

Correspondence



Race and Responsiveness to Drugs for Heart Failure

To the Editor: As Wood (May 3 issue)¹ points out, individual and racial differences in the responses to drugs are increasingly often shown to reflect, at least in part, varying distributions of polymorphisms in drug receptors or drug-metabolizing enzymes among different populations. In several instances, a lesser response was found in nonwhite patients than in white patients to such drugs as the angiotensin-converting-enzyme (ACE) inhibitor enalapril, as reported by Exner et al. (May 3 issue),² and the beta-blocker bucindolol.³ These findings are valuable for guiding clinical practice.

From another perspective, it would be interesting to examine to what extent the selection processes that take place during the various phases of drug development and that have thus far been conducted in predominantly white American and European populations have led to the selection of drugs that are effective in Western populations but not necessarily in other populations. It is indeed likely that the development of several drugs that would have been effective in other populations has been abandoned because a genetic trait associated with a low response rate or with undesirable side effects is widespread in the predominantly white patients involved in early-stage pharmacologic studies.

A global response is required to tackle worldwide health challenges — particularly the spread of chronic diseases. This response requires the more systematic inclusion of nonwhite populations in clinical and population-based trials.

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1. Wood AJJ. Racial differences in the response to drugs — pointers to genetic differences. *N Engl J Med* 2001;344:1393-6.
2. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med* 2001;344:1351-7.
3. Ferguson JJ. Highlights of the 72nd Scientific Sessions of the American Heart Association. *Circulation* 2000;102:E1-E5.

To the Editor: In his May 3 editorial,¹ Dr. Schwartz assumes that comparative studies of different racial or ethnic populations are frivolous and ill founded and that they seek racial distinctions. Most of this work, however, is not anthropological but rather aims to determine the mechanistic basis for clinical observations. Although access to care and other nonmedical issues are important contributors to disparities in clinical outcomes, there are often genetic and physiological components of these problems. An understanding of an objective basis for observed differences would be much easier to integrate quickly into clinical decision making than would the sort of full-scale societal changes that would be necessary to achieve health equality (the ultimate goal).

The use of racial and ethnic populations in studies such as those of Yancy et al.² and Exner et al. creates a clinical scenario in which it is possible to discover the molecular basis of a clinical phenotype because of the inclusion of variants that have become segregated as a result of the migration of populations or other nongenetic factors. Such studies have been valuable for determining how a pharmacogenetic discovery will translate from one group to other populations³ and for defining the optimal clinical scenario for focused evaluation of the mechanisms of particular agents — that is, what sort of population is likely to help us find the clearest answer.

This type of translational research is not as provocative or sinister as Dr. Schwartz suggests; its goal is actually to eliminate skin pigment as a variable and replace it with an objective molecular end point. The pursuit of this goal needs to be expedited, not stifled, if the genome revolution⁴ is to lead to real improvements in our ability to select the optimal therapies for individual patients.

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1. Schwartz RS. Racial profiling in medical research. *N Engl J Med* 2001;344:1392-3.
2. Yancy CW, Fowler MB, Colucci WS, et al. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *N Engl J Med* 2001;344:1358-65.
3. Ameyaw MM, Regateiro F, Li T, et al. *MDR1* pharmacogenetics: frequency of the C3435T mutation in exon 26 is significantly influenced by ethnicity. *Pharmacogenetics* 2001;11:217-21.
4. Holtzman NA, Marteau TM. Will genetics revolutionize medicine? *N Engl J Med* 2000;343:141-4.

To the Editor: The editorial by Dr. Schwartz points out a fundamental flaw in the reasoning behind analyses such as that in the report by Exner et al., which describes racial differences in the response to ACE inhibitors as treatments for heart failure. The editorial argues that although race is a useful social construct, it does not hold up as a valid genetic concept.

