NCDB to qualify the statistical power of an analysis grounded actually in a sample of 1290 patients. They do not explain the reasons for selecting a control group of a size 4 times that of the target group. Could this decision be owing to the need of having sample size high enough to perform a multivariate analysis with minimal statistical guarantees? Finally, when I used the real figures of survival, provided by the authors, instead of an estimate obtained by an equation lacking the relevant variables, I found no differences in the survival rate between the 2 groups of cancer patients, CM and no CM.

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1. Johnson SB, Park HS, Gross CP, Yu JB. Complementary medicine, refusal of conventional cancer therapy, and survival among patients with curable cancers. *JAMA Oncol*. 2018;4(10):1375-1381. doi:10.1001/jamaoncol.2018.2487

In Reply We appreciate the correspondence regarding our article[1] and are happy for the opportunity to respond. The main critiques were that (1) we did not properly identify complementary medicine (CM), (2) we underascertained the number of patients who underwent CM, and (3) the definition of CM was not accurate.

In response to the first critique, we identified the CM group as those patients who received "Other-Unproven: Cancer treatments administered by nonmedical personnel." This likely includes treatments for cancer with a proposed, albeit unproven, biological mechanism, safety, and effectiveness. This is distinct from those therapies used for improvement of quality of life, including mind-body therapies such as yoga, meditation, prayer, or acupuncture, which were most likely therapies not included within the CM group. The use of CM as defined by this variable was recorded by physicians and interpreted by trained cancer registrars.

Regarding the second critique, we agree that we likely undercounted the patients who used CM and that some patients in the non-CM group likely used some form of CM (contamination). However, given the definition of CM that we used (ie, unproven treatment used as an anticancer therapy), the use of CM according to this definition is likely far less than that seen in self-reported surveys. Furthermore, contamination would likely bias our findings toward the null.

In response to the final critique, we previously studied unproven cancer treatment use in patients who did not receive any conventional cancer treatment; this was defined as alternative medicine (AM).[2] In contrast, the present study identified patients who combined unproven therapies with 1 or more conventional cancer therapies, which is defined as CM. Although many in the CM cohort were treated with all recommended strategies, we learned that some patients were refusing a component of conventional cancer treatment. As stated within the discussion section of the article,[1] AM and CM likely exist along a continuum and not within a strict dichotomization.

Lastly, we find it interesting that Lee and Douthit have highlighted preclinical work on fasting to potentially justify dietary modification as CM along with chemotherapy and radiation. This is in direct contrast to current nutritional guidelines for patients with cancer that state that without firm evidence of a benefit and with a potential for harm, short-term fasting cannot be recommended.[3] Adoption of preclinical data or making recommendations in the absence of data, regardless of whether treatment is classified as CM, AM, or medicine, may not be in the best interest of patients. We hope that our study findings encourage the rigorous evaluation of unproven CM prior to incorporation into clinical cancer practice, and we discourage the adoption of any unproven therapy if it is used to justify refusal of evidence-based conventional cancer treatment.

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1. Johnson SB, Park HS, Gross CP, Yu JB. Complementary medicine, refusal of conventional cancer therapy, and survival among patients with curable cancers. *JAMA Oncol*. 2018;4(10):1375-1381. doi:10.1001/jamaoncol.2018.2487

2. Johnson SB, Park HS, Gross CP, Yu JB. Use of alternative medicine for cancer and its impact on survival. *J Natl Cancer Inst*. 2018;110(1):121-124. doi:10.1093/jnci/djx145

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Improving the Nuclear-Localized Androgen Receptor Splice Variant 7 Test

To the Editor We read with great interest the article by Scher et al.[1] The aim of the study was to evaluate the clinical use of the Epic Sciences nuclear-localized androgen receptor splice variant 7 (AR-V7) test in circulating tumor cells (CTCs) to determine the best therapeutic strategy for patients with metastatic castration-resistant prostate cancer. The issue is interesting and addresses an important challenge of precision medicine. However, we would like to make a few remarks, which are mainly technical in nature. Although the assay used for analysis of the CTCs is highly sophisticated, we believe that the use of the fluorescence microscopy is a limiting factor that might directly affect results. Notably, the authors considered only AR-V7–positive CTCs exhibiting a nuclear-specific localization (according to AR-V7 scoring criteria) and discarded those with a diffuse signal.[2] We believe that fluorescence analysis using confocal technology would be useful.

