

SPECIAL ARTICLE

SHATTUCK LECTURE

Clinical Research to Clinical Practice — Lost in Translation?

Claude Lenfant, M.D.

Practice is science touched with emotion.

Confessio Medici
Stephen Paget, 1909

From the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md., and the Department of Health and Human Services, Washington, D.C. Address reprint requests to Dr. Lenfant at the National Heart, Lung, and Blood Institute, National Institutes of Health, 9000 Rockville Pike, Bldg. 31, Room 5A52, Bethesda, MD 20892.

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DURING THE 20TH CENTURY, ENORMOUS PROGRESS WAS MADE IN IMPROVING the health and therefore the life span of all Americans. The average life expectancy at birth increased by nearly 30 years between 1900 and 2000. Although the largest gains were made in the early part of the century, we still managed to add another 1.5 years between 1990 and 2000.

Much of our continued success in extending life expectancy over the past several decades is almost certainly due to research supported by the National Institutes of Health (NIH) and generously funded by the American public. NIH-supported research has not only made possible the development of new and improved treatments for a wide range of human diseases; it has also provided the knowledge of disease risk factors needed to formulate effective approaches to prevent them. For example, research supported by the National Heart, Lung, and Blood Institute has identified important cardiovascular risk factors, has established the effectiveness of approaches to prevent or control them, and has assessed the effectiveness of treatment interventions for established disease.

As director of the National Heart, Lung, and Blood Institute, I am especially gratified to be able to point out that the lion's share of our recent gains in life expectancy in the United States has come from reductions in rates of death from heart disease and stroke. According to data provided by the National Center for Health Statistics, life expectancy increased by six years between 1970 and 2000, and nearly two thirds of that increase can be attributed to reductions in mortality due to cardiovascular disease (Fig. 1). And although primary prevention has played an important part in the reductions, it appears, at least for coronary heart disease, that secondary prevention and other treatments have had a significantly greater effect. According to one analysis of the decline in mortality due to coronary heart disease that occurred between 1980 and 1990, the reduction was due largely to secondary prevention and other improvements in treatment, with primary prevention accounting for only one quarter of the decline.¹

Still, one might question whether we have enjoyed the maximal return on the more than \$250 billion that this country has invested in the NIH since 1950. Consider that in 2000 the life expectancy at birth for men and women in the United States lagged behind that of 22 other countries, ranging from Japan to Israel and including Canada and most of western Europe. If we view the longevity of citizens in our sister nations as an indication of what is possible in the modern world, then we must question why our reality is falling short. Some may believe that the difference between life expectancy in the United States and that in other economically developed countries is largely a manifestation of societal differences. I, however, believe the answer is this: we in the United

States, both health providers and members of the public, are not applying what we know.

Indeed, medical researchers and public and political leaders are increasingly talking about the lack of success we have had in translating research findings into medical practice and personal behavior. Regardless of the reasons cited for this phenomenon — structural, economic, or motivational — the result is the same: we are not reaping the full public health benefits of our investment in research. Given the ever-growing sophistication of our scientific knowledge and the additional new discoveries that are likely in the future, many of us harbor an uneasy, but quite realistic, suspicion that this gap between what we know about diseases and what we do to prevent and treat them will become ever wider. And it is not just recent research results that are not finding their way into clinical practice and public health behaviors; there is plenty of evidence that “old” research outcomes have been lost in translation as well.

In part 1 of *Harrison's Principles of Internal Medicine*, entitled “Introduction to Clinical Medicine,” the editors express their view that “the practice of medicine combines both science and art. . . . The role of science in medicine is clear.” What may be less clear is the “art” part of medicine. To the editors of *Harrison's*, the art of medicine is “the combination of medical knowledge, intuition and judgment.” Today, everyone recognizes that a great deal of the “knowledge” element of this combination is there for the taking; libraries cannot be built fast enough to keep up with modern scientific output. But moving this knowledge off the shelves and into practice, making it relevant and accessible to practitioners and patients, achieving a true marriage of knowledge with intuition and judgment — all this requires translation. And that is, indeed, a delicate and elusive art. Robert Frost, possibly one of the greatest American poets, contended that, “Poetry is what is lost in translation.” I think that we have to ask ourselves whether much of the output of biomedical science is also getting lost in translation — and if it is, why it is, and what we can do about it.

