I would dispute the notion that the derivation of nonexercise estimates of CRF is challenging. Health care professionals can choose to download one of several readily available apps or instruct the patient/client to do the same. In this way, the end user can easily self-monitor improvements in CRF that follow increases in physical activity and/or reductions in body weight. More importantly perhaps, health care professionals’ estimates of CRF would provide unique opportunities to counsel patients on the importance of improving CRF by increasing physical activity levels—a win-win scenario.

Langland concludes with the suggestion that health care professionals should focus on promoting physical activity until CRF can be more easily measured in clinical settings. While I fully agree that physical activity levels should be assessed in all patients, this should not be accomplished at the expense of estimating CRF. Indeed, trying to separate physical activity from CRF is like trying to separate heat from the sun—we cannot, and should not, do it.

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Immune Checkpoint Inhibitor—Induced Type 1 Diabetes: An Underestimated Risk

To the Editor: Drs Marin-Acevedo and colleagues nicely summarize the toxicities associated with immune checkpoint inhibitor therapy. We want to further emphasize immune checkpoint inhibitor—induced type 1 diabetes (ICI-T1D), as it frequently presents with life-threatening diabetic ketoacidosis. The authors report the frequency of ICI-T1D as 0.2% citing a meta-analysis that assessed premarketing registration trials. We believe this is an underestimate for several reasons. First, premarketing clinical trials excluded patients with a pre-existing autoimmune disorder, and in recent years immune checkpoint inhibitor use and indications have dramatically increased. Second, at large medical centers such as Mayo Clinic and Yale, the frequency of ICI-T1D is reported between 1% and 1.8%, which represents thousands of patients who have received immune checkpoint inhibitor therapies. Furthermore, in the past 2 years, there has been a significant increase in reports of diabetes following immune checkpoint inhibitor therapy in VigiBase, the World Health Organization’s database for individual case safety reports. This evidence indicates that the frequency of ICI-T1D is far more common than reported here.

ICI-T1D has been reported mainly with monoclonal antibodies targeting anti—programmed cell death 1 and anti-programmed cell death 1 ligand but not with anti-cytotoxic T lymphocyte associated antigen 4. This adverse event frequently presents with severe diabetic ketoacidosis and almost half of the cases have T1D associated antibodies at presentation. Patients presenting with T1D-associated antibodies have a more rapid onset and higher incidence of diabetic ketoacidosis than those without antibodies. Human leukocyte antigen (HLA) risk genes for childhood-onset T1D, such as HLA-DR4 and DR3, are predominant in individuals who develop ICI-T1D. Rapid onset, lack of a honeymoon phase, presentation with severe diabetic ketoacidosis, and low or absent C-peptide levels at presentation, which is a measure of residual beta cell function, are more common in ICI-T1D compared with childhood-onset disease. However, both require permanent lifelong treatment with insulin therapy.

Health care providers need to be aware of this adverse event to prevent morbidity and mortality in vulnerable cancer patients. Guidelines to assess risk and monitor patients at high risk during treatment for ICI-T1D are needed to reduce severe diabetic ketoacidosis.

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2. Akturk HK, Alkanani A, Zhao Z, Yu L, Michels AW. PD-1 Inhibitor immune-related adverse events in...
In Reply — Immune Checkpoint Inhibitor—Induced Type 1 Diabetes: An Underestimated Risk

In reply: We thank Drs Akturk and Michels1 for their interest in our article and for further expanding on the importance of immune checkpoint inhibitor (ICI)—induced diabetes. The incidence of ICI-induced diabetes has increased from a few case reports in 2015 to a recently reported incidence of 1.8% based on our experience at Mayo Clinic.2,3 The increased incidence may be associated, at least in part, with the expanding use of these medications.4 In addition, according to this retrospective analysis from our institution, this adverse event appears to occur more often with the anti—programmed cell death 1 ligand pembrolizumab, followed by the anti—programmed cell death 1 agent nivolumab.3 No cases were seen with ipilimumab, an anti—cytotoxic T lymphocyte associated antigen 4 agent.5

As pointed out by the authors of the Letter to the Editor on their recent meta-analysis, diabetes induced by ICIs tends to present with severe diabetic ketoacidosis, particularly in patients with type 1 diabetes—associated antibodies.6 The onset of diabetes can be rapid.5 In addition, it can occur early after initiation of therapy or up to a year after initiation of these medications, and will often require permanent insulin replacement therapy.3,6 Considering the expected increase in the usage of ICIs, we agree that increasing the awareness of this immune-related adverse event is of utmost importance.

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Legacy of Nutritionist Ancel Keys

To the Editor: A diet high in saturated fat increases risk for heart disease and stroke. We know this, but few can recall who first uncovered the connection. It was Ancel Keys — a name to note and remember. Some 60 years ago, he was a luminary in medical science with a reputation that reached ordinary Americans. In 1961, his image graced the cover of TIME magazine. He was the first to promote the health benefits of the Mediterranean diet. An esteemed professor at the University of Minnesota, Ancel Keys was brilliant, bold, and worldly.

A life full of adventures and discoveries, his story is extraordinary.1,3 Born to teenagers in 1904, Ancel was raised in Berkeley, California, where the family struggled. Growing up, he worked unusual jobs for a city boy: as a gofer in a lumber camp, powder monkey in a Colorado gold mine, and guano shoveler in an Arizona bat cave. In 1922, he started at the University of California at Berkeley. The summer after his first year he signed on as an oiler on a steamship to Asia, learning Chinese on the side. After 3 months at sea, he returned to campus and completed his undergraduate degree in 2 years. After a brief stint at a Woolworth store — where “the work soon became intolerably dull” — he returned to UC-Berkeley, found topics that interested him, and, with his substantial intellect, breezed through, earning a PhD in biology in 1930.1

A 2-year fellowship took him to Copenhagen to work under August Krogh, a Nobel laureate in physiology. Next, he went to the University of Cambridge, and, under mentor Joseph Barcroft, became intrigued with studying how the human body adapts to extreme conditions; in 1936 he was awarded a second PhD (in physiology). Then L.J. Henderson, director of the acclaimed Harvard Fatigue Laboratory, cabled him with an offer, so off he went to join D.B. Dill, the lab’s research leader, and his elite cadre of physiologists and biochemists. This led to his pioneering work on the oxygen-carrying capacity of blood. At the age of 29 years, Ancel Keys,