To the Editor:

We read with interest the article in CHEST (March 2012) by Good et al on the application of bronchoscopy to improve the management of patients with refractory asthma. In this study, patients with refractory asthma underwent bronchoscopy with the aim of (1) obtaining data to define the refractory asthma phenotype and (2) individualizing therapy based on bronchoscopically defined refractory asthma phenotype. Outcomes measured included changes in Asthma Control Test scores and FEV1. The study reported significant improvements in these outcomes for four out of the five bronchoscopically defined phenotypes at 12 to 60 weeks postprocedure. These findings are interesting because they enhance the possibility of personalized care for patients with refractory asthma and extend the clinical usefulness of bronchoscopy. However, caution is required in interpreting these data. The lack of a separate control arm and the nonrandomized design of the trial raise the following issues:

1. The role of a placebo effect in asthma was highlighted in a study by Wechsler et al, in which treatment with either a placebo inhaler or sham acupuncture led to equivalent improvement in subjective perception of asthma, as did treatment with active albuterol. Both placebos were superior to no intervention. It is not clear how much of the improvement in asthma control in response to bronchoscopy-directed therapy can be attributed to a placebo effect and how much to a true treatment effect.

2. The subjects in the study were enrolled from the authors’ clinic. Subjects with asthma are more likely to seek an encounter with health-care providers when their disease is uncontrolled or getting out of control. Hence, a regression to the mean is likely if the same cohort is evaluated at a later time point. Lack of a control group limits evaluation of the true efficacy of bronchoscopy-directed care.

As a proof of principle, the findings of this study are novel, significant, and provocative. A well-designed randomized controlled trial is now required to clearly delineate the true treatment effect attributable to a bronchoscopy-directed strategy of care. Judgment on the usefulness of bronchoscopy in defining refractory asthma phenotype and the therapeutic benefit accruing from this approach must wait until such a study has been performed.

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Response

To the Editor:

We appreciate the comments by Drs Rehman and deBoisblanc. These concerns were addressed within our article, but are important to address further.

The first comment was regarding the lack of a separate control arm and, thus, the possibility of a placebo effect from individualized therapy. As discussed in our publication, we compared two groups of patients; we did not use a true, matched, placebo control. The first was the initial 20 patients with defined refractory asthma who were referred for evaluation and treatment at National Jewish Health. These patients then had an additional 4 months of intensified treatment without any improvement in the FEV1 or the Asthma Control Test. Only after specific directed therapy, with a reduction in other asthma-related medications, did these outcomes improve. If a placebo effect were to explain the outcomes, then after being referred to a tertiary/quaternary center, changing medications, and so forth, one would expect to see some placebo effect occurring after the additional 4 months of treatment, but no such improvement was observed.

The second group was the nonspecific group, which did have bronchoscopy and guideline-based increase in therapy. This group did not have a significant improvement in FEV1 or the Asthma Control Test. Thus, the question would be: Why is this group immune to the placebo effect?

The second comment by Drs Rehman and deBoisblanc is somewhat unclear to us. We strictly defined this group of patients as refractory, the definition of which dictates at least 1 year of high-dose therapies. We agree with the correspondents that bronchoscopy in patients who are “getting out of control” not only “limits evaluation” of bronchoscopy, but should not be done. We cannot comment on regression to the mean as we were not investigating “out of control” patients.

Finally, our study was more of a real-world investigation, not a randomized control trial (RCT). Both are valuable, and both have associated problems. It is poorly perceived that RCTs are only able to enroll about 3% to 5% of the entire asthma population due to inclusion/exclusion criteria, yet this type of evaluation is then