Unfortunately, this flaw is not widely understood. As consultants for a nationwide effort of the Health Care Financing Administration to improve the care of patients with heart failure,¹ we have assisted in developing measures for assessing the quality of care for patients with heart failure. Recently, some physicians objected to the measure for assessing the need to prescribe ACE inhibitors for patients with left ventricular systolic dysfunction. These critics claimed that the indicators should be responsive to the latest data published in the *Journal*, and thus that black race should constitute an accepted reason for not prescribing ACE inhibitors.

Although we cannot be certain that this belief is common, it is disturbing that it exists at all. This simple-minded interpretation of the study by Exner et al. is not only distasteful, it is dangerous, potentially placing blacks at risk for inappropriate undertreatment. The data presented in the report are provocative but not definitive. They should inspire further research, not change accepted practice. We support the publication of this study and value the debate it generates. We believe, however, that authors — and readers — of such studies should exercise extreme care in interpreting these data given the inherent difficulties in using the construct of race as a predictor of the outcome of treatment.

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1. Jencks SF, Cuedon T, Burwen DR, et al. Quality of medical care delivered to Medicare beneficiaries: a profile at state and national levels. *JAMA* 2000;284:1670-6.

To the Editor: We disagree with the conclusion of Exner et al. that it is “appropriate to consider current therapeutic recommendations as applying to white patients but not necessarily to black patients.” The analysis that is presented is not a sufficient basis for withholding ACE inhibitors from black patients with heart failure. Black patients did have responses to enalapril, but these patients were undertreated. The importance of increasing the dose of ACE inhibitors to achieve the maximal therapeutic benefit has been demonstrated in patients with heart failure¹ and in those with hypertension.^{2,3} An alternative interpretation of the

study by Exner et al. is that patients with hypertension-induced heart failure have worse outcomes when they receive suboptimal treatment with aspirin, beta-blockade, and ACE inhibition.

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1. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting-enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999;100:2312-8.
2. Saunders E, Weir MR, Kong BW, et al. A comparison of the efficacy and safety of a beta-blocker, a calcium channel blocker, and a converting enzyme inhibitor in hypertensive blacks. *Arch Intern Med* 1990;150:1707-13.
3. Weir MR, Gray M, Paster R, Saunders E. Differing mechanisms of action of angiotensin-converting enzyme inhibition in black and white hypertensive patients. *Hypertension* 1995;26:124-30.

The authors reply:

To the Editor: We agree with Wood, Bovet and Paccaud, and McLeod. Differences in therapeutic response probably relate, in part, to polymorphisms in drug receptors, drug-metabolizing enzymes, or other factors. The frequency of polymorphisms in the gene for ACE I differs in whites and blacks,¹ and these polymorphisms correlate with the ACE concentration and blood pressure.^{1,2} Although individual polymorphisms do not fully explain the differences in phenotypic expression, interaction among the polymorphisms appears to be important.² These and other data refute the assertion of Schwartz that categorizing groups on the basis of self-reported race has “no plausible biologic justification.” Evaluating differences in therapeutic response within subgroups of the population is an important initial step in identifying important polymorphisms.

We are concerned about the assertion of Masoudi and Havranek that some physicians have claimed, on the basis of our findings, that black race should be an accepted reason for not prescribing an ACE inhibitor for heart failure, and we agree with Ofili et al. that our results must be viewed in the proper context. There is substantive evidence that ACE inhibitors reduce morbidity and mortality in patients with a low ejection fraction and heart failure. On the basis of the entirety of the evidence, ACE inhibitors should continue to be prescribed to all patients with this syndrome in whom there is not a contraindication to their use. Our results and other analyses³ should remind the reader, however, that ACE inhibitors have not been proved effective, on average, in black patients.

Whether different therapeutic agents or higher doses of ACE inhibitors are more effective than the usual doses of ACE inhibitors in this population is not known but warrants further study. The optimal means of addressing these questions — whether through targeted population studies or by means of subgroup analyses in large trials that include patients of both sexes and from many racial and ethnic groups — is open to debate. We echo the concern of Bovet and Paccaud regarding the problems related to the

underrepresentation of certain groups in clinical trials and believe that our results highlight this issue.

