the trial to assess for differences in clinically significant cancer in the subgroups with different coil strengths. Eighteen of 62 men in the 1.5-T MRI group (29%; 95% confidence interval [CI], 19 to 41) and 75 of 184 men in the 3.0-T MRI group (41%; 95% CI, 34 to 48) had clinically significant cancer. Since men were not randomly assigned to undergo MRI performed with 1.5-T or 3.0-T scanners, the differences observed may be confounded by other factors. The Prostate MRI Imaging Study (PROMIS), a multicenter study involving 576 men, used only 1.5-T MRI machines and showed that MRI was superior to transrectal ultrasonography–guided prostate biopsy for the detection of clinically significant cancer.[1]

We agree with Vickers and Ehdaie that urologists have been performing transrectal ultrasonography–guided biopsies for decades, but we would assert that tradition alone is an insufficient reason not to change practice in the face of growing scientific evidence. Transrectal ultrasonography–guided biopsy has been shown to miss more than 50% of clinically significant cancers in men.[1] Many men undergo repeat transrectal ultrasonography–guided biopsy, with a 2 to 4% risk of sepsis and costs to health services.[2] The Danish Cancer Registry study cited by Vickers et al. showed that in 17% of men with negative results on transrectal ultrasonography–guided biopsy who underwent repeat biopsy, prostate cancer of Gleason sum 8 was missed.[3] This is undesirable for a diagnostic test. In the PRECISION trial, with the use of the same threshold for clinically significant cancers as described by Vickers et al., MRI with or without targeted biopsy detected 6% (95% CI, 1 to 10) more cancers of Gleason sum 8 or worse than transrectal ultrasonography–guided biopsy. In addition, 13% (95% CI, 7 to 19) fewer men in the MRI-targeted biopsy group than in the standard-biopsy group received a diagnosis of clinically insignificant cancer — a diagnosis that can lead to considerable overtreatment and harm to men. Other studies have also shown that MRI-targeted biopsy detects more clinically significant cancer and less clinically insignificant cancer than transrectal ultrasonography–guided biopsy.[4] We acknowledge that there is uncertainty as to the prognosis of clinically significant cancer identified by MRI-targeted biopsy,[5] although future studies, and not conjecture, may ascertain the risk of death among these patients.

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Since publication of their article, the authors report no further potential conflict of interest.

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Single-Inhaler Triple versus Dual Therapy in Patients with COPD

TO THE EDITOR: In the randomized Informing the Pathway of COPD Treatment (IMPACT) trial involving more than 10,000 patients with chronic obstructive pulmonary disease (COPD), Lipson and colleagues (May 3 issue)[1] compared a once-daily combination of fluticasone furoate (an inhaled glucocorticoid), umeclidinium (a long-acting muscarinic antagonist [LAMA]), and vilanterol (a long-acting β_2-agonist [LABA]) with an inhaled glucocorticoid–LABA or a LABA–LAMA combination. The primary outcome was the annual rate of moderate or severe COPD exacerbations. Since a large fraction of COPD exacerbations are infectious in origin,[2] we wonder whether there were any differences among the three groups with respect to the proportion of patients who

had received annual influenza and pneumococcal vaccinations.

A meta-analysis of two randomized trials involving patients with COPD[3] showed that seasonal influenza vaccine had significantly better efficacy in preventing exacerbations than placebo. In addition, in a recently updated Cochrane meta-analysis, pneumococcal vaccination was associated with significant efficacy not only against community-acquired pneumonia but also in the prevention of acute exacerbations in patients with COPD.[4]

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

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TO THE EDITOR: Lipson and colleagues mention differences between the FLAME trial[1,2] and the IMPACT trial with respect to trial design. These differences were not likely to account for the differences in prevention of exacerbations. During the 4-week run-in period in the FLAME trial (when all patients received inhaled tiotropium), only 3.6% of the patients discontinued treatment because of exacerbations, and no additional patients were excluded because of findings on spirometry.

A critical difference was the careful exclusion of patients with any history of asthma in the FLAME trial, whereas in the IMPACT trial, a history of asthma was acceptable.[3] Many of the patients with moderate airflow limitation and frequent exacerbations included in the IMPACT trial may have had a history of asthma. In patients with concomitant asthma, abrupt withdrawal of inhaled glucocorticoids would plausibly lead to an acute increase in symptoms and early exacerbations[4] and would affect the patients' health status and all clinical outcomes during follow-up.

Trials involving patients with COPD that include treatment groups that do not receive inhaled glucocorticoids should have a standardized run-in period and exclude patients with concomitant asthma. Otherwise, there are potential biases and clinically significant harmful effects of withdrawal of inhaled glucocorticoids in such patients.

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TO THE EDITOR: The IMPACT trial showed a significantly lower rate of moderate or severe COPD exacerbations among patients who received triple combination therapy with an inhaled glucocorticoid–LABA–LAMA (0.91 per year) than among those who received LABA–inhaled glucocorticoid combination therapy (1.07 per year) or LABA–LAMA combination therapy (1.21 per year). The results of this trial should be interpreted with caution, since more than 70% of the patients were receiving a regimen containing inhaled glucocorticoids at randomization. Magnussen et al. previously established the safety of withdrawal of inhaled glucocorticoids in a three-step withdrawal process over a 12-week period in patients with stable COPD.[1]

In the present trial, inhaled glucocorticoid therapy was abruptly discontinued at randomization. All included patients had symptomatic COPD at baseline, and the patient population was not similar to that in the trial conducted by Magnussen et al. To accurately address the question of the efficacy of triple therapy as compared with LABA–LAMA combination therapy, patients included in the trial should either not have been receiving inhaled glucocorticoid therapy at baseline or appropriate procedures for the withdrawal of inhaled glucocorticoids should have been followed.

