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More on Reevaluating PSA Testing Rates in the PLCO Trial

TO THE EDITOR: In their letter to the Editor, Shoag et al. (May 5 issue)[1] note that men in the control group in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial[2] reported having undergone more cumulative prostate-specific antigen (PSA) testing than did men in the intervention group. The supplemental figure in the Supplementary Appendix (available with the full text of their letter at NEJM.org) shows that the proportions of men who reported a history of PSA testing over study years 6 through 12 were 85% in the control group and 80% in the intervention group.

However, the authors have misinterpreted the data obtained from the Health Status Questionnaire (HSQ). For the intervention group, the HSQ specifically asks about any PSA tests taken "outside of the PLCO study"[3] and after the last PLCO PSA screening test. Therefore, the reported rates are not cumulative rates of PSA testing among men in the intervention group. The actual rate of ever having undergone PSA testing among men in the intervention group, including the tests in the trial, was 99%.

Furthermore, Shoag et al. do not cite results from a prior article in which essentially the same finding was reported: 80 to 90% of men in the PLCO control group reported ever having undergone PSA testing.[4] Thus, the initially reported 50% rate of PSA testing among men in the control group has already been reevaluated; this was an estimate of yearly, not cumulative, testing.[2]

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Pinsky and Prorok corroborate that approximately 90% of men in the control group in the PLCO trial reported having undergone PSA testing. As a consequence of the data presentation in the article by Andriole et al. in 2009 and the article by Pinsky et al. in 2010 (both of which were referred to by Pinsky and Prorok), before our correspondence, guideline panels had not recognized this very high rate of screening contamination when formulating recommendations. However, Pinsky and Prorok still understate the rate of annual testing in the control group as 50%; this rate excludes many men who responded that they had undergone a "PSA blood test for prostate cancer" within the past year.

Only our quantification of PSA testing in the intervention group in Figure 1 in the Supplementary Appendix of our letter is challenged, not our quantification of screening contamination in the control group. The existence of a separate intervention-group survey was not mentioned in any information published or made available to us by the National Cancer Institute, nor was this wording disclosed despite specific, detailed discussion of this comparison. Now that Pinsky and Prorok have made their methods clear, we agree that the word "cumulative" in reference to our Supplementary Appendix should be qualified to reflect more testing in men in the control group only in the later years of the trial. Since men tend to underreport PSA screening on surveys,[1] it is misleading to compare trial data combined with survey data in the intervention group (as Pinsky and Prorok did to arrive at a 99% testing rate) with survey data alone in the control group.

It should now be clear that the very high rate

of PSA testing in the control group of the PLCO trial presents a serious limitation. Millions of men have not been offered PSA screening because of a lack of knowledge of this shortcoming; this underscores the importance of clarity in clinical trials and scientific reporting.

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Dr. Hu reports receiving speaker's fees from Intuitive Surgical. An updated disclosure form has been posted with the letter at NEJM.org. Since publication of the letter, Dr. Hu reports receiving speaker's fees from Genomic Health. No further potential conflict of interest relevant to this letter was reported.

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Targeting CD38 in Refractory Extranodal Natural Killer Cell–T-Cell Lymphoma

TO THE EDITOR: Relapse of natural killer (NK) cell–T-cell neoplasms in the leukemic phase in a patient who has received L-asparaginase–based combination therapy and undergone allogeneic hematopoietic-cell transplantation is generally fatal within days, and there is no known standard of care.[1] We report a sustained response to an anti-CD38 antibody, daratumumab, in a patient with relapsed, refractory nasal-type extranodal NK cell–T-cell lymphoma. Daratumumab is approved for use in patients with myeloma that is relapsed, refractory, or both.[2]

In September 2014, a 56-year-old woman of Taiwanese descent received a diagnosis of extranodal NK cell–T-cell lymphoma that was stage IE according to Ann Arbor staging (localized involvement of an extralymphatic organ or site with at least one involved lymph-node region on the same side of the diaphragm). Immunohistochemical analysis of a tumor-biopsy specimen showed that the tumor was positive for CD2, cytoplasmic CD3, CD56, and TIA-1 and negative for CD4, CD5, CD7, CD8, CD20, and CD30. Epstein–Barr virus (EBV)–encoded RNA (EBER) in situ hybridization and a plasma polymerase-chain-reaction (PCR) assay to detect EBV DNA were also positive.

Six weeks after the patient underwent radiotherapy and received concurrent cisplatin followed by consolidation chemotherapy with cisplatin, etoposide, and ifosfamide, the disease relapsed with extensive soft-tissue, bone, brain, and spinal cord lesions and spinal-fluid involvement. She received pegylated asparaginase–based combination chemotherapy (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide)[3] and intrathecal chemotherapy followed by allogeneic hematopoietic-cell transplantation.

At day 21 after transplantation, the disease relapsed in the patient's central nervous system, and aberrant NK cells in the cerebrospinal fluid were detected by means of flow cytometry. At day 90, systemic relapse was detected by means of a positive plasma PCR assay for EBV DNA and flow-cytometric analysis of a peripheral-blood sample that showed aberrant NK cells. Plasma EBV PCR, a sensitive disease marker that correlates with tumor load, is useful for assessing response and detecting recurrence.[4]

Withdrawal of immunosuppression and two additional cycles of chemotherapy with gemcitabine, oxaliplatin, and pegylated asparaginase did not induce systemic remission, although the cerebrospinal fluid became intermittently negative for NK cells. Five months after transplantation, persistent disease was manifested by plasma EBV positivity and circulating aberrant CD38+ NK cells (Fig. 1).

The patient then received off-label therapy with daratumumab at a dose of 16 mg per kilogram of body weight per week with no other chemotherapy. Plasma EBV PCR titers are provided in Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org. The dosing schedule and the adverse events observed are also described in the Supplementary Appendix.

During the first 4 weeks of treatment, plasma EBV titers increased by a factor of 10 to more than 20,000 copies per milliliter. However, after