Diagnosis of Adrenal Insufficiency

Richard I. Dorin, MD; Clifford R. Qualls, PhD; and Lawrence M. Crapo, MD, PhD

Background: **The cosyntropin stimulation test is the initial endocrine evaluation of suspected primary or secondary adrenal insufficiency.**

Purpose: **To critically review the utility of the cosyntropin stimulation test for evaluating adrenal insufficiency.**

Data Sources: **The MEDLINE database was searched from 1966 to 2002 for all English-language papers related to the diagnosis of adrenal insufficiency.**

Study Selection: **Studies with fewer than 5 persons with primary or secondary adrenal insufficiency or with fewer than 10 persons as normal controls were excluded. For secondary adrenal insufficiency, only studies that stratified participants by integrated tests of adrenal function were included.**

Data Extraction: **Summary receiver-operating characteristic (ROC) curves were generated from all studies that provided sensitivity and specificity data for 250-μg and 1-μg cosyntropin tests; these curves were then compared by using area under the curve (AUC) methods. All estimated values are given with 95% CIs.**

Data Synthesis: **At a specificity of 95%, sensitivities were 97%, 57%, and 61% for summary ROC curves in tests for primary adrenal insufficiency (250-μg cosyntropin test), secondary adrenal insufficiency (250-μg cosyntropin test), and secondary adrenal insufficiency (1-μg cosyntropin test), respectively. The area under the curve for primary adrenal insufficiency was significantly greater than the AUC for secondary adrenal insufficiency for the high-dose cosyntropin test ($P < 0.001$), but AUCs for the 250-μg and 1-μg cosyntropin tests did not differ significantly ($P > 0.5$) for secondary adrenal insufficiency. At a specificity of 95%, summary ROC analysis for the 250-μg cosyntropin test yielded a positive likelihood ratio of 11.5 (95% CI, 8.7 to 14.2) and a negative likelihood ratio of 0.45 (CI, 0.30 to 0.60) for the diagnosis of secondary adrenal insufficiency.**

Conclusions: **Cortisol response to cosyntropin varies considerably among healthy persons. The cosyntropin test performs well in patients with primary adrenal insufficiency, but the lower sensitivity in patients with secondary adrenal insufficiency necessitates use of tests involving stimulation of the hypothalamus if the pretest probability is sufficiently high. The operating characteristics of the 250-μg and 1-μg cosyntropin tests are similar.**

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For author affiliations, see end of text.

Adrenal insufficiency is an uncommon clinical disorder that results from an inadequate basal or stress level of plasma cortisol. It is important to diagnose adrenal insufficiency because the disorder may be fatal if left unrecognized or untreated. With diagnosis and appropriate adrenocortical hormone replacement, normal quality of life and longevity can be achieved. The presentation of adrenal insufficiency may be insidious and thus difficult to recognize. Once suspected, however, the definitive diagnosis can be confirmed by laboratory evaluation of adrenocortical function.

Although many different tests for adrenal insufficiency have been developed, few have been adequately studied and many are inconvenient for testing in the outpatient clinical setting. By contrast, the cosyntropin stimulation test is widely used in many different clinical settings and is easy to perform. In addition, data on test performance in various clinical settings are plentiful. The cosyntropin stimulation test has therefore emerged as the initial test used to evaluate patients for both primary and secondary adrenal insufficiency.

METHODS

We reviewed all English-language studies in humans identified in the MEDLINE database (1966 to 2002) through the Ovid search service. Search terms were *adrenal gland hypofunction* restricted to *diagnosis*. For the normal response to high-dose cosyntropin, we selected studies with 10 or more participants. For the diagnosis of primary adrenal insufficiency, we selected studies with 5 or more participants. For evaluation of the sensitivity and specificity of cosyntropin tests in secondary adrenal insufficiency, we selected only studies that stratified all participants with suspected adrenal insufficiency by integrated tests of adrenal function (insulin tolerance or metyrapone tests).

Summary receiver-operating characteristic (ROC) curves were developed from sensitivity and specificity values derived from individual studies, as described by Littenberg, Moses, and colleagues (1, 2) (see the Appendix, available at www.annals.org, for detailed formulas). Summary ROC curves were compared by using area under the curves (AUCs), as described by Walter (3). For our data sets, we verify the condition ($B \cong 0$; see the Appendix, available at www.annals.org) that yields explicit formulas for AUC and its CI for the summary ROC curves. The slope parameter (B) did not differ significantly from 0 for all data sets used to generate summary ROC curves.

We compared ROC curves for data paired by individual participants using likelihood methods with a program (ROCKIT 0.9B) developed by Metz and colleagues (4) (available at www-radiology.uchicago.edu/cgi-bin/software.cgi).

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DATA SYNTHESIS

High-Dose Cosyntropin Stimulation Test

The standard cosyntropin test is performed by administering one ampule (250 μg) of cosyntropin intramuscularly or intravenously and measuring serum or plasma cortisol levels 30 to 60 minutes later. With a normal (negative) test result, the serum cortisol level after cosyntropin stimulation is generally greater than 500 nmol/L. A subnormal cortisol response (<500 nmol/L) is defined as a positive test result and indicates an increased probability of either primary or secondary adrenal insufficiency. The cosyntropin test may be performed at any time of the day. In patients with suspected adrenal insufficiency, a basal plasma cortisol level is not usually necessary because neither the absolute nor the percentage change from the basal level is useful as a diagnostic criterion for the cosyntropin test (5). However, in the absence of corticosteroid-binding globulin deficiency, an unstimulated serum cortisol level, determined between 6:00 and 8:00 a.m., may be helpful because a level less than 80 nmol/L strongly suggests adrenal insufficiency (5).

Normal Response to the High-Dose Cosyntropin Test

In healthy persons without evidence of adrenal insufficiency, serum cortisol response 30 or 60 minutes after 250 μg of cosyntropin is administered intramuscularly or intravenously has been studied extensively (6–22). The responses to intramuscular and intravenous injections are similar, and the responses among normal persons vary. In 10 studies that included a total of 288 participants and that reported the entire range of postcosyntropin serum cortisol levels, the levels ranged from 415 to 2200 nmol/L (9, 10, 12–15, 17, 19–21). The broad range of normal responses to cosyntropin stimulation reflects various factors, including differences in hypothalamic–pituitary–adrenal axis set point, serum corticosteroid-binding globulin level, stress level, body composition, time of testing, and performance characteristics of the cortisol assay used.