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1. Borecki IB, Province MA, Ludwig EH, et al. Associations of candidate loci angiotensinogen and angiotensin-converting enzyme with severe hypertension: the NHLBI Family Heart Study. *Ann Epidemiol* 1997;7:13-21.
2. Zhu X, Bouzekri N, Southam L, et al. Linkage and association analysis of angiotensin I-converting enzyme (ACE)-gene polymorphisms with ACE concentration and blood pressure. *Am J Hum Genet* 2001;68:1139-48.
3. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the Vasodilator-Heart Failure Trials. *J Card Fail* 1999;5:178-87.

The editorialist replies:

To the Editor: I agree with McLeod that biomedical research should aim for an “objective molecular end point.” Indeed, that was the main point of my editorial. McLeod suggests that we could “discover the molecular basis of a clinical phenotype” through research on “racial populations.” The problem with his approach is that it entails the vague idea of “racial populations.” The rapidly advancing field of molecular genetics — especially the new methods of genomics and haplotyping — has erased the color line. It is unnecessary in biomedical research to make arbitrary decisions about who is white, black, yellow, or red. The main requirement now is to have a biologically plausible hypothesis.

The letter from Masoudi and Havranek indicates how dangerous the idea of race can be when it is incorporated into medical practice. Physicians who would base clinical decisions on a patient’s supposed race ignore not only the extraordinary diversity of humans but also the past 100 years of history.

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Vancomycin-Resistant Enterococci in Health Care Facilities

To the Editor: The report by Ostrowsky et al. (May 10 issue)¹ provides evidence that active infection-control interventions can reduce or eliminate the transmission of vancomycin-resistant enterococci in health care facilities. One limitation of that study, as they point out, is the relatively small proportion of patients in acute health care facilities who participated in the study, which may have limited its ability to assess the true prevalence of vancomycin-resistant enterococci.

We recently experienced an outbreak of vancomycin-resistant enterococci in a 560-bed university teaching hospi-

tal. Vancomycin-resistant enterococci were first isolated from a clinical specimen in November 1998. A point-prevalence survey of all hospitalized patients revealed that 46 patients (8.2 percent) were colonized with vancomycin-resistant enterococci. All isolates were *vanA*-containing *Enterococcus faecium*. A predominant strain (pulsovar S2) was characterized by pulsed-field gel electrophoresis.

A system of surveillance cultures, infection-control procedures, and educational efforts was implemented according to the recommendations of the Centers for Disease Control and Prevention.² Despite these measures, by March 1999, more than 150 patients had tested positive for vancomycin-resistant enterococci. We then began to use a newly validated, highly accurate polymerase-chain-reaction (PCR) assay for the rapid detection (in less than 24 hours) of vancomycin-resistant enterococci in rectal specimens.³ This assay permitted us to intensify our efforts to prevent the spread of vancomycin-resistant enterococci. Its use allowed us to screen patients more often and reduced the delay before the implementation of preventive measures. A questionnaire was introduced in the emergency room to identify and screen readmitted patients. All patients who tested positive were isolated on the same ward. The number of patients with vancomycin-resistant enterococci declined sharply during the next three months. Since then, no cross-contamination has been observed, suggesting that the transmission of vancomycin-resistant enterococci has been eliminated in our center.

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1. Ostrowsky BE, Trick WE, Sohn AH, et al. Control of vancomycin-resistant enterococcus in health care facilities in a region. *N Engl J Med* 2001;344:1427-33.
2. Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Morb Mortal Wkly Rep* 1995;44(RR-12):1-13.
3. Roger M, Faucher MC, Forest P, St-Antoine P, Coultée F. Evaluation of a *vanA*-specific PCR assay for detection of vancomycin-resistant *Enterococcus faecium* during a hospital outbreak. *J Clin Microbiol* 1999;37:3348-9. [Erratum, *J Clin Microbiol* 2000;38:945.]