WHERE IS THE PROBLEM?

During the past few years, a number of publications have commented on how health might be improved if only we did a better job of applying what we have learned through research.^{2,3} The paradigm for the translation of new information from research bench

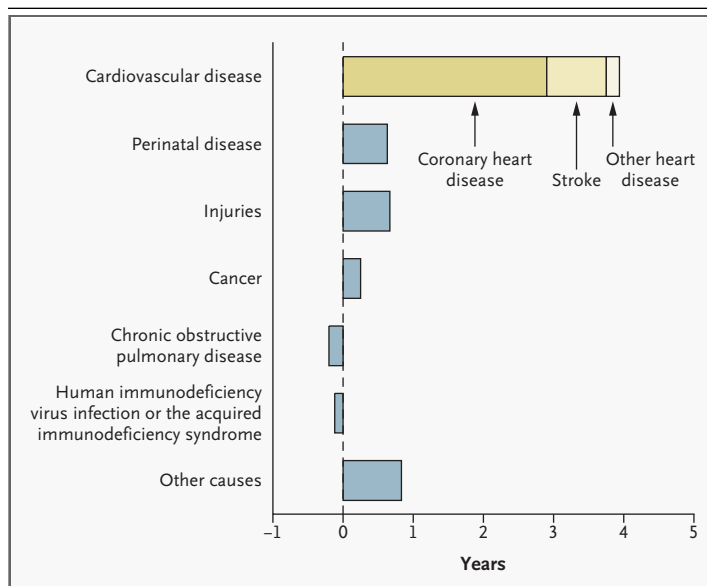


Figure 1. Change in U.S. Life Expectancy between 1970 and 2000.

Between 1970 and 2000, life expectancy in the United States increased by 6.0 years overall, with 3.9 years of the increase due to reductions in mortality from cardiovascular causes. The data are from the Centers for Disease Control and Prevention.

to bedside has been conceptualized by some as a highway, a “translational highway.”⁴ A recent article identified some of its roadblocks and detours and offered challenging solutions.⁵ However, that analysis and most of the others that have attempted to address the issue have focused only on the broad, high-speed part of the highway — that is, the part that is concerned with taking the findings of basic research and translating them into clinical investigations, and not on the last and perhaps most important segment, the segment that is concerned with taking the findings of clinical investigations and translating them into the practice of medicine at the community level.

In reality, most medical care is delivered in local health systems, including the private and group offices of general practitioners or specialists. This is where the highway reaches its end and divides into a number of smaller avenues and lanes, and it is also where vehicles and concepts may get lost.

In our efforts to take a systematic and careful look at how we translate research results into clinical medicine and public health, we must consider the environment or neighborhood in which healing and disease prevention take place. In this context, there are effectively several levels of activity at

which translation occurs, including the behavior of physicians and that of patients. Is translation at these levels successful? The following examples seem to cast some doubt.