In one detailed study of 100 healthy persons, the distribution curves of serum cortisol levels obtained 30 and 60 minutes after a 250-μg intramuscular injection of cosyntropin displayed a non-Gaussian configuration for each of four separate cortisol assays, with the distribution skewed to the right toward higher cortisol levels (22). The 5th percentile lower cortisol cutoff limit for these four assays ranged from 510 to 615 nmol/L at 30 minutes and from 620 to 675 nmol/L at 60 minutes. Other studies also show increases in the cortisol response at 60 minutes compared with 30 minutes (16, 18, 20). In 11 studies involving 340 healthy participants, the data presented as the mean minus 2 SDs show lower limits ranging from 390 to 620 nmol/L at 30 minutes (6–10, 16–20) and from 500 to 725 nmol/L at 60 minutes (11, 16, 18, 20). Because the distribution curve is non-Gaussian, no conclusion can be drawn from these studies about the percentage of healthy persons with serum cortisol levels less than the lower cutoff limit.

The studies described show that an appreciable number of normal persons will have a postcosyntropin cortisol level less than a cutoff limit of 500 nmol/L. However, none of the 288 participants in the 10 studies described earlier (in which the entire range of cortisol responses was reported) had a cortisol level less than 415 nmol/L.

Diagnosis of Primary Adrenal Insufficiency

Primary adrenal insufficiency (often called Addison disease) is an uncommon disorder that often presents with a slowly progressive increase in nonspecific symptoms. The prevalence of this disorder in the community is approximately 100 cases per 1 million people (23–26); the incidence is 5 cases per year per 1 million people (26). The prevalence of primary adrenal insufficiency is higher (although not precisely known) in persons with HIV disease, family histories of adrenoleukodystrophy, autoimmune endocrine disorders, metastatic cancer, and granulomatous disease.

The prevalence among persons with nonspecific symptoms, such as tiredness, fatigue, weakness, listlessness, weight loss, nausea, and anorexia, is not known. More specific symptoms, such as unexplained darkening of the skin, orthostatic dizziness, and salt-craving, may not be among presenting symptoms.

Cosyntropin Stimulation Tests in Primary Adrenal Insufficiency

Table 1 summarizes the results of 8 studies in which 122 patients with primary adrenal insufficiency and controls were given 250 μg of cosyntropin intravenously or intramuscularly and the serum cortisol levels were measured 30 or 60 minutes later. None of the patients in these studies underwent consecutive prospective evaluation for adrenal insufficiency; rather, they were selected for study either because previous evaluation showed that they had typical Addison disease (13, 14, 20, 27–29) or because their cosyntropin tests were compared with historical controls in retrospective surveys (23, 30). Controls in these studies varied from healthy volunteers (13, 14, 23) to participants with nonendocrine illness (14, 27) or suspected adrenal insufficiency (29). Thus, case-patients and controls were not recruited from the same setting. In general, the case-patients with Addison disease in these studies were selected on the basis of typical clinical and nonendocrine laboratory criteria, such as hyperkalemia, supplemented in many cases with elevated plasma adrenocorticotropic hormone (ACTH) levels and low urine steroid responses to intravenous ACTH infusions. In several retrospective analyses using historical controls, cosyntropin tests may have contributed to the diagnosis of Addison disease, but several patients with Addison disease in each of these surveys had normal cosyntropin test results. None of the studies indicated that patients with borderline cosyntropin test results were selectively excluded. However, it is clear that the cases

Table 1. **The 250-μg Cosyntropin Stimulation Test in Patients with Primary Adrenal Insufficiency***

Study (Reference)†	Cosyntropin Route and Time after Injection‡	Serum Cortisol Cutoff Level	Sensitivity§	Specificity§	Positive Likelihood Ratio‖	Negative Likelihood Ratio‖
	min	*nmol/L*	*% (n/n)*			
Speckart et al. (27)	IV, 60	415	100 (6/6)	100 (9/9)	>100	0
Nelson and Tindall (14)	IV, 60	415	100 (7/7)	100 (69/69)	>100	0
Oelkers et al. (28)	IM, 60	415	100 (41/41)	–	–	–
Fiad et al. (29)	IV, 60	415	100 (12/12)	100 (55/55)	>100	0
Kong and Jeffcoate (23)	IV, 60	415	75 (6/8)	–	–	–
Gonzalez-Gonzalez et al. (20)	IV, 60	415	82 (9/11)	100 (46/46)	>100	0.18
Soule (30)	IV, 60	415	95 (35/37)	–	–	–
Speckart et al. (27)	IV, 30	415	100 (6/6)	88 (7/8)	8.3	0
Dluhy et al. (13)	IM, 30	415	100 (5/5)	100 (12/12)	>100	0
Oelkers et al. (28)	IM, 30	415	100 (41/41)	–	–	–
Kong and Jeffcoate (23)	IV, 30	415	89 (16/18)	–	–	–
Gonzalez-Gonzalez et al. (20)	IV, 30	415	82 (9/11)	100 (46/46)	>100	0.18

* IM = intramuscular; IV = intravenous.
† In six studies (13, 14, 20, 27–29), cases of typical Addison disease (proven by clinical criteria, low urine steroids levels, or high serum adrenocorticotropic hormone levels) were selected for cosyntropin testing from outpatient clinics. Two studies (23, 30) are retrospective surveys of patients with suspected Addison disease who had cosyntropin testing and were compared with historical controls. Control groups were historical (23, 28, 30), healthy volunteers (13, 14, 20), persons with nonendocrine illness (14, 27), or persons with suspected adrenal insufficiency with a normal metyrapone test result (29).
‡ Time after injection is when the serum cortisol is drawn in minutes after the 250-μg cosyntropin injection.
§ Sensitivity is the percentage calculated from raw data (shown in parentheses) indicating the number of persons with positive cosyntropin test results among true-positive persons. Specificity is the percentage calculated from raw data (shown in parentheses), indicating the number of persons with negative cosyntropin test results among true-negative persons.
‖ Definitions of positive and negative likelihood ratios are shown in equation A2 in the Appendix (available at www.annals.org).

of Addison disease selected in these studies were more advanced and easily recognized by well-established clinical and laboratory criteria. Thus, in most cases in these studies, the diagnosis of Addison disease was based on clinical evidence supported by serum electrolyte, plasma ACTH, and urine steroid levels. Cosyntropin tests were then performed in these patients, and the results were interpreted independently of the original diagnostic criteria.