The authors reply:

To the Editor: We agree with Dr. Roger and colleagues that the control of vancomycin-resistant enterococcus (and other pathogens resistant to antimicrobial agents) in health care settings requires active surveillance, the use of barrier precautions or isolation, and compliance by health care workers with current recommendations.¹ They note that one of the limitations of our study was the lower rate of patient participation in the acute care facilities than in the long-term care facilities. Although the participation rate in acute care facilities was lower, the rate of inclusion of high-risk patients was higher (e.g., 74 to 100 percent of the patients in some intensive and intermediate care units). Most of the patients not included in our study were patients at low risk for vancomycin-resistant enterococci (e.g., patients with short hospitalizations — day-surgery or obstetrical patients and those with little exposure to antimicrobial agents).

Thus, we believe (and the results confirm) that we were able to identify the majority of patients colonized with vancomycin-resistant enterococci. The acute care facilities were also tracking vancomycin-resistant enterococci and found similar decreases throughout the year (not just on the yearly point-prevalence surveys).

The experience of Dr. Roger et al. in trying to control the transmission of vancomycin-resistant enterococci at their facility is similar to that reported by many others.²⁻⁴ It would be interesting to know what the compliance rate of health care workers was when they implemented the infection-control measures throughout the hospital. Many studies have documented poor rates of compliance with infection-control recommendations²⁻⁴; this may explain why their outbreak was not terminated until they placed all the patients colonized with vancomycin-resistant enterococci on one ward. Trying to control vancomycin-resistant enterococci throughout an institution is much more difficult⁴ than isolating all such patients on a single ward.^{2,4}

Thus, it is not clear in this instance whether improved rates of compliance by health care workers or the use of the PCR test was responsible for controlling vancomycin-resistant enterococci. We are unaware of any data that show that either the detection of patients with low levels of vancomycin-resistant enterococci (presumably not detected by culture and probably at lower risk for transmitting the pathogen to others) or the more rapid detection of patients colonized with vancomycin-resistant enterococci (one day with PCR as compared with two to three days with culture) results in decreased transmission. On the other hand, the requirements for technical expertise and the cost of PCR are greater than those of routine culture. As an alternative, some of the facilities in the Siouxland region isolated high-risk patients until their vancomycin-resistant enterococci status was known (thereby implementing prevention measures early).

Regardless of the approach, our data and those of Roger et al. demonstrate that vancomycin-resistant enterococci (and presumably other antimicrobial-resistant pathogens) can be controlled by the use of active screening and enhanced infection-control precautions. These examples should encourage efforts by others to control the transmission of these pathogens.

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1. Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practice Advisory Committee (HICPAC). *MMWR Morb Mortal Wkly Rep* 1995;44 (RR-12):1-13.
2. Shay DK, Maloney SA, Montecalvo M, et al. Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. *J Infect Dis* 1995;172:993-1000.
3. Morris JG Jr, Shay DK, Hebden JN, et al. Enterococci resistant to multiple antimicrobial agents, including vancomycin: establishment of endemicity in a university medical center. *Ann Intern Med* 1995;123:250-9.
4. Montecalvo MA, Jarvis WR, Uman J, et al. Infection-control measures reduce transmission of vancomycin-resistant enterococci in an endemic setting. *Ann Intern Med* 1999;131:269-72.

Spontaneous Intracerebral Hemorrhage

To the Editor: Qureshi et al., in their review of spontaneous intracerebral hemorrhage (May 10 issue),¹ point out that a low Glasgow Coma Scale score, a hematoma of large volume, and the presence of ventricular blood on the initial computed tomographic (CT) scan of the brain consistently predict a high mortality rate. Genetic determinants of outcome after acute brain injury may provide future opportunities for successful medical intervention. It has been well established that patients carrying the $\epsilon 4$ allele of the apolipoprotein E gene have a poorer outcome after acute head injury than those who do not carry $\epsilon 4$.² This remains true after adjustment for age, Glasgow Coma Scale scores, and CT findings. Evidence is emerging that the apolipoprotein E $\epsilon 4$ allele is also associated with a worse outcome in intracerebral hemorrhage³⁻⁵ but not ischemic stroke,⁴ although the mechanism underlying the association in intracerebral hemorrhage (a local brain effect or a systemic effect) remains to be established.

