academic institutions, and business groups. The campaign to pass it is financed largely by Jim and Virginia Stowers, founders of the Stowers Institute for Medical Research in Kansas City, which hopes to become a powerhouse of stem-cell research. Rubin, who heads a pro-science coalition in St. Louis, maintains that the quality of science, medical care, and the biotechnology industry in Missouri are at stake. "If our state were to pass laws that threaten to jail scientists merely for . . . seeking cures, it would have a devastating effect on our ability to continue to attract the best and the brightest," he said.

Danforth, who has just published a book about the influence of religion on politics in the United States, said he sees a moral distinction between abortion and embryonic stem-cell research. The early-stage embryos from which stem cells are derived "have not been implanted in a uterus. They cannot become walking, talking, breathing human beings," he said. In Danforth's view, linking stem-cell research to the hope of cures is both justified and politically necessary in order to pass the amendment. "What we're saying is researchers think this is very promising," he said. "The point is to find cures. The clearer the connection between research and results that you can make politically, the better off you are."

In California, the political debate over stem-cell research is largely over, and the state-funded scientific enterprise is poised to begin. In approving the loan to CIRM, Schwarzenegger sought to gain political capital in his race for reelection against Democratic state treasurer Phil Angelides, a longtime supporter of the stem-cell initiative. CIRM recently issued requests for proposals for seed grants, designed to attract new investigators with funding of up to $200,000 per year for 2 years, and for comprehensive grants, providing up to $400,000 per year for 4 years to scientists with a record of accomplishment in human embryonic stem-cell research or a closely related field. "We are expecting an onslaught," said CIRM's Hall, who hopes to announce the grant recipients by March. CIRM also plans to fund 15 California facilities that will provide laboratory space and technical support for culturing human embryonic stem cells, permitting researchers to do projects with nonapproved stem-cell lines.

Last April, CIRM won an important victory when an Alameda County Superior Court judge rejected lawsuits brought by taxpayer and religious groups challenging the organization's legality. The decision has been appealed, and the case may reach the California Supreme Court, but Hall hopes it will be resolved by the end of 2007. Meanwhile, at research institutions around the state, the mood is upbeat. Hall listed eight established stem-cell investigators who have moved to California in the past 2 years or are preparing to do so, including one from Australia and others from Harvard University, Johns Hopkins School of Medicine, Washington University in St. Louis, the University of Michigan, and the Hospital for Sick Children in Toronto. "Everybody's ready to go," said Hall. "People are excited. The phone is ringing off the hook here."

Dr. Okie is a contributing editor of the *Journal*.

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America's New Refugees — Seeking Affordable Surgery Offshore

Arnold Milstein, M.D., M.P.H., and Mark Smith, M.D., M.B.A.

The mainstream media have begun to highlight the plight of some new refugees: seriously ill Americans who receive treatment at advanced private hospitals in low-income countries. These patients are not "medical tourists" seeking low-cost aesthetic enhancement. They are middle-income Americans evading impoverishment by expensive, medically necessary operations, as health care services are increasingly included in international economic trade.[1]

At a recent Senate hearing, two stories were recounted that illustrated the physical and financial perils driving patients to pursue care abroad.[2] In the first story, Howard Staab, a self-employed, uninsured, middle-aged carpenter from urban North Carolina who considered health insurance premiums unaffordable, had an

Blue Ridge Paper Products.

Courtesy of the Asheville Citizen-Times.

acute mitral-valve prolapse, and his physician recommended surgery. The estimated total fees at the nearest regional hospital were $200,000, with a 50% deposit required in advance. A sympathetic hospital employee suggested that if the patient allowed his condition to deteriorate to a life-threatening emergency, the hospital would be compelled to provide the surgery and would afterward pursue debt collection. When he shopped elsewhere in the United States, he found a still-unaffordable best price of $40,000 at a hospital in Texas. Then, faced with the need to sell the family home, the patient's son, a medical student, found a cardiovascular surgeon, Naresh Trehan, who had trained at New York University and was practicing at a new, privately funded hospital in New Delhi, India. Trehan treated Staab, who paid combined hospital and physician fees of $6,700, and Staab returned to North Carolina and to work.

