migraine and headache were collected separately. Of the 800 patients treated with enzalutamide, 3 (0.4%) were reported to have had a migraine. Headaches were reported in 93 patients treated with enzalutamide (11.6%) and in 22 of the 399 patients treated with placebo (5.5%). In the enzalutamide group, the majority of reports were for grade 1 headache that did not require treatment. No patient was treated for headache with glucocorticoids. One patient reporting seizure in AFFIRM reported a headache 5 months before the report of seizure.

Berruti et al. state that headaches were not reported as a relevant symptom in patients receiving abiraterone acetate plus prednisone in a recent phase 3 study. However, the clinical review of abiraterone acetate by the Food and Drug Administration (new drug application number, 202379) reported a similar frequency of headache in the two study groups (11.9% of patients in the abiraterone-plus-prednisone group and 10.7% of those in the placebo-plus-prednisone group).

Overall, these data do not support the suggestion by Berruti et al. that the headaches observed in the enzalutamide study reflect migraines, nor that patients who had a headache during treatment with enzalutamide are at increased risk for seizure.

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Understanding Low Sugar from NICE-SUGAR

TO THE EDITOR: In his editorial about the Normo-glycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, Hirsch (Sept. 20 issue) declares, “For surgical patients, especially those who have undergone cardiac procedures, hospitals that can safely achieve lower targets should do so.” No justification for this statement is provided. Concerns exist regarding the generalizability of studies of glycemic control in other populations of patients treated in intensive care units (ICUs) that have shown either harm or no benefit and regarding both the generalizability and applicability of studies that have shown benefit. Accordingly, the effect of maintaining the blood sugar levels of surgical patients admitted to the ICU below those of the control group in the NICE-SUGAR study remains uncertain. We believe the targeting of blood glucose levels below that of the control group in this study should occur only in the context of well-designed clinical trials. To do otherwise exposes surgical patients admitted to the ICU to a therapy of uncertain benefit and that is associated with harm in other ICU patient populations.

It also promotes the inefficient use of valuable health care resources at a time when the Journal is fostering debate around this challenging issue.

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THE EDITORIALIST REPLIES: French and McGain bring up an important point. The most recent
recommendation referenced in my editorial states, “Although strong evidence is lacking, somewhat lower glucose targets may be appropriate in selected patients.”2 Although we do not have a prospective and randomized trial in patients undergoing cardiac surgery, there are data that suggest that lower glucose levels are beneficial.2 Unfortunately, lower glucose levels are difficult to accomplish without hypoglycemia, given the current available technology at the majority of hospitals. Nevertheless, some institutions report that it is possible to achieve lower targets without excessive hypoglycemia.3-5 At the University of Washington Medical Center, we target the glucose level in patients undergoing cardiothoracic surgery at 100 to 140 mg per deciliter (5.6 to 7.8 mmol per liter), with a 1% rate of hypoglycemia (blood glucose, <70 mg per deciliter [3.9 mmol per liter]). Although French and McGain are correct that the NICE-SUGAR population showed no benefit from this level of glucose control, it must be appreciated that that population did not include patients undergoing cardiac surgery. Therefore, we feel comfortable in targeting these lower glucose values if it can be done safely. One hopes that there will be prospective data for these and other populations with the introduction of continuous glucose monitoring.

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PTEN Haploinsufficiency, Obesity, and Insulin Sensitivity

TO THE EDITOR: Pal and colleagues (Sept. 13 issue)1 state that heightened insulin sensitivity can paradoxically coexist with obesity in patients with PTEN haploinsufficiency, which causes the Cowden syndrome. However, we believe that some conclusions described by the authors are not supported by their findings. Although carriers of PTEN mutations are similar to controls (matched according to body-mass index [BMI]) with respect to lean body mass, bone mineral content, total fat, and fat distribution, their higher BMI relative to age- and sex-matched population controls cannot yet be attributed to increased adiposity because this latter comparison remains unproven by dual-energy x-ray absorptiometry (DXA). The authors’ interpretation of greater partitioning of visceral fat into subcutaneous fat was not supported by a significant difference detected in skinfold anthropometry. Because 80 to 90% of infused glucose during hyperinsulinemic-euglycemic clamping was metabolized by the skeletal muscles in patients with the Cowden syndrome, an increase in lean mass rather than adiposity may drive the elevated BMI with concomitant elevated insulin sensitivity.2 Because mice that overexpress Pten have increased energy expenditure, an assay of mitochondrial substrate oxidation by skeletal muscles and a demonstration of elevated numbers of brown or beige (brite) adipocytes might shed light on the cellular and biochemical mechanisms underlying obesity associated with enhanced insulin sensitivity in PTEN-mutation carriers.3

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