For the summary ROC curve, which is based on four of the studies in **Table 1** (14, 20, 27, 29), the point on the summary ROC where sensitivity and specificity are equal was 96.5% (95% CI, 94.5% to 98.5%) for the diagnosis of primary adrenal insufficiency. When specificity is set at 95%, this summary ROC curve yields a sensitivity of 97.5% (CI, 95% to 100%), with a corresponding positive likelihood ratio of 19.5 (CI, 19.0 to 20.0) and a negative likelihood ratio of 0.026 (CI, 0 to 0.6). The AUC for this summary ROC curve was 0.99 (CI, 0.985 to 1.000), indicating excellent test discrimination.

As a result of the selection bias in these studies toward patients with severe Addison disease, the cosyntropin test performance characteristics derived from **Table 1** are most applicable to such patients. Patients with mild Addison disease or subclinical Addison disease probably have cosyntropin test performance characteristics that would be considerably less robust than those in **Table 1**. After a positive cosyntropin test result, the diagnosis of primary adrenal insufficiency may be confirmed by an elevation of plasma ACTH level (5, 28), whereas patients with secondary adrenal insufficiency typically have normal or low plasma ACTH levels.

Problems of Diagnosis in Primary Adrenal Insufficiency

Diagnosis of Mild Primary Adrenal Insufficiency. One difficulty in the diagnosis of primary adrenal insufficiency is the nonspecific nature of presentation and the resultant lack of clinical suspicion for the disorder. There is a continuum of adrenal insufficiency ranging from subclinical hypoadrenalism (characterized by a normal cortisol response to cosyntropin and an elevated basal or corticotropin-releasing hormone–stimulated plasma ACTH level) to overt primary adrenal insufficiency (characterized by a negligible cortisol response to cosyntropin and a very high plasma ACTH level). Most of the patients with primary adrenal insufficiency in **Table 1** had cortisol responses to cosyntropin substantially less than 275 nmol/L, which poses no problem in laboratory diagnosis. However, several patients in **Table 1** had a normal response to cosyntropin, with cortisol levels greater than 550 nmol/L and simultaneously high plasma ACTH levels. These patients clinically improved after receiving glucocorticoid therapy. Longitudinal follow-up of patients with subclinical hypoadrenalism who were identified among the patients with HIV disease, adrenal autoantibodies, or a family history of adrenoleukodystrophy or adrenomyeloneuropathy (32–35) demonstrates progression to overt primary adrenal insufficiency in some patients (33). Thus, the cortisol response to cosyntropin depends on the degree of adrenal gland failure, and the sensitivity of the cosyntropin stimulation test depends on whether patients have mild or severe primary adrenal insufficiency.

Because patients with mild primary adrenal insufficiency sometimes have a normal cosyntropin stimulation

test result (20, 23, 30), other tests, such as the plasma ACTH–cortisol ratio or the plasma renin activity–aldosterone ratio in paired blood samples (28), may be appropriate. However, few studies of this type have been reported, and the renin–aldosterone ratio is elevated in other, more common medical conditions.

Diagnosis of Primary Adrenal Insufficiency in Acute Settings. The variability of basal serum cortisol and cosyntropin-stimulated serum cortisol levels is even greater in acutely ill persons than in healthy persons; basal levels range from 140 to 11 000 nmol/L (36–63). Measurements of cortisol levels in critically ill patients in intensive care or the emergency department (36–48), patients with sepsis or septic shock (49–57), and surgical patients in the postoperative period (58–63) show a broad range of cortisol responses to stress and to cosyntropin; therefore, determining which patients have adrenal insufficiency is not straightforward. The problem of diagnosis is particularly difficult in patients with well-documented septic shock, as illustrated in one study in which almost 20% of the surviving patients with sepsis had initial basal cortisol levels less than 275 nmol/L and cosyntropin-stimulated levels less than 500 nmol/L (56). Subsequently, all survivors demonstrated a normal response to cosyntropin. Thus, the diagnosis of adrenal insufficiency in the acute setting is exceedingly difficult.

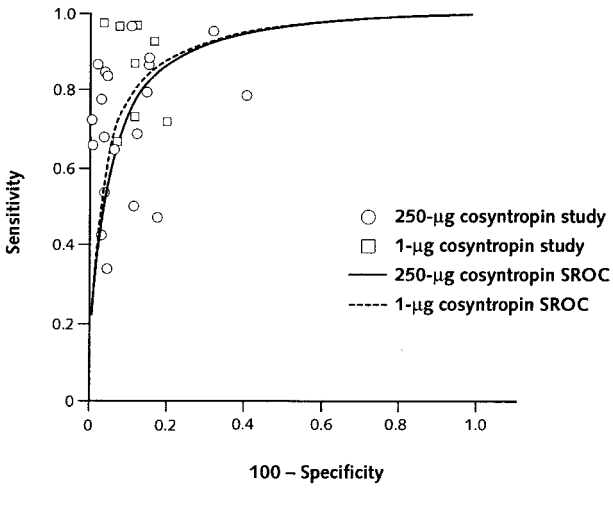
Postcosyntropin Cortisol Cutoff Level. As will be discussed, a higher cortisol cutoff level is required to achieve a reasonable level of sensitivity in secondary adrenal insufficiency. Therefore, if the diagnostic application of the cosyntropin test can be restricted to primary adrenal insufficiency on the basis of clinical or nonsteroid laboratory findings, it may be useful to use a lower cortisol cutoff level, such as 415 nmol/L (**Table 1**). In clinical practice, this distinction is not always possible and a higher cortisol cutoff level (500 to 600 nmol/L) should be applied to achieve reasonable sensitivity for secondary adrenal insufficiency. The risk of a higher cutoff level for primary adrenal insufficiency is a false-positive cosyntropin test result, leading to potentially lifelong, physiologic corticosteroid replacement therapy for the euadrenal patient. This can be avoided by using adjunctive tests, such as the plasma ACTH test, to confirm the diagnosis of primary adrenal insufficiency.