Bonnie Blackley, a health benefits manager for Blue Ridge Paper Products, in Canton, North Carolina, told the second story. Rather than allow their mill to be put out of business by global competition, unionized workers had found private investors to help them buy the company. Although the company offered employees health insurance, Blackley had to pay close attention to health care spending. After implementing all conventional cost-management techniques, she decided to offer employees incentives of up to $10,000 per operation if they underwent required complex procedures, such as open-heart surgery and major joint replacements, at a credentialed hospital in India. She plans to begin with the nonunionized workforce and may later propose it in collective bargaining with unionized workers.

It is impossible to obtain trustworthy information on the magnitude of this trend in care seeking, because payments to foreign hospitals and physicians are not tracked as a distinct category in balance-of-trade statistics. But advanced hospitals in low-income countries such as India and Thailand report steady annual growth in the numbers of American patients they see. At Bangkok's Bumrungrad International Hospital, for example, 55,000 Americans were treated this past year, 30% more than in the previous year[3]; about 83% of them underwent noncosmetic treatments.

The enormous price advantage obtained by the Staab family and others seeking offshore surgery primarily reflects the lower wages paid to physicians and other health care workers in those countries. It also reflects cheaper prices offered in low-income countries by global suppliers of medical devices and other health care products.

To ensure both significant savings net of travel expenses and patients' safety, such offshore care must be limited to nonurgent, short-duration treatments costing more than $15,000 to $20,000 in the United States for conditions that aren't exacerbated by air travel; these include major cardiac and orthopedic procedures. We estimate that treatments meeting these criteria currently account for less than 2% of U.S. spending on noncosmetic health care for worker households (excluding care for U.S. residents who live along the Mexican border).

The trend is driven by the escalation of out-of-pocket spending for health care and insurance premiums beyond the grasp of low- and middle-income Americans — an escalation that is forcing many workers to forgo health care and insurance coverage. There is a direct relationship between the cost of insurance premiums as a percentage of income and the proportion of employees who decline coverage; in

some low-wage industries, more than 75% of workers who are eligible for benefits turn down employer-provided health insurance. This response is understandable: in 2006, the average health care expenditures for a family of four for the first time exceeded the entire annual earnings of a minimum-wage worker.[4] As health care spending continues to increase more rapidly than the gross domestic product, coverage is becoming unaffordable for more and more working people; the proportion of worker households doing without health insurance is growing most rapidly among middle-income workers, who are not eligible to receive state- or employer-sponsored low-income subsidies.

Unlike Americans who earn lower wages, many carpenters like Staab and paper-mill workers like those at Blue Ridge have substantial home equity and other financial assets that they want to protect from the collectors of health care debts, whose position has been strengthened by newly tightened criteria for declaring personal bankruptcy.

One important question about advanced foreign hospitals is whether their quality of care is similar to that in the average U.S. hospital. In recent years, many such hospitals have passed muster with one or both of two international quality-assessment organizations. Certification bodies accredited by the International Organization for Standardization, known as the ISO, have certified hospital quality-management programs in, for example, Mexico, India, Thailand, Lebanon, and Pakistan. The Joint Commission on Accreditation of Healthcare Organizations, which accredits most U.S. hospitals for participation in the Medicare program, has accredited more than 80 non-U.S. hospitals in India, Thailand, Singapore, China, and Saudi Arabia, among other countries, through its Joint Commission International (JCI) affiliate. Many of the ISO-certified and JCI-accredited hospitals employ physicians like Tehran who trained and often obtained board certification in the United States or another high-income country.

Since the United States and most other countries do not require their hospitals to measure and report surgical outcomes or to participate in international performance-measurement systems, it's hard to assess relative quality. We doubt, however, that the average U.S. hospital can offer better outcomes for common complex operations such as coronary-artery bypass grafting, for which several JCI-accredited offshore hospitals report gross mortality rates of less than 1%. Moreover, with respect to the patient's subjective experience, Howard Staab's wife describes her family's recent care at U.S. hospitals as far worse than that her husband received in New Delhi. However, had her husband suffered from medical negligence abroad, the avenues for redress would have proved more limited than those available in the United States.