THE PHYSICIAN AND TRANSLATION

Let us first consider the extent to which physicians' behavior reflects research findings. In 1981, the results of the β -Blocker Heart Attack Trial were reported by way of a clinical alert published in the *Journal of the American Medical Association*.⁶ Actually, this announcement was made six months before the originally scheduled end of the trial, because by that time the findings had already conclusively established the benefits of beta-blockers for patients who were recovering from myocardial infarction. Subsequently, other reports corroborated the findings unequivocally. Yet in 1996, 15 years after the results of the β -Blocker Heart Attack Trial had been made known, beta-blockers were being prescribed for only 62.5 percent of patients who had had a myocardial infarction.⁷

Likewise, since the late 1980s, numerous studies have demonstrated the benefits of cholesterol lowering in patients with coronary heart disease. However, data from a national sample show that only half to three quarters of patients who have had a myocardial infarction are even being screened for elevated serum cholesterol levels, much less being prescribed cholesterol-lowering regimens.⁸

A third example is the use of aspirin as a cardiovascular drug. Research has shown that aspirin is highly effective when given as short-term therapy for acute myocardial infarction, as therapy for unstable angina, and as long-term, secondary preventive therapy in a wide range of patients with established cardiovascular disease.⁹ Nonetheless, according to data from two independent representative samples of visits to office-based physicians in the United States, it appears that as late as 2000, aspirin was being prescribed for at most one third of patients with coronary artery disease for whom there were no contraindications to its use.¹⁰

These three examples of relatively simple, and certainly not prohibitively expensive, practices show that we have a problem in getting providers to apply knowledge gained through research. In this case, it is truly an issue that develops at the end of the highway, not at the level where research outcomes are produced. Admittedly, it is hard to know and evaluate the reasons for this situation.

Let us move on to an example of a more complex treatment: percutaneous transluminal coronary angioplasty, which is of interest because it demonstrates both the underuse and possible overuse of a therapeutic strategy. It is a more difficult situation to evaluate because the procedure is performed by specialists, albeit not all of them in academic centers or tertiary hospitals. Research results have consistently shown marked benefits of early intervention to achieve reperfusion in patients with acute myocardial infarction. With the use of these research data, treatment guidelines were developed and promulgated jointly by the American College of Cardiology and the American Heart Association in 1996¹¹ and were reissued in revised form in 1999.¹² The guidelines advocate rapid treatment with percutaneous transluminal coronary angioplasty or fibrinolysis, with the former being preferentially recommended. Yet recent data from the National Registry of Myocardial Infarction show that in the last quarter of 2002, nearly one third of all patients nationwide who presented with an acute myocardial infarction and who were eligible for reperfusion received neither of these therapies.¹³ By itself, this failure to take advantage of a beneficial treatment is unsettling, but it is even more disturbing when one notes that the current rate of under-treatment is actually identical to the rate in 1994.¹⁴ These observations suggest that despite widespread agreement that early reperfusion is imperative and despite the dissemination of guidelines for its use, patients were no better off in 2002 than they had been eight years earlier.

On the flip side of the coin, a recent review of Medicare records in five geographically distributed states found that percutaneous transluminal coronary angioplasty was performed inappropriately, on average, in 14 percent of patients (range, 4 to 24 percent).¹⁵ Similarly, a study of coronary-artery bypass grafting in four states showed inappropriate use in 10 to 14 percent of patients.¹⁵ Quite a lot, it seems, is being lost in translation.

PATIENTS' BEHAVIOR

From the viewpoint of public health, whatever conclusions one can draw from the examples cited above must be balanced by an understanding of the extent to which patients assume (or fail to assume) their share of responsibility for their health. In fact, in a wide range of situations, patients themselves are the indispensable players. At one extreme

is the case of adherence to a prescribed medication regimen.

Returning to aspirin as an example, let us consider the findings of a study on its use as reported by patients who had undergone coronary angiography at a major medical center, had documented coronary artery disease, and had been routinely followed up by means of a mailed questionnaire.¹⁶ Even in this population of presumably highly motivated patients with access to state-of-the-art medical care, reported daily aspirin use was only about 60 percent in 1995 and 80 percent in 1999. And this is a therapeutic regimen that is easy, painless, and cheap.