Table 2. **Usefulness of the 250-μg Cosyntropin Stimulation Test in Patients Who Are Taking Glucocorticoids or Have Pituitary Disease***

Study (Reference)†	Cosyntropin Route and Time after Injection‡	Serum Cortisol or Deoxycortisol Cutoff Level after Stimulation§			Sensitivity¶	Specificity¶	Positive Likelihood Ratio**	Negative Likelihood Ratio**
		ITT‖	MT‖	Cosyntropin Test				
	min	*nmol/L*			*% (n/n)*			
Kehlet et al. (73)	IV, 30	500		500	90 (9/10)	87 (13/15)	6.9	0.11
Lindholm et al. (74)	IV, 30	500		500	85 (29/34)	96 (54/56)	21.3	0.16
Cunningham et al. (75)	IM, 60	550	175	500	40 (8/20)	100 (15/15)	>100	0.58
Lindholm and Kehlet (76)	IV, 30	500		500	73 (19/26)	99 (135/136)	73	0.27
Stewart et al. (77)	IM, 30	500		550	90 (9/10)	85 (51/60)	6.0	0.12
Hartzband et al. (78)	IV, peak	500		500	80 (8/10)	100 (13/13)	>100	0.20
Jackson et al. (79)	IV, 30	550		550	69 (9/13)	100 (11/11)	>100	0.31
Tordjman et al. (80)	IV, 30	500	200	550	50 (8/16)	89 (33/37)	4.5	0.56
Kane et al. (81)	IM, 30	500		500	100 (9/9)	69 (9/13)	3.2	0.00
Hurel et al. (16)	IV, 30	520		385	33 (20/60)	95 (101/106)	6.6	0.71
Rasmuson et al. (82)	IV, peak	500		550	81 (13/16)	91 (10/11)	9.0	0.21
Ammari et al. (83)	IV, 30	550		550	47 (8/17)	85 (11/13)	2.6	0.65
Orme et al. (84)	IM, peak	500		550	83 (5/6)	60 (6/10)	2.1	0.28
Mukherjee et al. (85)	IM, 30	580		580	71 (5/7)	91 (10/11)	6.3	0.41
Weintrob et al. (19)	IV, peak	520		520	90 (9/10)	100 (20/20)	>100	0.10
Mayenknecht et al. (18)	IV, 30	550	200	620	65 (15/23)	95 (20/21)	13.0	0.37
Bangar and Clayton (86)	IV, 30	500		600	85 (17/20)	96 (47/49)	21.2	0.16
Talwar et al. (87)	IV, peak	550		550	54 (7/13)	100 (11/11)	>100	0.46
Abdu et al. (31)	IV, 30	500		500	100 (12/12)	90 (27/30)	10.0	0.00
Suliman et al. (88)	IV, 30	–	200	500	67 (10/15)	100 (36/36)	<100	0.33

* IM = intramuscular; ITT = insulin tolerance test; IV = intravenous; MT = overnight metyrapone test.
† All studies are prospective except two retrospective reviews (16, 86). In five studies, most of the patients with suspected adrenal insufficiency had excessive glucocorticoid exposure (75, 78, 81, 87, 88). Otherwise, patients with suspected adrenal insufficiency had known or suspected hypothalamic or pituitary disease. Two studies included consecutive patients (76, 83).
‡ Time after injection is when serum cortisol is drawn after the 250-μg cosyntropin injection. Peak denotes the time (usually 60 minutes) at which the serum cortisol level is maximal.
§ All MT values are for deoxycortisol. In one study (75), the MT cutoff level for deoxycortisol is 175 nmol/L, and in three studies (18, 80, 88), it is 200 nmol/L. In one study (80), if a postcosyntropin cortisol cutoff level of 500 nmol/L is applied, the sensitivity is only 6% (1/16); from the receiver-operating characteristic curve of Tordjman and colleagues (80), we have selected a cutoff level of 550 nmol/L, which yields a sensitivity of 50%.
‖ Diagnostic reference standard for secondary adrenal insufficiency.
¶ Sensitivity is the percentage calculated from raw data (shown in parentheses) indicating the number of persons with positive cosyntropin test results among true-positive persons (as defined by a metyrapone or insulin tolerance test). Specificity is the percentage calculated from raw data (shown in parentheses), indicating the number of persons with negative cosyntropin test results among true-negative persons.
** Definitions of positive and negative likelihood ratios are shown in equation A2 in the Appendix (available at www.annals.org).

Figure 1. **Summary receiver-operating characteristic (*SROC*) curves for high-dose (250-μg) and low-dose (1-μg) cosyntropin tests in secondary adrenal insufficiency.**



The SROC curve for the high-dose cosyntropin test was derived from SROC analysis of 20 independent studies (Table 2), where each point (*white circles*) represents an individual study. The SROC curve for the low-dose cosyntropin test was derived from 9 independent studies (Table 4), where each point (*white squares*) represents an individual study.

Establishing the Cause of Primary Adrenal Insufficiency

It is important to search for the cause of primary adrenal insufficiency after the diagnosis is determined. Of particular interest are treatable disorders, such as tuberculosis and other granulomatous diseases, as well as HIV disease and its associated infections. In addition to careful investigation of family history, medical history, and clinical evaluation, it may be useful to perform specific laboratory studies, such as determining very-long-chain fatty acid levels to confirm adrenoleukodystrophy or adrenomyeloneuropathy or determining antiadrenal antibodies to confirm an autoimmune cause. Imaging procedures, such as chest radiography, adrenal computed tomography, or magnetic resonance imaging, may help establish the cause of adrenal insufficiency; adrenal biopsy to establish cause is appropriate in selected cases.

Diagnosis of Secondary Adrenal Insufficiency

The prevalence of secondary adrenal insufficiency is much higher than that of primary adrenal insufficiency, primarily because of the common use of glucocorticoid hormones. In patients who have taken moderate to high doses of exogenous glucocorticoid for long periods, the prevalence of secondary adrenal insufficiency can be as high as 50%. Secondary adrenal insufficiency occurs in about 30% of patients who have a pituitary macroadenoma or who have had a transsphenoidal hypophysectomy or pituitary irradiation; secondary adrenal insufficiency always occurs after the surgical cure of Cushing syndrome but is generally not permanent.

Nonprovocative tests, such as measuring morning serum cortisol levels or an overnight urine-free cortisol increment (64), seem to have limited sensitivity for secondary adrenal insufficiency. Provocative tests, which use a physiologic stimulus to cortisol secretion, include both component and integrated tests. Component tests include the rapid high-dose or low-dose infusion of cosyntropin, which acts directly on the adrenal cortex to stimulate cortisol secretion, and intravenous infusion of corticotropin-releasing hormone, which acts directly on the pituitary to release ACTH (5, 65–69). Integrated tests require contributions of all three components of the hypothalamic–pituitary–adrenal axis to activate cortisol secretion. Integrated tests use a central stimulus, hypoglycemia, in the insulin tolerance test (5,70–72) and a decrease in serum cortisol in the metyrapone test (5, 29, 70) to activate release of hypothalamic corticotropin-releasing hormone, vasopressin, and other ACTH secretagogues. Integrated tests require more time and experience to perform and are generally considered to be the "gold standard" against which simpler component tests are compared.

High-Dose (250-μg) Cosyntropin Test in Secondary Adrenal Insufficiency

The 250-μg cosyntropin stimulation test is useful in the diagnosis of secondary adrenal insufficiency because the adrenal cortex atrophies when ACTH is deficient. The duration and degree of ACTH deficiency determine the degree of atrophy.