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1. Qureshi AI, Tuhim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. *N Engl J Med* 2001;344:1450-60.
2. Teasdale GM, Nicoll JA, Murray G, Fiddes M. Association of apolipoprotein E polymorphism with outcome after head injury. *Lancet* 1997;350:1069-71.
3. Alberts MJ, Graffagnino C, McClenny C, et al. ApoE genotype and survival from intracerebral hemorrhage. *Lancet* 1995;346:575.
4. McCarron MO, Muir KW, Weir CJ, et al. The apolipoprotein E $\epsilon 4$ allele and outcome in cerebrovascular disease. *Stroke* 1998;29:1882-7.
5. Nicoll JAR, McCarron MO, Weir CJ, et al. Apolipoprotein E polymorphism and in-hospital mortality following intracerebral hemorrhage. *Neurology* 2000;54:Suppl 3:A386-A387.

To the Editor: What Qureshi and colleagues fail to address is the optimal treatment of patients with devastating deficits, those at the extremes of age, or those with serious coexisting illnesses for whom a return to any form of independent existence is impossible. Do we not have a duty as physicians to provide compassionate, palliative care to these patients, rather than assiduously prolong their life through the indignities of such procedures as tracheostomy and nasogastric feeding? I do not believe that the complexities of management options for this group of patients can be dismissed in a box in an algorithm that says that if there is no improvement within 14 days a tracheostomy should be performed. My fear, however, is that many will believe that reviews such as this, published in the *Journal*, represent the standard of care, deviation from which would represent malpractice.

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To the Editor: In the review article by Qureshi et al., the discussion of risk factors does not mention or refer to a possible increased risk from sustained use of substantial doses of vitamin E, warfarin, or aspirin (or other nonsteroidal antiinflammatory drugs, such as cyclooxygenase-2 inhibitors). Is there evidence that any of these increases the risk of intracerebral hemorrhage?

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The authors reply:

To the Editor: We agree with O'Leary that treatment strategies and patient care need to be individualized according to circumstances. There are no objective data to define precisely the severity of disease and its interaction with important factors such as advanced age and coexisting illnesses. The information and algorithms that we provide in our article are meant to serve as general principles if maximal care is to be undertaken. We agree that in individual patients who have other medical conditions that preclude any reasonable chance of meaningful recovery, other options, such as the withdrawal of care and do-not-resuscitate status, should be fully discussed with the family.

Waugh points out other factors, related to medication and dietary intake, that may influence the risk of intracerebral hemorrhage. Long-term warfarin use is associated with an increase in the risk of intracranial hemorrhage by a factor of 7 to 10, with an absolute incidence of warfarin-associated intracranial hemorrhage of approximately 1 percent per year.¹ Fihn et al.² reported a rate of intracerebral hemorrhage of 0.5 per 100 patient-years of treatment in an analysis of 928 patients treated in anticoagulation clinics. Long-term aspirin use is associated with an estimated excess incidence of one hemorrhage per 1000 persons treated. Saloheimo et al.³ reported an increased risk of intracerebral hemorrhage in patients who use aspirin, particularly in association with epistaxis. With regard to vitamin E intake, Hirvonen et al.⁴ were unable to find an association between dietary vitamin E intake and new intracerebral hemorrhage in a study of 26,593 male smokers followed for 6.1 years.

McCarron and Nicoll appropriately point out the emerging evidence suggesting that genetic factors may influence outcome after intracerebral hemorrhage. In an excellent study by McCarron and colleagues of 102 patients with intracerebral hemorrhage,⁵ patients with the apolipoprotein E $\epsilon 4$ allele were found to have a higher mortality rate (38 percent) than those without it (24 percent). The in-hospital mortality rate was 14 percentage points higher in the patients with an apolipoprotein E $\epsilon 4$ allele than in those without it (a relative increase of 58 percent). The effect of the apolipoprotein E $\epsilon 4$ allele was independent of the volume of intracerebral hemorrhage and edema. There is a substantial up-regulation of apolipoprotein E in the brain after hemorrhagic insults.⁵ The immunomodulatory, antioxidant, and neurotropic effects of apolipoprotein E are isoform-specific,⁵ and therefore, the presence of a particular isoform of apolipoprotein E (that encoded by the $\epsilon 4$

allele) may reflect the brain's potential for recovery after injury.

