than white patients but who have considerable adverse effects.[2] However, low-dose peginterferon alfa-2b may also lead to a significantly higher rate of treatment discontinuation due to virologic nonresponse. Whether this result could be extrapolated to low-dose peginterferon alfa-2a therapy remains to be examined. Finally, several factors have been reported to affect early viral kinetic responses and relapse in patients infected with hepatitis C virus (HCV) genotype 1 who are receiving the current standard of care.[3] Their roles in the low-dose peginterferon regimen remain unknown.

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THE AUTHORS REPLY: Hsu and Kao rightly point out that reported treatment response rates are higher among Asian patients with chronic HCV infection than among other patients. In the Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study, response rates among self-reported Asian patients were also high: 62% (13 of 21 patients) among patients who received peginterferon alfa-2b at a dose of 1.0 μg per kilogram of body weight per week, 70% (7 of 10 patients) among patients who received peginterferon alfa-2b at a dose of 1.5 μg per kilogram per week, and 50% (10 of 20 patients) among patients who received peginterferon alfa-2a at a dose of 180 μg per week. Recently, the response to treatment for HCV infection has been strongly associated with a genetic interleukin-28B variant that resides on chromosome 19. The "favorable" allele is more prevalent in East Asian populations[1]; this may, in part, explain the favorable response observed in this patient group.

We also agree that a low dose of peginterferon alfa-2b was well tolerated and associated with a similar overall efficacy in our study, but not in all subpopulations. Similar findings have been reported with peginterferon alfa-2b monotherapy (at a dose of 135 μg weekly)[2] and peginterferon alfa-2a monotherapy (at a dose of 180 μg weekly).[3]

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Hearing Improvement after Bevacizumab for Neurofibromatosis Type 2

TO THE EDITOR: Plotkin et al. (July 23 issue)[1] report a sustained tumor-volume reduction in 4 of 10 patients and a hearing response in 4 of 10 patients with neurofibromatosis type 2 after bevacizumab treatment. The authors' conclusion that tumor shrinkage and hearing improvement are effects of bevacizumab treatment is not convincing, because the study did not involve a control group. Shrinkage of a vestibular schwannoma, especially in cystic tumors in patients with neurofibromatosis type 2, can also occur during an observation period without any treatment.[2] In addition, some patients who have been assigned to wait-and-scan observation show hearing improvement over time without any treatment.[3] The nonblinded design of the study might have biased the investigators and patients during the hearing tests. Otherwise, how do Plotkin et al. explain the poor

correlation between tumor-volume shrinkage and hearing improvement? Also, how do they explain the poor correlation between pure-tone thresholds and word-recognition results? Instead of only using subjective acoustic hearing tests, it would have been worthwhile to use objective test methods such as brain-stem auditory evoked response.

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TO THE EDITOR: Plotkin et al. report that vascular endothelial growth factor (VEGF) blockade with bevacizumab improved hearing and decreased the volume of vestibular schwannomas in some patients with neurofibromatosis type 2. Dynamic contrast-enhanced magnetic resonance imaging data indicated that bevacizumab normalized the function of tumor vessels. We wonder whether vascular normalization is the real or unique mechanism of anti-VEGF therapy for vestibular schwannomas. In some clinical trials, vascular normalization might provide benefit by killing tumor cells in synergy with chemotherapy; this is accomplished by improving the delivery of cytotoxic agents to tumors. However, in this study, 10 patients received bevacizumab as monotherapy. Otherwise, VEGF inhibition might have had direct cytotoxic effects on tumor cells that express VEGF receptors and that depend on VEGF for survival.[1,2] The authors and other groups have detected VEGF and its receptors in schwannomas, and increased levels of these factors correlate with increased rates of tumor growth.[3,4] Therefore, it is not known whether the curative effect is due to the direct killing of tumor cells and increase in apoptosis by bevacizumab or to vascular normalization.