Will the growing number of visits by U.S. citizens seeking surgery abroad adversely affect residents of developing countries? A recent analysis by a World Bank economist suggested that this risk was minimal and that the influx of revenue associated with this practice might bolster the health care industry in developing countries, providing an opportunity for them to repatriate health care professionals — who currently account for a substantial fraction of the physician and registered-nurse workforces in the United States.[5]

American physicians who are concerned about the growth of this phenomenon have two choices: they can denounce and attempt to restrict it, or they can lead and more actively support efforts by others to speed the discovery and uptake of more efficient domestic health care delivery methods. The opportunity is substantial. In a 2005 Institute of Medicine (IOM) report on the application of systems-engineering approaches to care delivery, one author estimated that 30 to 40% of current U.S. health care expenditures are wasted, primarily on the provision of services unlikely to boost patients' health status or their satisfaction and on the inefficient provision of valuable services.

Offshore surgery, which currently represents an opportunity to lower prices for at most 1 to 2% of total U.S. health care spending for worker households, is a symptom of, not a solution to, our affordability problem. The symbolism of such "offshoring" of lifesaving operations, however, should not be lost on U.S. physician–leaders. In response to the IOM's new report on pay-for-performance initiatives, they will once again consider the institute's call for the redesign of clinical work to better achieve the essential aims of health care. With regard to the aim of efficiency, low- and middle-income Americans need physicians to re-

spond quickly and affirmatively, and they need the resulting reconstructive procedure to be fundamental, rather than cosmetic.

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Surviving Sepsis — Practice Guidelines, Marketing Campaigns, and Eli Lilly

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Practice guidelines approved by expert panels are intended to standardize care in such a way as to improve health outcomes. In recent years, the developers of such standards have started grouping evidence-based interventions into "bundles," on the theory that inducing physicians to follow multiple recommendations written into a single protocol has a measurable effect on patients' outcomes. As a side effect, bundled performance measures are ready-made for use in pay-for-performance initiatives, which can base reimbursement on compliance with all the components.

Unfortunately, the development of such clusters is vulnerable to manipulation for inappropriate — and possibly harmful — ends. Seeing in these bundles a potentially powerful vehicle for promoting their products, pharmaceutical and medical-device companies have begun to invest in influencing the adoption of guidelines that serve their own financial goals. A case in point is the development of guidelines for the treatment of sepsis, which was orchestrated as an extension of a pharmaceutical marketing campaign.[1,2] Although its advocates viewed this effort as an important approach to reducing sepsis-related mortality, the campaign appears to have usurped guideline development for commercial purposes, possibly compromising highly regarded, third-party arbiters of medical quality in the process. Such intrusion into an initiative to benefit public health is of particular concern in this instance, since the drug incorporated into the performance measures was endorsed on the basis of a single controversial phase 3 trial that was still being called into question by additional studies even as the committee did its work.

In 2001, the Food and Drug Administration (FDA) approved Eli Lilly's Xigris (recombinant human activated protein C, or rhAPC, also known as drotrecogin alfa [activated]) for the treatment of sepsis. This approval was based primarily on a single phase 3 randomized, controlled trial — the Recombinant Activated Human Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study, published the same year — which showed a significant overall survival benefit at 28 days. The FDA acknowledged that there was controversy surrounding this decision, and half the members of the agency's advisory panel, pointing to methodologic and other important problems with the PROWESS study, voted to require that a confirmatory trial be performed before approval was granted. In its approval statement, the FDA recommended using rhAPC in patients deemed, on the basis of an Acute Physiology and Chronic Health Evaluation II score of 25 or more, to have a particularly high risk of death; since this criterion had not been prospectively validated, the agency asked Lilly to perform additional testing in selected subgroups. In the face of such uncertainty, initial sales of rhAPC fell short of market expectations (see timeline).[3]

To improve sales of rhAPC, in 2002, Lilly hired Belsito and Company, a public relations firm, to develop and help implement a three-pronged marketing strate-