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2. Fihn SD, McDonnell M, Martin D, et al. Risk factors for complications of chronic anticoagulation: a multicenter study. *Ann Intern Med* 1993;118:511-20.
3. Saloheimo P, Juvela S, Hillbom M. Use of aspirin, epistaxis, and untreated hypertension as risk factors for primary intracerebral hemorrhage in middle-aged and elderly people. *Stroke* 2001;32:399-404.
4. Hirvonen T, Virtamo J, Korhonen P, Albanes D, Pietinen P. Intake of flavonoids, carotenoids, vitamin C and E, and risk of stroke in male smokers. *Stroke* 2000;31:2301-6.
5. McCarron MO, Hoffmann KL, DeLong DM, Gray L, Saunders AM, Alberts MJ. Intracerebral hemorrhage outcome: apolipoprotein E genotype, hematoma, and edema volumes. *Neurology* 1999;53:2176-9.

Controlling Health Care Expenditures

To the Editor: Blumenthal, in his excellent article on controlling health care expenditures (March 8 issue),¹ did not discuss the variation in expenditures across states and regions. With Health Care Financing Administration data, it can be calculated that per capita personal health care expenditures ranged from \$2,760 in Idaho to \$4,889 in Massachusetts in 1998,² and much of this variation persists after adjustment for factors such as residence in one state but receipt of health care in another.^{3,4} There is no evidence that people who live in states with higher expenditures are more healthy than those who live in states with lower expenditures.

It is possible that reducing this variation could be part of a strategy to control overall health care spending. Wennberg, for example, has estimated that a Medicare pharmacy benefit of \$450 per person (a total of about \$20 billion) could be funded by reallocating Medicare Part A and Part B dollars from hospital-referral regions with expenditures that are higher than the moderate level of expenditures in the Atlanta region.⁵

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2. State health care expenditures: personal health care, 1998. Baltimore: Health Care Financing Administration. (Accessed August 17, 2001, at <http://www.hcfa.gov/stats/nhe-oact/stateestimates/tables98/>.)
3. Basu J, Lazenby HC, Levit KR. Medicare spending by state: the border-crossing adjustment. *Health Care Financ Rev* 1995;17:219-41.
4. Kindig DA, Libby DL. Setting state health spending limits. *Health Aff (Millwood)* 1994;13(2):288-9.

5. Wennberg JE. A strategy for creating a pharmacy benefit by reallocating Medicare spending. Testimony to Congress, March 12, 1999.

To the Editor: The conventional wisdom about health care expenditures fails to acknowledge the possibilities that expenditures for services with no measurable health benefits might be rational consumption expenditures and that expenditures for consumption-type health care services could justifiably increase more rapidly than the gross domestic product.

Pure consumption-type health care expenditures are those that increase consumer satisfaction in the absence of measurable improvements in health. For example, prenatal ultrasound screening is not a cost-effective use of resources for low-risk mothers, yet ultrasound screening remains a popular benefit.¹ Low-risk mothers want ultrasound screening because of the immediate peace of mind they expect the results will bring, not because they expect any improvements in health for themselves or their infants.

Many of the remedies for our rising health care expenditures cannot succeed if consumers want to spend their rising incomes on consumption-type health care services. Any proposed reform that does not take into account the value to consumers of these expenditures will fail.

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To the Editor: Blumenthal discusses three strategies for reducing health care spending: strengthening market forces, strengthening government controls, and improving the management of health care services. A strategy not discussed by Blumenthal but of greater potential value in reducing health care costs is to promote patients' accountability for health care. For example, the costly medical complications of obesity, injuries from alcohol-induced automobile collisions, high-risk sexual behavior, and smoking are almost entirely preventable. The three strategies discussed by Blumenthal are unlikely to reduce expenditures as much as personal accountability is.