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THE AUTHORS REPLY: Guntinas-Lichius raises an important issue about trial design in studies of vestibular schwannomas. Recently, a group of experts endorsed the objective radiographic response rate as the appropriate choice for initial single-group drug trials because the rates of spontaneous tumor shrinkage in untreated vestibular schwannomas are low.[1] In the study cited by Guntinas-Lichius,[2] extremely few tumors decreased in size during the observation period (0.9%), whereas the majority of tumors were either stable (70.2%) or increased in size (28.9%). In our study, 60% of tumors had a radiographic response; this rate far exceeded the rate of spontaneous tumor shrinkage. Moreover, the median annual growth rate of the tumors before bevacizumab therapy was 63%, whereas many of the tumors in the previous study were not growing at baseline. In a companion study[3] to the study cited by Guntinas-Lichius, the rate of spontaneous hearing improvement without treatment was 2.7%, which is far lower than the reported rate of hearing improvement in our study (57%). Together, these findings provide strong evidence that changes in tumor size and hearing after treatment were related to the effects of bevacizumab.

We do not fully understand why word recognition improved more than detection of pure tones. However, we disagree with the assertions that the hearing measurements were subjective and that bias may explain the findings. Standardized methods exist for the determination of pure-tone averages and measurement of word recognition. In hearing loss due to vestibular schwannomas, word recognition typically is affected more than the detection of pure tones.[1] Thus, greater improvement might be expected in word recognition than in the ability to hear pure tones after effective treatment of vestibular schwannomas. Although brain-stem auditory evoked response measurements would have been worthwhile, we did not include them because we did not have sufficient data for comparisons among patients.

We agree with Diao et al. that inhibiting VEGF in vestibular schwannomas probably affects both the vasculature and tumor cells. Our data do not permit us to estimate the relative contributions of vascular permeability and direct killing of tumor cells to clinical response. However, these two processes might explain why the effect of bevacizumab on tumor size and hearing was not tightly correlated.

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Since publication of the article, Dr. di Tomaso reports being employed by the Novartis Institutes for BioMedical Research. No other potential conflict of interest relevant to this letter was reported.

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Death in a Gene-Therapy Trial

TO THE EDITOR: Frank et al. (July 9 issue)[1] do not discuss the issue of therapeutic misconception[2] — namely, the belief by a research subject that the investigational agent is actually therapeutic. Admittedly, there was no concrete evidence for this issue here, but on the basis of the nature and timing of events, the issue was relevant and became an important part of the report and recommendations of the Recombinant DNA Advisory Committee of the National Institutes of Health.

Therapeutic misconception for the subject can be addressed during the consenting procedure.[3,4] However, therapeutic misconception is also an issue for investigators for whom conflicting commitments can blur the line between research and treatment. Therefore, the protocol itself becomes the main protection for safety in this regard. In addition to recommending screening tests and laboratory requirements before the initiation of therapy, the advisory committee recommended that subjects carry a medical card containing key information about the investigational agent, as well as phone numbers for ready contact with the study's principal investigator. The protocol should clearly state how to proceed in the event of any unforeseen illness.

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Dr. Zaia reports being a member, and Dr. Federoff reports being chair, of the Recombinant DNA Advisory Committee, which reviewed this adverse event. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Frank et al. examined the role of a tumor necrosis factor α (TNF-α) antagonist, delivered through an adeno-associated virus, as a precipitating cause of death in a gene-therapy trial. When a patient is receiving a TNF-α blocker, education about the risk of opportunistic infection, especially histoplasmosis and tuberculosis, is a requisite. A survey of infectious-disease consultants in the United States revealed that histoplasmosis occurred more often than tuberculosis in patients receiving TNF-α blockers.[1] Perhaps because of the regional occurrence of histoplasmosis in the United States, many physicians may fail to entertain the diagnosis of this infection. Since the presenting clinical features are nonspecific and exposure often goes unrecognized, physicians should include histoplasmosis in such evaluations. The role of reactivation of latent in-