

a nonselective agent, and the authors present no evidence that the 100-mg daily dose inhibited ACAT2. In fact, this treatment had no effect on plasma cholesterol levels, which suggests that ACAT2 inhibition was insufficient.

We believe the jury is still out with respect to the specific inhibition of ACAT2. Studies that are designed to test ACAT2 inhibition in humans are needed to determine whether this strategy reduces atherosclerosis.

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1. Nissen SE, Tuzcu EM, Brewer HB, et al. Effect of ACAT inhibition on the progression of coronary atherosclerosis. *N Engl J Med* 2006;354:1253-63.
2. Accad M, Smith SJ, Newland DL, et al. Massive xanthomatosis and altered composition of atherosclerotic lesions in hyperlipidemic mice lacking acyl CoA:cholesterol acyltransferase 1. *J Clin Invest* 2000;105:711-9.
3. Fazio S, Major AS, Swift LL, et al. Increased atherosclerosis in LDL receptor-null mice lacking ACAT1 in macrophages. *J Clin Invest* 2001;107:163-71.
4. Willner EL, Tow B, Buhman KK, et al. Deficiency of acyl CoA:cholesterol acyltransferase 2 prevents atherosclerosis in apolipoprotein E-deficient mice. *Proc Natl Acad Sci U S A* 2003;100:1262-7.
5. Lee RG, Kelley KL, Sawyer JK, Farese RV Jr, Parks JS, Rudel LL. Plasma cholesteryl esters provided by lecithin:cholesterol acyltransferase and acyl-coenzyme A:cholesterol acyltransferase 2 have opposite atherosclerotic potential. *Circ Res* 2004;95:998-1004.

**DR. NISSEN REPLIES:** My colleagues and I were very careful to point out that other ACAT inhibitors might be successfully developed but warned that “if other agents in this class are studied in patients with coronary disease, there should be reasonable evidence that their biologic effects differ from those of pactimibe. Clinical trials of other ACAT inhibitors will require warnings in the informed-consent form and close monitoring by an independent data and safety monitoring board.”

We deliberately did not suggest that further study was inappropriate. With close monitoring, we believe that additional trials of ACAT2 inhibitors could be conducted ethically. However, we are very doubtful that a successful agent can be developed. To our knowledge, no ACAT inhibitor, administered at any dose, has been associated with a reduction in cholesterol levels in humans. In fact, pactimibe inhibited ACAT2 at the 100-mg dose used in the ACTIVATE trial, and avasimibe inhibited ACAT2 in the Avasimibe and Progression of Lesions on Ultrasound (A-PLUS) trial, but neither agent reduced cholesterol.<sup>1</sup> Accordingly, we think that developers of therapies to treat atherosclerosis are best served by looking elsewhere for successful approaches.

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1. Tardif JC, Gregoire J, L'Allier PL, et al. Effects of the acyl coenzyme A:cholesterol acyltransferase inhibitor avasimibe on human atherosclerotic lesions. *Circulation* 2004;110:3372-7.

## Who Is at Greatest Risk for Receiving Poor-Quality Health Care?

**TO THE EDITOR:** The finding by Asch and colleagues (March 16 issue)<sup>1</sup> that the quality of recommended care received by patients who are members of minority groups is higher than that received by whites conflicts markedly with the weight of the evidence,<sup>2,3</sup> which consistently finds poorer quality of care for many minority groups after adjustment for all major confounding variables.

Before generalizing from the study by Asch et al., it is therefore important to examine the study's limitations. There was potential selection bias in the sample, which included only 37 percent of those initially eligible for participation in

the study. It is difficult to generalize the findings of this study, which included disproportionately few uninsured persons and patients enrolled in Medicaid, to the nation as a whole. Finally, despite their conclusion about race or ethnic background and the quality of care, the authors state that disparities were evident when their analysis was limited to categories in which racial or ethnic disparities had been found in other studies.

Given these limitations and the magnitude of other evidence, the study provides inadequate support for the conclusion that interventions focused on disparities in health care warrant less

attention than general quality improvement. Both types of efforts should continue.

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1. Asch SM, Kerr EA, Keeseey J, et al. Who is at greatest risk for receiving poor-quality health care? *N Engl J Med* 2006;354:1147-56.
2. Smedley BD, Stith AY, Nelson AR, eds. *Unequal treatment: confronting racial and ethnic disparities in health care*. Washington, D.C.: National Academy Press, 2003.
3. *Racial/ethnic differences in cardiac care: the weight of the evidence*. Menlo Park, Calif.: Henry J. Kaiser Family Foundation, American College of Cardiology, October 2002.

**TO THE EDITOR:** The article by Asch et al. reports the rather shocking result that physicians in the United States ordered only 54.9 percent of recommended care. This result is combined with the puzzling finding that these results had little variability among socioeconomic classes or races, groups that have significantly different life expectancies and health outcomes.<sup>1</sup> When faced with such a nonintuitive result, one should look at the “examination,” or criteria, that produced these results.

It is not clear that the RAND criteria of 439 specific recommendations, generated by panels of experts, apply seamlessly to medical care as it is delivered on a daily basis. Are all of the 439 recommendations of equal importance? Is there a general consensus in the medical community about the importance of each measure? If these measures do not vary among groups with markedly differing health outcomes, just how relevant are the criteria?

In the Discussion section, virtually no mention is made of the validity of the medical criteria. The results of this study cast doubt on the relevance of the criteria to medical outcomes.