In addition, evidence that strengthening government controls reduces health care costs is frequently based on nonpayment or underpayment to physicians and hospitals. Nonpayment or underpayment for necessary medical services is not an effective method to control costs.¹

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To the Editor: A patient requested that I order a follow-up magnetic resonance imaging (MRI) study of his cervi-

cal spine. He had not experienced any increase in neck pain and had no neurologic deficits or new symptoms. He said that he had already met his insurance deductible for 2001 and was curious about what changes, if any, had occurred since the initial MRI study, performed six months earlier. He claimed that the test would cost him nothing, and therefore he wanted me to schedule it.

On a daily basis, family doctors prepare to write a prescription for 10 to 15 Claritin (loratadine) tablets to alleviate the symptoms of rhinitis. But the patient says, "It will cost me \$15 for up to 90 pills. I will use the Claritin eventually. Just make that prescription for 90 with a refill."

These are examples of reimbursement policies that increase the costs of health care delivery. The patient and doctor are both insulated from the costs of care. The doctor wishes to end the visit on a positive note. The patient wishes to obtain the most comprehensive service at the lowest cost.

After a copayment has been made or a deductible has been met, expenditures are typically covered in full by health insurance plans. One way to control expenditures is to require that health insurance plans cover only a fraction of the incremental cost of each service. Patients will then weigh the personal cost of treatments. Some might suggest that capitation should be used to address these cost issues. However, capitation only makes the physician an agent of the insurance industry. The physician becomes the adversary of each patient rather than the patient's advocate.

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Dr. Blumenthal replies:

To the Editor: Drs. Kindig and Jayakumar correctly highlight the wide variation in expenditures among regions of the United States. Presumably, some areas with high expenditures have overutilization, and if it were reduced or eliminated, health care expenditures could be reduced. However, capturing these potential savings would not be easy. Devising interventions that reduce inappropriate care without also reducing appropriate care has been difficult, in part because the mechanisms often involve administrative or fiscal approaches (utilization review or capitation) that physicians and patients find problematic. Indeed, managed care can be seen as a national strategy to reduce unjustified variation, a strategy that has now been rejected as overly intrusive. This is one reason why market-based approaches, which put the onus on the patient to reduce the use of services, have become increasingly popular, for better or worse.

Dr. Woodward provides the theoretical rationale for this market-based approach by noting that health care services are sometimes used as pure "consumption goods." One way to limit the use of consumption goods is to ensure that consumers incur the cost of these services and thus can make trade-offs between the benefits of health care and those of other consumption goods. However, some health care services are not typical consumption goods, but necessities. When consumers pay more out of pocket for health care services, low-income and chronically ill patients find themselves forgoing necessities as well as luxuries. This is why it is difficult to obtain political consensus on market-based

strategies to reduce the use of health care services in the absence of guarantees of universal access to care.

Dr. Kirkland argues for increased personal accountability for high-risk behavior as a strategy for controlling health care expenditures. This strategy is promising in theory but untested in practice and potentially problematic. Some types of behavior that Dr. Kirkland believes to be “almost entirely preventable” may well result from a genetic predisposition to self-destructive behavior, including addiction to alcohol or nicotine. Appropriate treatment of such behavior may be very cost effective but may not reduce expenditures in the short term. Penalizing persons who are genetically disposed to high-risk behavior (e.g., by charging higher insurance premiums) creates ethical problems.

The scenarios described by Dr. Guttler undoubtedly occur often. He is correct in stating that cost sharing by patients — a market-based strategy — is a potentially effective deterrent. The problem, as I noted, is to create a cost-sharing program that takes patients’ ability to pay and disease status into account, in order to ensure an equitable health care system.

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Littoral-Cell Angioma as a Cause of Splenomegaly

To the Editor: Littoral-cell angioma is a rare primary tumor of the spleen.¹ Considered a benign condition, littoral-cell angioma arises from the normal littoral cells lining the sinus channels of the splenic red pulp.