Table 2 summarizes 20 studies in which all patients with suspected secondary adrenal insufficiency underwent both a 250-μg cosyntropin stimulation test and an insulin tolerance test or metyrapone test (16, 18, 19, 31, 73–88). In general, these studies are better designed than those for primary adrenal insufficiency because case-patients and controls are recruited from the same setting and have a continuous range of abnormality. Therefore, these studies of secondary adrenal insufficiency do not tend to overestimate test performance to the degree seen in the studies of primary adrenal insufficiency.

Figure 1 shows summary ROC analysis of the 250-μg cosyntropin stimulation test in secondary adrenal insufficiency. When sensitivity and specificity are equal, the summary ROC curve yields an overall sensitivity and specificity of 83.5% (CI, 79.6% to 87.4%); the AUC is 0.90 (CI, 0.87 to 0.94). When specificity is set at 95%, the summary ROC curve for the 250-μg cosyntropin test yields a sensitivity of 57% (CI, 44% to 71%), with a corresponding positive likelihood ratio of 11.5 (CI, 8.7 to 14.2) and a negative likelihood ratio of 0.45 (CI, 0.30 to 0.60).

Thus, at clinically useful cutoff levels (postcosyntropin cortisol level, 500 to 600 nmol/L), where specificity is approximately 95%, a positive cosyntropin test result substantially increases the likelihood that the patient has secondary adrenal insufficiency. This is influenced by the

Table 3. **Bayes Theorem in Testing for Secondary Adrenal Insufficiency***

Pretest Probability of Secondary Adrenal Insufficiency	Post-Test Probability of Secondary Adrenal Insufficiency after a Normal (Negative) Cosyntropin Stimulation Test Result (95% CI)	Post-Test Probability of Secondary Adrenal Insufficiency after an Abnormal (Positive) Cosyntropin Stimulation Test Result (95% CI)
	%	
1	0.3 (0.2–0.4)	7.0 (6.0–7.9)
5	1.5 (0.9–2.1)	28.0 (25.1–31.0)
10	3.1 (1.9–4.4)	45.1 (41.5–48.7)
25	8.8 (5.5–12.1)	71.1 (68.1–74.1)
50	22.5 (15.2–29.7)	88.1 (86.6–89.6)
75	46.5 (36.1–56.8)	95.7 (95.1–96.3)
90	72.3 (63.9–80.6)	98.5 (98.3–98.7)

* See the Appendix (available at www.annals.org), which describes how to use Bayes theorem to calculate the post-test probability of secondary adrenal insufficiency based on a likelihood ratio.

pretest probability of disease, as indicated by using Bayesian analysis (**Table 3**). Conversely, a negative (normal) test result only modestly decreases the likelihood that the patient has secondary adrenal insufficiency (**Table 3**), particularly if the pretest probability is high. Thus, the 250-μg cosyntropin test is helpful for ruling in but not ruling out secondary adrenal insufficiency. The data that demonstrate limited sensitivity for the high-dose cosyntropin test in secondary adrenal insufficiency suggest that when the pretest probability of adrenal insufficiency is high and the cosyntropin test result is normal, additional evaluation using tests with better sensitivity should be performed.

Comparison of High-Dose Cosyntropin Test Performance in Primary and Secondary Adrenal Insufficiency

Comparison of the AUC for summary ROC curves for the high-dose cosyntropin test in primary (**Table 1**) and secondary (**Table 2**) adrenal insufficiency showed significantly ($P < 0.001$) better performance in the clinical setting of primary adrenal insufficiency (AUC, 0.99 [CI, 0.985 to 1.000]) than in secondary adrenal insufficiency (AUC, 0.90 [CI, 0.76 to 0.97]).

Low-Dose Cosyntropin Tests in Secondary Adrenal Insufficiency

Dose-response studies in normal persons indicate that cosyntropin doses as low as 0.5 to 1 μg will give a near-maximal cortisol response within 15 to 30 minutes (89–94). The performance characteristics of the low-dose 1-μg cosyntropin stimulation test could be superior to the conventional-dose 250-μg test for diagnosing secondary adrenal insufficiency because the plasma ACTH level is closer to the physiologic range (18, 90, 95–97). However, recent reviews comparing these two tests offer conflicting conclusions (98–103). Several investigators have performed the 1-μg cosyntropin stimulation test, which requires intravenous administration and timed blood sampling to obtain the peak cortisol response, in patients with suspected secondary adrenal insufficiency (18, 19, 31, 80, 82, 87, 88, 104, 105) (**Table 4**).

Receiver-operating characteristic curves, which provide an analysis of test performance over a range of cortisol cutoff levels, have been developed to directly compare the high-dose and low-dose tests. In an analysis by Abdu and colleagues (31, 106), the performance characteristics of the

Table 4. **Usefulness of 1-μg Cosyntropin Stimulation Test in Patients Who Are Taking Glucocorticoids or Have Pituitary Disease***

Study (Reference)	Cosyntropin Route and Time after Injection†	Serum Cortisol or Deoxycortisol Cutoff Level after Stimulation‡			Sensitivity‖	Specificity‖	Positive Likelihood Ratio¶	Negative Likelihood Ratio¶
		ITT§	MT§	Cosyntropin Test				
	min	*nmol/L*			% (*n*/*n*)			
Tordjman et al. (80)	IV, peak	500	200	500	95 (18/19)	84 (36/43)	5.9	0.06
Rasmuson et al. (82)	IV, peak	500		550	100 (16/16)	100 (11/11)	>100	0
Weintrob et al. (19)	IV, peak	520		520	90 (9/10)	90 (18/20)	9.0	0.11
Mayenknecht et al. (18)	IV, 30	550	200	535	65 (15/23)	95 (20/21)	13.0	0.37
Ambrosi et al. (104)	IV, peak	500		500	71 (40/43)	93 (40/43)	10.1	0.31
Talwar et al. (87)	IV, peak	550		550	100 (13/13)	91 (10/11)	11.0	0
Abdu et al. (31)	IV, peak	500		500	100 (12/12)	93 (28/30)	14.3	0
Suliman et al. (88)	IV, 30	–	200	500	73 (11/15)	81 (29/36)	3.8	0.33
Soule et al. (105)	IV, 30	–	200	500	75 (9/12)	88 (47/53)	6.3	0.28

