The median time to onset of endocrine toxicities is 14.5 weeks with a range of 1.5-130 weeks.[9] Presenting symptoms related to immune therapy-induced endocrinopathies vary and may include headache and visual changes, especially visual field changes in pituitary swelling. Presenting symptoms of hypothyroidism can include cold intolerance, dry skin, constipation, weight gain, and/or fatigue. Palpitations, heat intolerance, insomnia, frequent bowel movements, or weight loss may be present with thyrotoxicosis and nausea, vomiting, abdominal pain, weight loss, lightheadedness or orthostasis or syncope, and profound fatigue may be symptoms of adrenal insufficiency. Diabetes or diabetic ketoacidosis (DKA) may present with polyuria or polydipsia, nausea or vomiting, abdominal pain, and/or visual blurring.

Refer to Table 4 for a complete set of recommendations, definition of grades, and additional considerations for endocrine toxicities.

Discussion. Endocrine AEs with immune checkpoint therapy present a unique clinical challenge for the nonendocrinologist who faces the need to identify endocrine dysfunction in a patient with often nonspecific symptoms or complex abnormal laboratory findings. In a systematic review and meta-analysis that included 7,551 patients in 38 randomized trials, the overall incidence of clinically significant endocrinopathies was approximately 10% of patients treated with checkpoint inhibitors.[124] Diverse therapies and ICPi combinations have varied rates of targeting individual organs; for example, hypophysitis is most commonly seen when ipilimumab is used,[125-128] and primary ovarian failure has not yet been reported.[124] However, there are sporadic autoimmune diseases (ADs) known for all endocrine organs and we anticipate the possibility of any endocrine organ may be a target of an irAE as the use of ICPis becomes more widespread.

Clinical measures of both the primary hormone and the corresponding pituitary hormone are needed to localize disease for the classically regulated axes and morning serum hormone values are required. For example, low morning cortisol suggests adrenal insufficiency but does not indicate whether the problem is pituitary or adrenal. Hypophysitis, pituitary mass, or iatrogenic causes are suggested if a simultaneously measured adrenocorticotropic hormone (ACTH) is low; in primary adrenal insufficiency (eg, Addison's or adrenal hemorrhage), the morning ACTH will be elevated. The same applies in evaluating the thyroid axis, where clinicians typically screen with the pituitary hormone rather than the primary hormone. Low thyroid-stimulating hormone (TSH) may be consistent with either hyperthyroidism or central hypothyroidism; so, a free thyroxine (FT4) level is needed to confirm a diagnosis. Drawing both TSH and FT4 is especially important when patients are symptomatic and hypothyroidism is suspected because, in hypophysitis, TSH can remain within the reference range in the laboratory assays but lack function as a result of altered glycosylation because of the pituitary disease, so that only an FT4 will pick up on the presence of hypothyroidism.

Distinguishing primary from secondary hormonal problems is necessary to ensure the appropriate treatment. For example, a critical step for preventing harm with hormone replacement is using hydrocortisone first when multiple pituitary hormones are missing. If thyroid hormone is replaced first when cortisol is low, the increase in cortisol metabolism can trigger an adrenal crisis. Thus, recognizing that a patient has central hypothyroidism can prompt evaluation for secondary adrenal insufficiency, the second most common hormonal loss with hypophysitis.[124] Similarly, fludrocortisone is needed in addition to hydrocortisone in most cases of primary adrenal insufficiency, which involves the loss of mineralocorticoid as well as glucocorticoid production by the adrenal gland, leading to more-profound blood pressure and electrolyte abnormalities,[129] but is generally not necessary in those with secondary or central adrenal insufficiency. Monitoring is also affected by localization, as pituitary hormones are not reliable indicators of status with central disease. TSH, in particular, is not helpful in monitoring therapy with levothyroxine in patients with central hypothyroidism, and FT4 should be used instead.[130]

Diagnosis of endocrine dysfunction is complicated by the physiologic changes in hormone levels that accompany acute illness and by the administration of medications that affect pituitary function, including many therapies that patients with cancer are on, such as narcotics and megestrol acetate. Most relevant for the patients administered ICPis is the effect of corticosteroids, given for many irAEs in diverse organ targets. High-dose corticosteroids suppress ACTH and may cause persistent central adrenal insufficiency when stopped as the system can take weeks to months to recover, depending on the length of exposure. Serum cortisol levels should not be routinely measured while patients are on corticosteroid therapy because of variable assay effects from synthetic corticosteroids, low endogenous levels from the exposure, and the fact that the patient is on supraphysiologic doses and therefore treated for any underlying adrenal insufficiency that might be present eventually. If a diagnosis is needed, for example, after acute treatment of presumed adrenal crisis is initiated, ACTH stimulation testing may be performed. Endogenous levels can also be directly measured 24 hours after the last dose of physiologic hydrocortisone replacement to assess for functional recovery. High-dose corticosteroids and the physiologic response to acute nonthyroidal illness can lead to a low T3 syndrome, with either central suppression of TSH or a mild elevation, which has not been shown to benefit from therapy.[65,66] Especially in difficult cases, endocrinology consult is recommended.