less discriminatory. DepressionDorsocervical fat pad ("buffalo hump")Hypertensionb. FatigueFacial fullnessIncidental adrenal mass Weight gainObesityVertebral osteoporosisb Back painSupraclavicular fullnessPolycystic ovary syndrome Changes in appetiteThin skinbType 2 diabetesb Decreased concentrationPeripheral edemaHypokalemia Decreased libidoAcneKidney stones Impaired memory (especially short term)Hirsutism or female baldingUnusual infections InsomniaPoor skin healing Irritability Menstrual abnormalities In children, slow growthIn children, abnormal genital virilizationIn children, short statureIn children, pseudoprecocious puberty or delayed pubertyPatients with multiple and progressive features, particularly those who are more predictive of Cushing's syndrome (Table 1) (1\$\DOO)\$Children with decreasing height percentile and increasing weight (1\$\DOO)\$.3.3 We recommend against widespread testing for Cushing's syndrome in any other patient group (1\$\DOO)\$.3.4 For the initial testing for Cushing's syndrome, we recommend one of the following tests based on its suitability for a given patient (Fig. With adequate written instructions for the patient, the LDDST is easily performed in the outpatient setting. As described above (Section 1.0), certain psychiatric conditions (depression, anxiety, obsessive compulsive disorder), morbid obesity, alcoholism, and diabetes mellitus can be characterized by overactivation of the HPA axis but without true Cushing's syndrome, i.e. hypercortisolism is not autonomous. A commitment from endocrine organizations and funding agencies to establish databases of consecutive patients tested for Cushing's syndrome allowing for prospective pooling of the diagnostic test information. However, with modern-day treatments the standard mortality ratio (SMR) after successful normalization of cortisol was similar to that of an age-matched population during 1-20 yr of follow-up evaluation in one study (13). In patients for whom clinical suspicion is high but initial tests are normal, follow-up is recommended with repeat testing, if possible to coincide with clinical symptoms. UFC appears to be less sensitive than the 1-mg DST or late-night cortisol for the identification of Cushing's syndrome in this population (20,21,22,23). The diagnosis of Cushing's syndrome is critically dependent on the quality and performance of cortisol assays, be they from serum, saliva, or urine and measured by RIA, ELISA, or LC-MS/MS. The absorption and metabolism of 1 mg dexamethasone, as well as the cortisol response, have been reported to be both normal and abnormal (107,108,109). False-positive results, with their attendant costs, are reduced if case detection is limited to individuals with an increased pretest probability of having the disorder. In these conditions, UFC measurements are less useful as an initial test, However, there is a wide spectrum of clinical manifestations at any given level of hypercortisolism. In children, precatheterization is essential so that a sleeping sample for serum cortisol can be obtained. The desmopressin stimulation test involves measurement of plasma ACTH just before and 10, 20, and 30 min after iv administration of 10 µg 1-desamino-8-d-arginine vasopressin. C. A widely cited normal response is a serum cortisol less than 5 µg/dl (see than 5 µg/dl) (see than 5 µg/dl

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