An analogous situation, but one with a major difference, is that of antihypertensive medications: these medications are used to treat a condition that may not yet have caused any illness, rather than to prevent the recurrence of a life-threatening event. During the past two or three decades, new classes of antihypertensive drugs have been developed, and several specific brands in each class are now on the market. As a group, antihypertensive medications are among the most frequently taken prescription drugs in the United States today.¹⁷ Yet the rates of blood-pressure control in the general population of patients with hypertension are shockingly poor, as reported by successive National Health and Nutrition Examination Surveys.

Is the reason for this that doctors are not prescribing the appropriate antihypertensive medications or that patients are not taking them? In truth, it is probably both, but lack of patient compliance appears to be a substantial part of the problem. A 1996 study reported that 47 percent of patients failed to take their antihypertensive medications as prescribed.¹⁸ A 1998 study of a cohort of 21,723 patients showed that between 29 and 56 percent of them, depending on the class of drug used, discontinued their antihypertensive therapy at 12 months and that only 6 to 9 percent switched to another class of drug.¹⁹

INTERVENTION BY PHYSICIANS TO KEEP PATIENTS ON THE ROAD

It is tempting to throw up our hands in despair when patients fail to follow doctors' orders — heaven, as they say, helps those who help themselves — but health care providers can certainly do much to correct this situation if they work at it. Indeed, although it admittedly reflects a special circumstance, one

study showed that with very careful monitoring and appropriate adjustment of the treatment regimen, physicians practicing in communities, not in academic centers, were able to increase the rate of blood-pressure control in a cohort of more than 42,000 patients from 27 percent to 66 percent (Fig. 2).²⁰ If there is a conclusion to be drawn from this observation regarding hypertension treatment, it is that applying known precedents or just using common good practice can make an enormous difference in patient compliance. Admittedly, the challenges associated with modifying patients' behavior are enormous and extend far beyond persuading them to take their pills. But difficulties do not constitute a dispensation. As physicians, we still have to try.

Consider obesity, for example — a modern epidemic that threatens to undo decades of progress against coronary heart disease. Extensive public health research has established some very straightforward measures to address this problem, and these research outcomes have been widely publicized for more than a decade. Yet, astonishingly enough, in 1999 one study reported that only 42 percent of 12,835 obese adults had been advised by their physician to lose weight.²¹ Similarly, the value of regular exercise has been the subject of considerable research. The health benefits of regular exercise for most people have been documented, as have been the debilitating effects of being sedentary. Yet a study of 9299 people, also published in 1999, reported that only 34 percent had been counseled about exercise during a regular visit to their physician.²²

CLOSING THE LOOP

What all the aforementioned examples have in common should be clear. The practices no longer require research to demonstrate efficacy and effectiveness; as a practical matter, everything that needs to be known is already known. Furthermore, translation of these research findings into actions that can be used in practice is very simple. In addition, because the actions are not prohibitively expensive, cost is not an obstacle, and in fact, cost effectiveness could be advanced as one more reason for their widespread adoption. Yet their application in the real world is not what it should be, and we need to find out why and to try new approaches to change this situation.

In fact, there is evidence that substantial im-

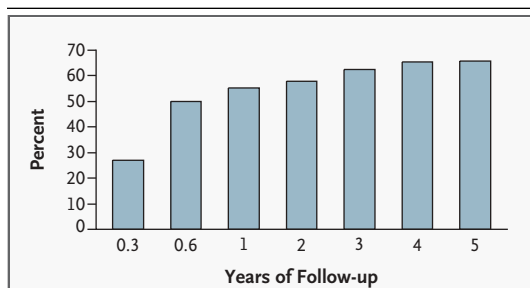


Figure 2. Control of High Blood Pressure in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

The values shown represent ALLHAT data from 42,418 patients in 623 health care centers. ALLHAT showed that the rate of blood-pressure control (i.e., a blood pressure <140/90 mm Hg) increased with the duration of participation in the trial. Adapted from Cushman et al.²⁰