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Dr. Petite reports receiving a new investigator grant from the American Society of Health-System Pharmacists Foundation. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We agree with Rolla and Brussino regarding the importance of vaccination in patients with COPD. In the IMPACT trial, we advocated for the best care of the patients and recommended that if these vaccinations were not up to date, all patients should be offered influenza vaccine, pneumococcal vaccine, or both. Unfortunately, overall global vaccination rates were low, and only 17% of the patients reported having received vaccinations. The vaccination rates were similar across the trial groups (17% in the triple-therapy group, 16% in the fluticasone furoate–vilanterol group, and 16% in the umeclidinium–vilanterol group). We think that further efforts should be made to help improve overall vaccination rates in clinical care.

We disagree with Wedzicha and colleagues and think that differences in trial design and patient populations clearly explain the differences between the FLAME trial[1] and the IMPACT trial. Wedzicha and colleagues also promulgate a circular argument, because if they think that withdrawal of inhaled glucocorticoids is harmful, they must also think that inhaled glucocorticoids are beneficial in some patients who have COPD. The evaluated trials have different patient populations; approximately 30% of the patients in the FLAME trial and approximately 70% in the IMPACT trial had Global Initiative for Chronic Obstructive Lung Disease severe (category D) disease (i.e., they had symptoms and had had two or more moderate or one severe exacerbation in the previous year), according to the current classification.[2] Our trial was designed to study a typical COPD population, with results that would be generalizable to clinical practice. Because of the exclusion of a current diagnosis of asthma and the use of the same criteria as previous trials, with inclusion of a history of asthma,[3] the population in the IMPACT trial is easily recognized by practicing physicians. All patients met American Thoracic Society–European Respiratory Society criteria[4] for COPD, had a mean age of 65 years, had fixed airflow limitation with a mean forced expiratory volume in 1 second of 45.5% of the predicted normal value, and had a history of heavy smoking (approximately 47 pack-years). The investigators in our trial excluded patients whose symptoms were not due to COPD. In contrast, the FLAME trial enrolled a population of patients who were unlikely to benefit from inhaled glucocorticoids, since the investigators enrolled only those patients who did not have COPD exacerbations during a 4-week run-in period with tiotropium. This effectively biased the trial against finding a benefit associated with inhaled glucocorticoids. The FLAME trial also excluded patients with blood eosinophil levels greater than 600 cells per microliter. The FLAME trial and the IMPACT trial involved different patient populations; clinicians should consider these differences in decision making.

Petite questions whether withdrawal of inhaled glucocorticoids contributed to the efficacy observed with triple therapy as compared with dual therapy. Our trial was not a glucocorticoid-withdrawal trial. Approximately 70% of the patients entered the trial while receiving an inhaled glucocorticoid–containing regimen, yet only 20% were randomly assigned to LAMA–LABA. Therefore, only 14% of the participants in our trial had withdrawal of inhaled glucocorticoids. This did not contribute significantly to the observed trial effects, and we continued to see COPD exacerbations throughout the trial, not only in the

first month, when the effect of withdrawal of inhaled glucocorticoids would be greatest.

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Adjuvant Pembrolizumab in Resected Stage III Melanoma

TO THE EDITOR: In the past 2 years, Eggermont et al. have reported the findings of two landmark trials of adjuvant immunotherapy for stage III melanoma: the European Organization for the Research and Treatment of Cancer (EORTC) 18071 trial of ipilimumab[1] and the EORTC 1325 trial of pembrolizumab (May 10 issue).[2] Both trials suggest that adjuvant immunotherapy had a smaller effect on preventing locoregional recurrence than on preventing distant metastases.

Neither article provides details on regional recurrence in patients at high risk for this event, such as those with macroscopic involvement of large or multiple lymph nodes or those with extracapsular extension. In the EORTC 1325 trial, hazard ratios for recurrence were higher for patients with high-risk lymph-node metastases (stages IIIB and IIIC, macroscopic nodes, and ≥4 positive nodes) than for those with low-risk lymph-node metastases (stage IIIA, microscopic nodes, and ≤3 positive nodes). Regional recurrence after lymphadenectomy may be mitigated by lymph node–directed radiation therapy[3]; it would be helpful to know whether adjuvant immunotherapy obviates the need for this. In the Discussion section of their current article, Eggermont et al. suggest that less intensive therapy may be appropriate for patients with melanoma who have low-risk lymph-node metastasis.[4] However, for patients with high-risk lymph-node metastases, further study of more effective treatments associated with fewer adverse events may be warranted.

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Dr. Barker reports that his institution receives research funding from Merck, Amgen, and Bristol-Myers Squibb for clinical trials that he leads or is participating in as an investigator. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: In reply to Barker: the median follow-up was 1.3 years in the EORTC 1325 trial of pembrolizumab and 5.3 years in the EORTC 18071 trial of ipilimumab.[1] Table 1 shows, for each trial according to treatment group, the number of patients who had a recurrence-free survival event (locoregional recurrence, distant recurrence, or both, or death without a reported recurrence), the 1.5-year estimate of recurrence-free survival rates for both trials, the 5-year estimate of the recurrence-free survival rate in the EORTC 18071