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1. Crimmins EM, Saito Y. Trends in healthy life expectancy in the United States, 1970-1990: gender, racial, and educational differences. *Soc Sci Med* 2001;52:1629-41.

**TO THE EDITOR:** The current economic model for U.S. health care is doing a spectacular job of what it is designed to do — foster fragmented, procedural care over integrated, comprehensive care. As measured by Asch et al., this evolution has been largely independent of race, sex, and socioeconomic status.

Quality indicators provide one measure of complexity and clinical work. For example, the care of a patient with diabetes, hypertension, depression, and new headache might be compared with the care of a patient who requires cataract extraction; the former entails up to 56 quality indicators and 2.18 relative-value units (RVUs)<sup>1,2</sup>; the latter entails 5 quality indicators and 18 RVUs.<sup>2</sup> In this example, the incentive index (RVU ÷ indicator) is nearly 100 times as great for procedural care (3.60) as for cognitive care (0.04).

With reimbursement disparities of this magnitude, should we be surprised at the diminishing workforce in generalism? The number of trainees choosing generalist careers is plummeting.<sup>3</sup> Yet a larger supply of generalists is associated with increased quality.<sup>4</sup> Analysis of current incentives can shed light on the manner by which the existing U.S. economic model puts all Americans at risk for poor quality of care.

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1. Current procedural terminology (CPT) 2006. Chicago: American Medical Association, 2005:10.
2. Center for Medicare and Medicaid Services. 2006 National physician fee schedule: relative value file. (Accessed May 25, 2006, at <http://www.cms.hhs.gov/PhysicianFeeSched/PFSRVF/list.asp>.)
3. Garibaldi RA, Popkave C, Bylsma W. Career plans for trainees in internal medicine residency programs. *Acad Med* 2005;80:507-12.
4. Starfield B, Shi L, Macinko J. Contributions of primary care to health systems and to health. *Milbank Q* 2005;83:457-502.

**THE AUTHORS REPLY:** Geiger et al. point out that we need not face a choice between broad quality-improvement efforts and those designed to address racial and other disparities. We agree completely. Previous studies have convincingly shown disparities in access to care or in the rates at which complex, expensive procedures are used; these areas were not the focus of our study. Together, these findings can help guide interventions to reduce disparities to areas where they have the greatest potential. However, given the

large difference between observed and desirable care for all groups in our study, it is clear that our health care system will need both interventions aimed at reducing disparities and the more general and systemic ones if the quality of care is to improve for everyone.

Geiger et al. and Sherrick bring up important methodologic concerns, and we have addressed them through extensive examination and modeling. We adjusted for nonresponse and tested the sensitivity of our findings to nonresponse bias. Although nonresponse bias explains some of the small differences we found among racial and ethnic groups, nonrespondent blacks would have to have had implausibly low (near zero) overall quality scores to produce differences of the magnitude (approximately 20 percent) often found in the literature on disparities. The criteria we used to measure the quality of care went through a scientifically established process. The evidence linking each measured process to a relevant health outcome was assembled and presented to a group of nationally known experts nominated by their specialty societies. The modified Delphi method is established and validated and has been shown to predict future trial results.<sup>1</sup> Limited empirical evidence also supports the relationship of similar measurement sets to observed outcomes.<sup>2,3</sup>

As Sherrick points out, other studies have documented very different outcomes among groups that had only limited overall differences in process quality in our study. Many factors other than

the quality of medical care processes affect health outcomes. These factors include access, environment, disease severity, health habits, and adherence. Undoubtedly, we have a long way to go to reduce disparities in outcomes for all patients. Nonetheless, it is reasonable to focus on validated process measures that are linked to outcomes because they are under the control of providers and managers and therefore directly amenable to quality-improvement efforts.

Sinsky's point that more highly remunerated care may have been delivered at higher rates of indicator compliance is interesting. Our study was not designed to address the relationship between reimbursement and quality, and future research should investigate it.

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1. Shekelle PG, Chassin MR, Park RE. Assessing the predictive validity of the RAND/UCLA appropriateness method criteria for performing carotid endarterectomy. *Int J Technol Assess Health Care* 1998;14:707-27.
2. Higashi T, Shekelle PG, Adams JL, et al. Quality of care is associated with survival in vulnerable older patients. *Ann Intern Med* 2005;143:274-81.
3. Asch SM, Kerr EA, Lapuerta P, Law A, McGlynn EA. A new approach for measuring quality of care for women with hypertension. *Arch Intern Med* 2001;161:1329-35.

## HER2 Mutation and Response to Trastuzumab Therapy in Non–Small-Cell Lung Cancer

**TO THE EDITOR:** Trastuzumab is a monoclonal antibody against HER2, a member of the epidermal growth factor receptor (EGFR) family, that improves the outcome of HER2-positive breast cancer.<sup>1</sup> Preclinical data have demonstrated that trastuzumab is effective in non–small-cell lung cancer, with additive or synergistic effects with various cytotoxic agents. However, trials of trastuzumab or other HER2-targeted agents, such as pertuzumab, failed to demonstrate clinical benefit in non–small-cell lung cancer when adminis-

tered as monotherapy or combined with chemotherapy.<sup>2</sup>

In these studies, HER2 status was assessed by immunohistochemical analysis, a method that is not optimal.<sup>3</sup> Moreover, the few patients whose tumors had *HER2* gene amplification and who were treated with trastuzumab had a response to trastuzumab.<sup>2</sup> Recently, activating mutations in *HER2* were reported in lung adenocarcinomas, offering the potential for therapy targeted at the altered protein.<sup>4</sup> Here, we report the case of a