* Cosyntropin was administered as an intravenous bolus of 1 μg in 7 studies (31, 80, 82, 87, 88, 104, 105), as an intravenous bolus of 1 μg/1.73 m^2 in 1 study (19), and as an intravenous bolus of 0.5 μg/m^2 in 1 study (18). Of the 402 patients in this table in whom secondary adrenal insufficiency was suspected, 364 had hypothalamic or pituitary disease, and 38 had received suppressive doses of glucocorticoids (3 in 1 study [82], 8 in 1 study [87], and 27 in 1 study [88]). In 1 study (105), a postcosyntropin cortisol cutoff level of 415 nmol/L yielded a sensitivity of 50%; on the basis of receiver-operating characteristic data presented, we selected an alternative cutoff level of 500 nmol/L that yielded a sensitivity of 75%. IM = intramuscular; ITT = insulin tolerance test; IV = intravenous; MT = overnight metyrapone test.
† Time after injection is when the serum cortisol is drawn after the 250-μg cosyntropin injection. Peak denotes the time (usually 30 minutes) at which the serum cortisol level is maximal.
‡ All MT values are for deoxycortisol.
§ Diagnostic reference standard for secondary adrenal insufficiency.
‖ Sensitivity is the percentage calculated from raw data (shown in parentheses) indicating the number of persons with positive cosyntropin test results among true-positive persons (as defined by a metyrapone or insulin tolerance test). Specificity is the percentage calculated from raw data (shown in parentheses), indicating the number of persons with negative cosyntropin test results among true-negative persons.
¶ Definitions of positive and negative likelihood ratios are shown in equation A2 in the Appendix (available at www.annals.org).

1-μg test were slightly superior to those of the 250-μg test. We also compared ROC curves for high-dose and low-dose tests in patients with secondary adrenal insufficiency; we used raw data provided by Mayenknecht and colleagues (18) and the method of Metz and colleagues (4). As shown in the **Appendix Figure** (available at www.annals.org), curves were similar for both high-dose and low-dose tests. Areas under the curve for high-dose and low-dose tests did not differ at the 30-minute time point (0.90 [CI, 0.76 to 0.97] vs. 0.86 [CI, 0.71 to 0.95]; $P = 0.18$); curves were also similar for the 60-minute data for the high-dose test (AUC, 0.88 [CI, 0.74 to 0.95]; $P = 0.5$). Differences in the study samples or analysis methods using the gold standard tests may account for the different results in these two ROC analyses.

Summary ROC analysis for patients who are taking glucocorticoids or have pituitary disease (**Table 4**) yields an overall sensitivity and specificity (when they are equal) of 84.6% (CI, 80.2% to 89.1%) and an AUC of 0.91 (CI, 0.87 to 0.95). At a specificity of 95%, sensitivity was 61.4% (CI, 45% to 78%), with a corresponding positive likelihood ratio of 12.3 (CI, 9.0 to 15.5) and a negative likelihood ratio of 0.41 (CI, 0.24 to 0.58). **Figure 1** shows a comparison of summary ROC curves for high-dose and low-dose tests using all available data in **Tables 2** and **4**. The summary ROC curves for high-dose and low-dose tests do not differ when sensitivity and specificity are equal ($P > 0.5$) or when the AUC method is used ($P > 0.5$).

Problems of Diagnosis in Secondary Adrenal Insufficiency

Limited Sensitivity and Lack of Confirmation Tests. At a specificity of 95%, the overall sensitivity of the cosyntropin stimulation test in primary adrenal insufficiency is high (97.5%), whereas the sensitivity is much lower in secondary adrenal insufficiency (57%). This difference in sensitivity occurs because patients with clinically apparent primary adrenal insufficiency generally tend to have a much lower adrenal cortex response to ACTH stimulation than do patients with secondary adrenal insufficiency; thus, overlap with the normal range is minimal. Occasionally, patients with primary adrenal insufficiency have a normal cortisol response to cosyntropin and patients with secondary adrenal insufficiency have a low flat-line response.

The diagnosis of primary adrenal insufficiency can be confirmed by an elevated plasma ACTH concentration. By contrast, plasma ACTH concentration has little value in secondary adrenal insufficiency, and no other confirmation tests are readily available. Therefore, the diagnosis of secondary adrenal insufficiency is often made and treatment is initiated on the basis of an abnormal cosyntropin stimulation test result alone.

Recent-Onset Secondary Adrenal Insufficiency. Because the cosyntropin test acts directly on the adrenal cortex, the utility of this test depends on the magnitude and duration of antecedent ACTH deficiency. Thus, the sensitivity of both high-dose and low-dose tests will be extremely limited in cases of acute or recent-onset secondary adrenal insufficiency.

Cortisol Cutoff Limits for Secondary Adrenal Insufficiency. A range of postcosyntropin cortisol cutoff levels (500 to 600 nmol/L) has been clinically applied to the diagnosis of secondary adrenal insufficiency. Use of a higher cutoff level (600 nmol/L) will trade off enhanced sensitivity for decreased specificity, leading to a higher rate of false-positive test results. Because secondary adrenal insufficiency is often diagnosed without additional confirmatory tests, false-positive test results may lead to lifelong physiologic corticosteroid replacement in euadrenal patients. An alternative approach is to use a lower cutoff level (500 nmol/L) to maximize specificity, with the understanding that persons with sufficiently high pretest probability who have stimulated cortisol levels greater than 500 nmol/L will undergo additional evaluation with more sensitive integrated tests. The precise cutoff levels for integrated tests of hypothalamic–pituitary–adrenal function are also uncertain.

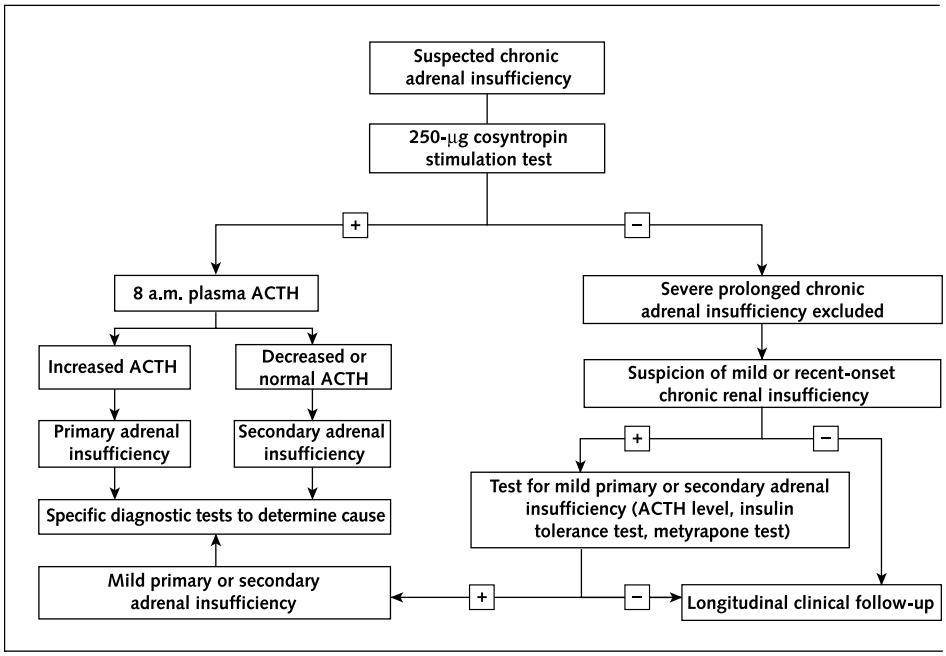
Utility of the Low-Dose (1-μg) Cosyntropin Stimulation Test