A 59-year-old woman with a six-month history of fatigue, low-grade fever, weight loss, sweats, and diffuse abdominal pain was admitted for an elective splenectomy. Physical examination revealed a palpable spleen. All laboratory tests were normal. An enhanced computed tomographic scan of the abdomen disclosed an enlarged spleen with multiple scattered low-attenuation nodular masses (Fig. 1). The 430-g resected spleen (16 by 13 by 7 cm) had a nodular surface. Cut sections revealed a spongy appearance and multiple nodular lesions measuring from 0.2 to 1.0 cm in diameter. Microscopically, the lesions consisted of anastomosing vascular channels, often with papillary projections and cyst-like spaces (Fig. 2). They were lined with endothelial cells showing hemophagocytosis. These cells were positive for both vascular (CD31) and histiomonocytic (CD68) markers. No atypical cells or cells in mitosis were seen. The results of karyotyping of spleen-cell suspensions were normal. Bone marrow and liver biopsies were normal. Twenty-four months after surgery, the patient was asymptomatic.

The combination of morphologic and immunohistochemical analyses showing a hybrid endothelial–histiocytic phenotype established the diagnosis of littoral-cell angioma.¹ Primary tumors of the spleen other than lymphoid and hematologic tumors are quite rare, and littoral-cell angioma should be considered in the differential diagnosis of multinodular splenomegaly.²⁻⁴ There may be similar findings with lymphomas, metastatic disease, some disseminated infections, and sarcoidosis.



Figure 1. Enhanced Computed Tomographic Scan Showing an Enlarged Spleen with Multiple Low-Attenuation Nodular Masses.

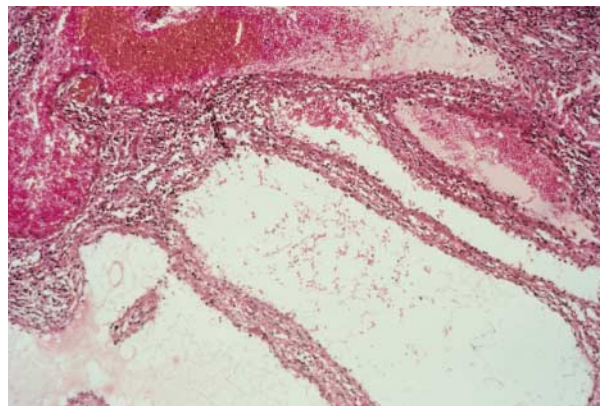


Figure 2. Spleen Specimen Showing Anastomosing Vascular Channels, with Papillary Projections and Cyst-like Spaces (Hematoxylin and Eosin, $\times 250$).

Although littoral-cell angioma itself is apparently benign and splenectomy is curative, one third of the previously reported cases⁵ were associated with cancers of visceral organs or malignant lymphomas. For this reason, we recommend close clinical follow-up of patients who have received the diagnosis of littoral-cell angioma.

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1. Falk S, Stutte HJ, Frizzera G. Littoral cell angioma: a novel splenic vascular lesion demonstrating histiocytic differentiation. *Am J Surg Pathol* 1991;15:1023-33.

CORRESPONDENCE

2. Arber DA, Strickler JG, Chen YY, Weiss LM. Splenic vascular tumors: a histologic, immunophenotypic, and virologic study. *Am J Surg Pathol* 1997;21:827-35.
3. Oliver-Goldaracena JM, Blanco A, Miralles M, Martin-Gonzalez MA. Littoral cell angioma of the spleen: US and MR imaging findings. *Abdom Imaging* 1998;23:636-9.
4. Sauer J, Treichel U, Kohler H-H, Schunk K, Junginger T. Uferzellang-

iom: eine seltene Differentialdiagnose von Milztumoren. *Dtsch Med Wochenschr* 1999;124:624-8.

5. Bisceglia M, Sickel JZ, Giangaspero F, Gomes V, Amini M, Michal M. Littoral cell angioma of the spleen: an additional report of four cases with emphasis on the association with visceral organ cancers. *Tumori* 1998;84:595-9.

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