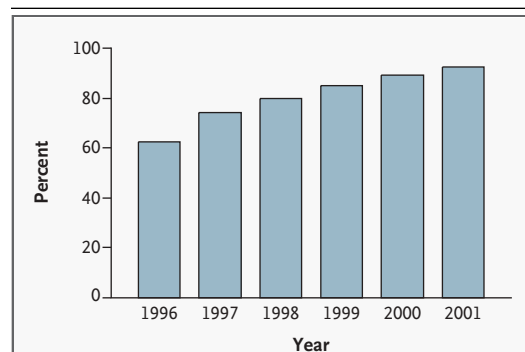


Figure 3. Beta-Blocker Treatment after Myocardial Infarction in Managed-Care Plans.

Among managed-care plans reporting data to the National Committee for Quality Assurance, the prescription of beta-blockers for patients who had an acute myocardial infarction increased every year from 1996 (62.6 percent of patients) to 2001 (92.5 percent of patients). The data are from the National Committee for Quality Assurance.^{7,8,23}

Improvements can be achieved simply by increasing the level of accountability of medical practice. For example, the National Committee for Quality Assurance (NCQA) provides a model of action with its Health Plan Employer Data and Information Set (HEDIS) measures. These tools are currently used by the majority of U.S. health plans to assess the quality of care and service. Of course, the value of these tools depends largely on the quality and acceptability of the benchmarks that are chosen to measure performance. NCQA benchmarks are based on widely accepted research findings that are analyzed and presented as recommendations or “guidelines” by relevant professional organizations such as the American College of Cardiology and the American Heart Association or by other authoritative sources, such as the various components of the NIH. In the latter case, the institutes themselves do not produce the recommendations, but they sponsor evidence-based consensus-development activities involving the participation of many interested professional groups.

During the past few years, significant improvements in the day-to-day use of research outcomes have been reported by the NCQA and its members.²³ For example, the rate of beta-blocker treatment among patients who had had a myocardial infarction rose from 62.5 percent in 1996 to 92.5 percent in 2001 (Fig. 3). Likewise, the rate of appropriate blood-pressure control among patients with hypertension increased from 39.0 percent in 1999 to 55.4 percent in 2001 — still not good, but better. Among

patients with asthma, the use of appropriate medications increased from 57.7 percent in 1999 to 65.6 percent in 2001.

It seems quite likely that the public availability of information on the performance of health plans has been a major contributor to the success of HEDIS measures. However, it is also likely that their success reflects the commitment of relevant professional societies to work together to reach consensus on the guidelines that underlie the measures. Thanks to their efforts, practitioners are less frequently faced with the need to select from or to reconcile potentially conflicting recommendations. This is not to overlook or undermine the role of independent judgment; recommendations are, after all, recommendations, even though they are often misnamed “guidelines.” The art of medicine will always be central to its responsible practice.

I believe, however, that professional organizations must also assume a greater role, if not the leading role, in our collective efforts to realize the full public health benefits of research by minimizing what gets lost in translation. Developing and publishing practice recommendations is an extremely valuable first step. As important, or more important, is ensuring that these recommendations actually influence the way medicine is practiced. Fortunately, there are encouraging signs that professional societies are moving beyond mere promulgation of

practice guidelines toward direct involvement in efforts to see that they are implemented. For example, the American Heart Association and the American Stroke Association recently announced that they have joined with the NCQA to recognize physician excellence in ambulatory cardiovascular and stroke care. The voluntary program, which is designed to assess physicians' performance on the basis of accepted clinical guidelines, is modeled on a successful collaborative effort initiated in 1997 by the NCQA and the American Diabetes Association, the Diabetes Physician Recognition Program. This program allows individual physicians and medical groups to submit performance data through the Internet for comparison with threshold values on a set of selected HEDIS measures that were carefully defined and tested for their relation to improved care for people with diabetes. Physicians and groups found to meet or exceed the threshold values are recognized on a dedicated page of the American Diabetes Association Web site, and callers to the association's toll-free number are referred to the list of recognized physicians.