Available data do not clearly establish the superiority of the 1-μg over the 250-μg cosyntropin test in secondary adrenal insufficiency. The 1-μg test requires accurate and reproducible dilution of cosyntropin; intravenous administration; and frequent, carefully timed venous sampling for cortisol levels. The 250-μg test, however, can be performed in the outpatient setting by intramuscular administration and a single cortisol determination, which does not require precise timing. Thus, the high-dose test is much easier to perform, and accuracy is similar to that of the low-dose test. Additional investigation is needed to determine whether the low-dose cosyntropin stimulation test has any role in diagnosing secondary adrenal insufficiency. In any case, the sensitivity and specificity of the low-dose test are not sufficient to replace integrated tests of hypothalamic–pituitary–adrenal function.

Discussion

The most common problem in diagnosing primary adrenal insufficiency is lack of clinical suspicion because the condition is rare and the signs and symptoms are nonspecific. The 250-μg cosyntropin test demonstrates excellent performance characteristics in diagnosing primary adrenal insufficiency; it is supported by a postcosyntropin cortisol level less than 415 nmol/L and is confirmed by an elevated plasma ACTH concentration. Conversely, a negative (normal) cosyntropin stimulation test result significantly decreases the post-test probability of primary adrenal insufficiency. However, patients with subclinical or mild primary adrenal insufficiency may have a normal cortisol response to cosyntropin, requiring close follow-up or adjunct tests of hypothalamic–pituitary–adrenal function. It

Figure 2. **Diagnostic pathway for suspected chronic adrenal insufficiency.**



The evaluation begins with a high-dose 250-μg cosyntropin stimulation test (intramuscular or intravenous); plasma cortisol levels are then measured 30 to 60 minutes after the test. The test result is considered positive (abnormal) when the stimulated cortisol level is less than 500 nmol/L. Because a negative (normal) test result does not exclude mild or recent-onset adrenal insufficiency, additional testing is necessary to confirm a clinical suspicion of these disorders. ACTH = adrenocorticotropic hormone.

is clear that cutoff levels for the cosyntropin test that are useful in the outpatient setting cannot be projected to the critical care setting. For example, recent studies in septic shock suggest that the increment between basal and postcosyntropin cortisol, rather than the absolute level of postcosyntropin cortisol, may be a more useful indicator of relative adrenal insufficiency in the acute setting (107–109). Additional studies are needed to better define who will benefit from corticosteroid replacement in both septic and nonseptic patients who are acutely ill.

The 250-μg cosyntropin stimulation test is useful for diagnosing secondary adrenal insufficiency; results are often positive in patients with long-standing and severe disease. Cosyntropin stimulation tests using either 250 μg or 1 μg tend to give false-negative (normal) results in patients with mild or recent-onset secondary adrenal insufficiency; thus, a negative cosyntropin test result does not rule out the possibility of secondary adrenal insufficiency. Analysis of ROC and summary ROC curves indicates that performance characteristics of both the high-dose (250 μg) and low-dose (1 μg) cosyntropin stimulation tests are similar for diagnosing secondary adrenal insufficiency.

In addition to appropriate selection of patients for cosyntropin testing, the clinician plays an important role in assessing the pretest probability of disease; classifying patients with suspected primary adrenal insufficiency, secondary adrenal insufficiency, or adrenal insufficiency of unknown type; and determining the cause of adrenal insufficiency. **Figure 2** is an algorithm for the laboratory diagnosis of patients with suspected primary or secondary adrenal insufficiency. The evaluation begins with the 250-μg cosyntropin stimulation test.

Patients with suspected adrenal insufficiency are distinguished from those without the disorder by a postcosyntropin plasma cortisol cutoff level generally in the range of 415 nmol/L for primary adrenal insufficiency and 500 to 600 nmol/L for secondary adrenal insufficiency. A more precise cutoff limit could be established for each type of cortisol assay at each time point, but this is rarely done in practice. A positive cosyntropin test result increases the probability of adrenal insufficiency (**Table 3**). In the absence of concurrent stress or illness, a plasma ACTH level at 8:00 a.m. will help distinguish between primary and secondary adrenal insufficiency. Clinical evaluation and additional laboratory and radiology studies will then determine the cause of the adrenal insufficiency.

Conversely, when the cosyntropin test result is negative, the probability of severe, long-standing adrenal insufficiency is substantially reduced, but the probability of mild, recent, or subclinical adrenal insufficiency is only modestly decreased (**Table 3**). A negative test result necessitates clinical reevaluation of the patient. If mild or recent secondary adrenal insufficiency is clinically suspected, additional testing, usually with a metyrapone or insulin tolerance test, is mandatory.

From New Mexico Veterans Administration Health Care System and University of New Mexico, Albuquerque, New Mexico; Santa Clara Val-

ley Medical Center, San Jose, California; and Stanford University, Palo Alto, California.

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Requests for Single Reprints: Richard Dorin, MD, Division of Endocrinology and Metabolism, New Mexico Veterans Administration Health Care System, Medical Service 111, 1501 San Pedro Boulevard SE, Albuquerque, NM 87108; e-mail, rdorin@salud.unm.edu.

Current author addresses are available at www.annals.org.