Confocal microscopy allows determination with absolute certainty of the cellular localization of a protein through an assessment of its 3-dimensional organization. The use of confocal microscopy would have clarified the predictive value of hormone therapy of CTCs with both nuclear and cytoplasmic AR-V7 localization. Furthermore, the establishment of a cut-off value of AR-V7–positive CTCs would be appreciated for predictive purposes in the clinical setting.

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1. Scher HI, Graf RP, Schreiber NA, et al. Assessment of the validity of nuclear-localized androgen receptor splice variant 7 in circulating tumor cells as a predictive biomarker for castration-resistant prostate cancer. *JAMA Oncol*. 2018;4(9):1179-1186. doi:10.1001/jamaoncol.2018.1621

2. Scher HI, Graf RP, Schreiber NA, et al. Nuclear-specific AR-V7 protein localization is necessary to guide treatment selection in metastatic castration-resistant prostate cancer. *Eur Urol*. 2017;71(6):874-882. doi:10.1016/j.eururo.2016.11.024

In Reply Nicolazzo and colleagues suggest that the use of confocal microscopy would improve the technical and clinical accuracy of the androgen receptor splice variant 7 (AR-V7) diagnostic test. It is hypothesized that limitations (unspecified) of the widefield optics limit the ability to determine the 3-dimensional cellular organization and the localization of protein. Although confocal microscopy is a suitable research tool for evaluating the subcellular localization of organelles and proteins, it is impractical for this application in the clinical setting and is redundant for accurately determining protein localization. As evidenced by our studies to date,[1,2] the specificity of the test to determine a poor outcome if a patient is treated with androgen receptor signaling inhibitors is extremely high, a finding independently corroborated in a separate cohort[3] and in the PROPHECY study presented at the 2018 annual meeting of the American Society of Clinical Oncology.[4]

We are currently using 650 nm/pixel for classification of nuclear-localized cells against diffuse cells. We have demonstrated that we are able to achieve equivalent technical and clinical performance at sampling rates as low as 1.17 um/pixel. This is achieved through a combination of an optimized cell preparation that ensures cells are free lying and consistently oriented to the imaging plane. The depth of field of the objective lens is selected to capture the entire orthogonal dimension without multiple focal planes, thereby capturing the spatial context of the nucleus and cytoplasm within a single image and without postprocessing. In contrast, confocal microscopy incurs orders of magnitude increased acquisition times, noise, computational expense, algorithmic fragility, and photo damage of samples.

Contrary to the assumption of Nicolazzo and colleagues, a clinical cut-off was indeed developed and is currently in use in clinical practice to generate a binary (positive or negative) result. The cut-off was proven to predict patient outcomes, a finding independently validated.[3] The clinical results, with suitably selected widefield optics showing nuclear-localized AR-V7, have already demonstrated a high degree of specificity for a poor outcome on androgen receptor signaling inhibitors and that these same patients have an improved survival when treated with taxane-based chemotherapy.[2,3]

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Questioning Lay Health Worker Influence on Goals-of-Care Documentation and Patient Satisfaction

To the Editor We read with interest the article by Patel et al[1] on evaluating the efficacy of a lay health worker (LHW) program in improving end-of-life care for patients with cancer. The authors reported that incorporating a LHW in cancer care not only improved goals-of-care documentation and increased patient satisfaction, but also led to reduced health care use and costs.

It is unclear from this study whether there are substantial differences in educational attainment between participants in the interventional and control arms. Oncology patients' ability to understand, process, and communicate their health