

## Quote to note

**"There is always an easy solution to every human problem—neat, plausible, and wrong."**

—H.L. Mencken

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# Medical Ethics

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## *The technology cost blues*

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**A**lthough unwritten, it is an axiomatic law of health reform analysis that, however bleak the assessment, it should try to deliver an upbeat conclusion. My take on the problem of controlling the high cost of medical technology will, on the whole, be bleak—but my conclusion will be a function of the optimism or pessimism that readers bring to the problem.

The problem itself can be briefly stated. Health care costs are rising at an annual rate of 6% a year, a pace projected to double health care spending from \$2.2 trillion now to \$4.2 trillion in 10 years, and to lead to the bankruptcy of Medicare over the same period. The Congressional Budget Office and numerous economic studies have determined that about 50% of the annual increase can be traced to new technologies or the intensified use of older ones.

The ideal goal of cost control would be to bring the annual rise of overall costs down to the level of the annual rise of the gross domestic product, about 3% a year. Since the annual cost increase has not once in 40 years come anywhere near that goal (and has sometimes been as high as 15%), it is an intimidating aspiration to get anywhere near that target.

### False Friends

Over the years, and intensified during the presidential race, many ideas were advanced to control costs, many of which have been taken up by President Barack Obama. They have all been put forward with great optimism. At the top

of the list are information technology, technology assessment and prevention, followed closely by improved competition among insurers, disease management programs, reducing regional cost variations, reducing hospital infection rates, coordinated care of the chronically ill and reducing fee-for-service physician care.

Of all those possibilities, only technology assessment and criticism of fee-for-medicine focus directly on technology costs, although many paeans for competition included claims of cost savings. Unfortunately, for almost all of the claims of cost control those various strategies are meant to serve, under closer scrutiny most are based on scanty evidence of likely success. They might all do some good, but not necessarily and not rapidly. In the meantime, the economic baseline of costs would continue to rise.

The control of technology costs poses some acute difficulties. America is a country intoxicated with the idea of medical progress and its main beloved offspring, innovative technologies. That proclivity can be traced back to the founding fathers, many of whom looked to science to cure illness and greatly increase life expectancy. That faith is still present, exemplified in the budget of the National Institutes of Health (NIH), now over \$30 billion a year and recently increased \$10 billion by the Obama stimulus package. The NIH budget has steadily increased since

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### *Technology cost—continued from page 1*

World War II, supported with an uncommon, uncontentious bipartisanship.

The public loves technology, supports research and has come to expect it in the medical care they receive. To be sure, there is also the fact that physicians in fee-for-service medicine have many unhelpful incentives to make use of technology, and no less a fact that the pharmaceutical, biotechnological and medical device industries furiously market their products and successfully lobby against price controls. But those sources of rising costs build upon a warm and welcoming culture as its foundation.

Only the United States and New Zealand allow direct-to-consumer advertising, but no strong public voice has been raised here against it. Everything else is advertised, so why should drugs and other medical treatments be excluded from the commercial bazaar? Anyway, as the pharmaceutical industry contends, direct-to-consumer advertising is not marketing but patient education. Who can object to education? That argument works.

### **The Intrinsic Cost of Progress**

A widespread assumption about escalating health care costs is that they reflect a wasteful, undisciplined and chaotic system. Since other countries get better health outcomes for less money, there is *prima facie* evidence of its truth. There are wide and often inexplicable variations in medical costs across regions in the country and often enough from hospital to hospital in the same city. There is excessive screening and the use of imaging devices, exorbitant prices for many drugs, and many surgical and other procedures that have not been assessed for their efficacy. It is hardly surprising that complaints about waste and inefficiency have had a long history, and no less a long history of failure to make much headway against

them. Taken together, all of those cost drivers might be thought of as extrinsic causes, that is, a function of the way our system is organized (or disorganized).