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Appendix

Summary Receiver-Operating Characteristic Curve, Area under the Curve, and Value of Sensitivity

Moses and colleagues (1, 2) suggest a meta-analysis of the performance of a diagnostic test with data from several studies and then summarizing the results in terms of a summary receiver-operating characteristic (ROC) curve. The estimated or fitted summary ROC curve is obtained by a simple (possibly weighted) regression of D on S, where

$$D = ln\left(\frac{Se}{1 - Se}\right) - ln\left(\frac{Sp}{1 - Sp}\right) \text{ and}$$

$$S = ln\left(\frac{Se}{1 - Se}\right) + ln\left(\frac{Sp}{1 - Sp}\right),$$

and Se is sensitivity and Sp is specificity. The regression equation $D = A + B \times S$ is transformed back to a summary ROC curve of sensitivity versus 1 − specificity (1 − Sp). If the slope B is not significantly different from 0, then $A \pm$ SE (A) may be computed as the mean (±SD) from the Ds of each study. We used weighted averages (the equivalent to weighted regression), in which each weight is the harmonic mean of the four cell counts for each study. Cell counts are increased by 0.5, which avoids weights that are too large or infinite. The mathematical model for the summary ROC becomes

$$Se = \frac{1}{1 + e^{-A}\dfrac{(1 - Sp)}{Sp}}. \quad \text{(A1)}$$

Additional summary ROC parameters of interest are the likelihood ratios

$$LR+ = \frac{Se}{1 - Sp} \quad \text{and} \quad \text{(A2)}$$

$$LR- = \frac{1 - Se}{Sp}$$

the area under the curve (AUC) (3),

$$AUC = \begin{cases} 1/2 & \text{for } A = 0, \text{ or} \\ \dfrac{1 - e^{-A} - Ae^{-A}}{(1 - e^{-A})^2} & \text{for } A \neq 0, \end{cases} \quad \text{(A3)}$$

and the value of sensitivity (Q^*) is defined as the point along the summary ROC curve where sensitivity equals specificity,

$$Q^* = \frac{1}{1 + e^{-A/2}}. \quad \text{(A4)}$$

The 95% CIs for our list of parameters (A1) to (A4) are based on the delta method and take the form of parameter ± 1.96 × SE (parameter). These SEs are

$$SE(Se) = Se(1 - Se)SE(A) \quad \text{(A5)}$$

where Se is the predicted sensitivity given by (A1) for a given specificity Sp, and

$$SE(LR+) = \frac{1}{1 - Sp} SE(Se) \quad \text{and} \quad \text{(A6)}$$

$$SE(LR-) = \frac{1}{Sp} SE(Se)$$

where Sp is a given specificity.

The SEs for AUC and Q^* are given in reference 3, but are expressed here in terms of A:

$$SE(AUC) = \begin{cases} \dfrac{1}{6} SE(A), & \text{for } A = 0, \\ \dfrac{e^{-A}(A(1 + e^{-A}) - 2(1 - e^{-A}))}{(1 - e^{-A})^3} SE(A) & \text{for } A \neq 0, \end{cases} \quad \text{and} \quad \text{(A7)}$$

$$SE(Q^*) = \frac{0.5}{(e^{A/4} + e^{-A/4})^2} SE(A). \quad \text{(A8)}$$

Comparison between summary ROC curves using Q* or AUC may be done as z tests.

Bayes Theorem Applied to Secondary Adrenal Insufficiency

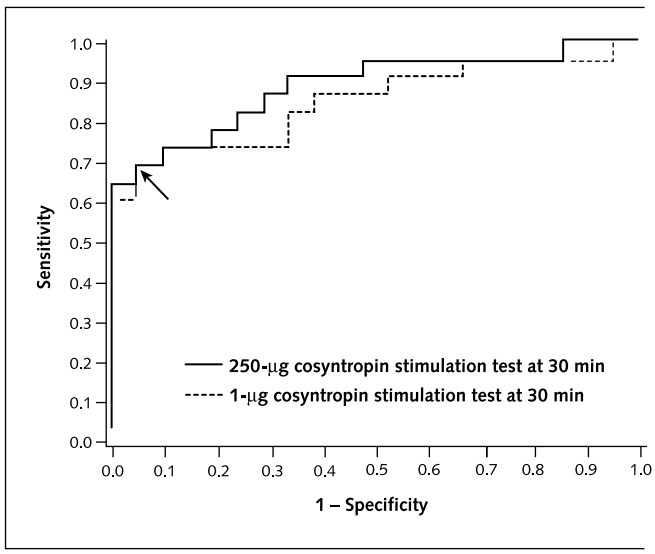
In **Table 3**, we calculate post-test probabilities of secondary adrenal insufficiency, given a normal or abnormal cosyntropin stimulation test result, for a representative sample of pretest probabilities using LR+ and LR− from the summary ROC curve for Table 2 when specificity is equal to 95%. This calculation is based on the knowledge of likelihood ratio computed from the summary ROC curve by using the Bayes theorem. The calculation of CI is based on the delta method: For a given prior probability of disease (P), the posterior probability of disease is

$$P(D) = \frac{LR \times P}{1 - P + LR \times P} \quad \text{and} \quad \text{(A9)}$$

$$SE(P(D)) = \frac{P(1 - P)}{(1 - P + LR \times P)^2} SE(LR), \quad \text{(A10)}$$

where $LR = LR+$ or $LR-$ depending on the outcome of the current test and P = prior probability of disease.

Appendix Figure. **Receiver-operating characteristic curves for high-dose (250-μg) and low-dose (1-μg) cosyntropin stimulation tests for plasma cortisol levels obtained at 30 minutes in secondary adrenal insufficiency.**



The curve for each test is generated from the raw data by determining the sensitivity and specificity for each test at many different plasma cortisol cutoff levels; the sensitivity increases as the plasma cortisol cutoff levels increase. The arrow denotes the point at which both tests yield identical sensitivities of 70% at a specificity of 95%; this breakpoint corresponds to plasma cortisol cutoff levels of 630 nmol/L for the high-dose test and 560 nmol/L for the low-dose test. For this assay, these plasma cortisol levels correspond to serum cortisol levels of 570 nmol/L for the high-dose cosyntropin test and 500 nmol/L for the low-dose cosyntropin test. These cutoff levels also produce identical positive and negative likelihood ratios (14.6 and 0.3, respectively). Data to calculate these curves were derived from a previously published study (18), and raw data were provided by Dr. Wolfgang Oelkers (University of Berlin).

Current Author Addresses: Dr. Dorin: Division of Endocrinology and Metabolism, New Mexico Veterans Administration Health Care System, Medical Service 111, 1501 San Pedro Boulevard SE, Albuquerque, NM 87108.

Dr. Qualls: Department of Mathematics and Statistics, General Clinical Research Center, University of New Mexico Hospital, 5-North, Camino de Salud, University of New Mexico, Albuquerque, NM 87131.

Dr. Crapo: Division of Endocrinology and Metabolism, Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, CA 95128.