Although there is no way to distinguish the effect of the Diabetes Physician Recognition Program from that of the overall HEDIS effort, clear improvements in diabetes care as reported by the NCQA were seen between 1999 and 2001. During those three years, the percentage of patients with diabetes in whom glycosylated hemoglobin was measured increased from 75.0 percent to 81.4 percent; the percentage in whom glycosylated hemoglobin was poorly controlled decreased from 44.9 percent to 36.9 percent; those in whom the complete lipid profile was determined increased from 69.0 percent to 81.4 percent; those in whom acceptable lipid control was achieved increased from 44.3 percent to 50.9 percent; those who underwent nephropathy screening increased from 36.0 percent to 46.3 percent; and those who underwent comprehensive eye examinations increased from 45.4 percent to 52.0 percent. These increases are all reflections of progress.

Of course, the focus on translation at the level of medical practice must not come at the expense of improving the entire translational highway. As has been widely recognized, we are today on the threshold of a new era in which gene-centered medicine will almost certainly be the star player. Although several basic-science pursuits such as immunology, cell biology, and molecular biology have been highly productive, genomic research clearly dominates cur-

rent interests and expectations. From it, a new type of medicine is being born: genetic medicine. The expectations are many, and already studies are reporting personalized prevention and treatment of specific conditions on the basis of individual gene variations. Moreover, specific polymorphisms have been found that may help to predict how fast some conditions will progress.²⁴⁻²⁷ However, the excitement is warranted only if these discoveries are used in clinical medicine.

Many scientific and academic leaders deplore our inertia (or is it our imperfect vision?) in moving from basic to clinical research in this area, and they despair of our readiness to bridge this gap. Not all, however, agree about the steps that should be taken to remedy the situation. This debate is cogently described and analyzed in a 2002 issue of *Science* focused on "The Puzzle of Complex Diseases." Its main message is that basic science, clinical discovery, and patient-oriented research are interdependent and not necessarily successive steps.^{28,29} Using the translational-highway metaphor, we need to widen the interstate and increase the number of its lanes.

Enthusiasm for gene-centered medicine is contagious, and I am certainly not immune to it. In my view, however, the fundamental issue remains the same. Enormous amounts of new knowledge are barreling down the information highway, but they are not arriving at the doorsteps of our patients. Given that so much is lost at the real-world level, as has been demonstrated time and time again with regard to relatively simple research outcomes, I believe that our approach to all patient-oriented research should be reconsidered.

Often, investigators appear to design and implement clinical trials and demonstration-research projects without first asking what should always be the threshold question — namely, "Are the results likely to be applied in a clinical setting?" Answering this question means considering not only the cost of a proposed intervention but also the degree of risk to patients that is entailed in implementing it. This issue of who will really benefit from research results is especially critical as we look toward applications of genomic research. And we must direct our attention, our commitment, our energies, our creativity, and our resourcefulness to making sure that the beneficiaries will be the patients — all the patients. Let's be realistic: If we didn't do it with aspirin, how can we expect to do it with DNA?

We must keep our focus on the public health, as have all good medical researchers through the ages. Thomas King Chambers expressed this goal in the Goulstonian Lecture in 1850:

To us, knowledge, how good and lovely soever it be for its own sake, must always be a by-end, a step merely towards the still better and lovelier goal of "good-will towards men."

Our object, then, in reviewing these researchers, and in adding to them such obser-

vations as our own sphere of action supplies, should be to deduce from them rules of practice, to gather from the tree of knowledge fruit for the solace and refreshment of mankind.

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REFERENCES

- Hunink MG, Goldman L, Tosteson AN, et al. The recent decline in mortality from coronary heart disease, 1980-1990: the effect of secular trends in risk factors and treatment. *JAMA* 1997;277:535-42.
- Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. Washington, D.C.: National Academy Press, 2001.
- Berwick DM. Disseminating innovations in health care. *JAMA* 2003;289:1969-75.
- Schwartz K, Vilquin JT. Building the translational highway: toward new partnerships between academia and the private sector. *Nat Med* 2003;9:493-5.
- Sung NS, Crowley WF Jr, Genel M, et al. Central challenges facing the national clinical research enterprise. *JAMA* 2003;289:1278-87.
- β -Blocker Heart Attack Study Group. The β -Blocker Heart Attack Trial. *JAMA* 1981;246:2073-4.
- The state of managed care quality. Washington, D.C.: National Committee for Quality Assurance, 1997.
- The state of managed care quality. Washington, D.C.: National Committee for Quality Assurance, 1999.
- Awtry EH, Loscalzo J. Aspirin. *Circulation* 2000;101:1206-18.
- Stafford RS, Radley DC. The underutilization of cardiac medications of proven benefit, 1990 to 2002. *J Am Coll Cardiol* 2003;41:56-61.
- Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation* 1996;94:2341-50.
- Ryan TJ, Antman EM, Brooks NH, et al. 1999 Update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation* 1999;100:1016-30.
- National Registry of Myocardial Infarction. NMRI 4 quarterly data report 2002. South San Francisco, Calif.: Genentech, 2002.
- O'Connor GT, Quinton HB, Traven ND, et al. Geographic variation in the treatment of acute myocardial infarction: the Cooperative Cardiovascular Project. *JAMA* 1999;281:627-33.
- Schneider EC, Leape LL, Weissman JS, Piana RN, Gatsonis C, Epstein AM. Racial differences in cardiac revascularization rates: does "overuse" explain higher rates among white patients? *Ann Intern Med* 2001;135:328-37.
- Califf RM, DeLong ER, Ostbye T, et al. Underuse of aspirin in a referral population with documented coronary artery disease. *Am J Cardiol* 2002;89:653-61.
- Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Sloan survey. *JAMA* 2002;287:337-44.
- Lee JY, Kusek JW, Greene PG, et al. Assessing medication adherence by pill count and electronic monitoring in the African American Study of Kidney Disease and Hypertension (AASK) Pilot Study. *Am J Hypertens* 1996;9:719-25.
- Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. *Clin Ther* 1998;20:671-81.
- Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Clin Hypertens (Greenwich)* 2002;4:393-405.
- Galuska DA, Will JC, Serdula MK, Ford ES. Are health care professionals advising obese patients to lose weight? *JAMA* 1999;282:1576-8.
- Wee CC, McCarthy EP, David RB, Phillips RS. Physician counseling about exercise. *JAMA* 1999;282:1583-8.
- The state of health care quality. Washington, D.C.: National Committee for Quality Assurance, 2002.
- Morrison AC, Doris PA, Folsom AR, Nieto FJ, Boerwinkle E. G-protein beta3 subunit and alpha-adducin polymorphisms and risk of subclinical and clinical stroke. *Stroke* 2001;32:822-9.
- Turner ST, Schwartz GL, Chapman AB, Boerwinkle E. C825T polymorphism of the G protein beta(3)-subunit and antihypertensive response to a thiazide diuretic. *Hypertension* 2001;37:739-43.
- Wu KK, Aleksic N, Ahn C, Boerwinkle E, Folsom AR, Juneja H. Thrombomodulin Ala455Val polymorphism and risk of coronary heart disease. *Circulation* 2001;103:1386-9.
- Small KM, Wagoner LE, Levin AM, Kardias SLR, Liggett SB. Synergistic polymorphism of β_1 - and α_2 -adrenergic receptors and the risk of congestive heart failure. *N Engl J Med* 2002;347:1135-42.
- Willett WC. Balancing life-style and genomics research for disease prevention. *Science* 2002;296:695-8.
- Rees J. Complex disease and the new clinical sciences. *Science* 2002;296:698-700.

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