Even granting the validity of the myriad complaints about our health care system, I have become increasingly struck by what I think of as the intrinsic drivers of health care costs. By that I mean rising costs that are a function of the successes, not the failures, of progress-driven medicine. Kidney dialysis is a good example of an expensive success. Even if many of the lives it saves are of poor quality, patients with renal failure usually want it, and dialysis does extend their lives. Over the years that patient population has grown enormously and has seen a steady increase in the number of elderly patients. Expensive surgery for heart disease and expensive drugs for cancer work no less to extend lives. The lives of those with lethal diseases, once quick to bring death, are now attenuated, and often for many years.

One result of these successes is what I call the mischievous perversity of medical progress. As our national health steadily improves and mortality rates decline, costs go up; as the incidence of many cancers continues to decline, the cost of caring for those who survive with cancer continues to rise; as money invested in medical research steadily grows, the cost of health care rises in parallel with it (a point acknowledged by economists); as health improves, the baseline of what the public counts as good health rises (the more good health we get, the more of it we want); and the endless innovation of new and expensive technologies aiming to keep the elderly alive still longer keeps increasing just as the baby-boom generation is beginning to retire.

### **Is There a Way Out?**

If I am correct in thinking that it is the successes of progress, not the failures and inefficiencies of our health

care system, that pose the most difficult long-range challenges, then we have a two-front struggle ahead of us. One is to find ways to hold down the costs of our present system, mainly by organizing and running it better—and I believe that universal care with strong government price controls is an imperative first step in that direction.

The other is to reconsider the idea of medical progress and to assess our enchantment with technological innovation more toughly. Just how far do we want to go in the ultimately unwinnable war against death? What is a tolerable balance between the length of life and the quality of life, and how should our research and health care delivery priorities be set to achieve it? Just how much marginal benefit in critical and chronic care patient treatment should we be willing to pay for—a few extra months of life with a lethal disease at the cost of tens of thousands of dollars? Is it a good trend for the future well-being of the country that the gap between health care spending on children and the old continues to grow?

Those are the kind of questions that should be part of our national health reform debate. But how do we get the medical profession, the health care industry and the public to take them up? That is a good question, and I have to admit I have no good answer. That's just not how we talk about health reform in this country. We are comfortable limiting the idea of reform to the managerial and organizational level, spiced up by a clash of liberal and conservative ideologies. That has not worked well in the past, and it is not likely to work well this time around. Well, at least it looks that way, but who knows, history sometimes takes surprising turns.

Daniel Callahan's recently published book is *Taming the Beloved Beast: How Medical Technology Costs Are Destroying Our Health Care System* (Princeton University Press). □





*Ask the ethicist:*

## *Who should pay for the medical care of indigent patients from other countries?*

**Q**uestion: A 37-year-old man with acute myelogenous leukemia was referred from a Caribbean island country to an American medical center for treatment because he had failed chemotherapy in his own country. He then completed induction chemotherapy, inducing a remission. He had unfavorable, high-risk cytogenetics and was a potential candidate for a stem cell transplant to prevent recurrence and possibly provide a cure.

When arrangements were being made for consultation at the transplant center approved by the Ministry of Health, the Ministry of Health of his country notified his hematologist that "there was no more money" in the budget to pay the estimated \$150,000–\$200,000 for this treatment. As a result, the transplant center refused even to see the patient. The country's consulate arranged for him to be returned to his home country without further treatment. Multiple attempts at further negotiation at several levels with the Ministry of Health were futile. Medical and nursing staff members were upset, knowing that their patient would likely die of a treatable disease. Should American medical centers simply pay for the necessary expensive treatment of foreign nationals in such cases?

**R**esponse: When decisions are made based wholly or in part on financial constraints, true cost is usually not considered accurately. The cost cited of \$150,000–\$200,000 undoubtedly represents the total estimated "full cost" of the procedure. The majority of cost in hospital-based procedures tends to be fixed cost, i.e., proceeding with this transplant would add little to the institution's overall operating expenses. Cost associated with expensive pharmaceuticals or devices sometimes can be mitigated by partnership with vendors willing to donate a product or service in the care of indigent patients. Therefore, the true cost to the provider typically is substantially less than that quoted.

If the true cost were presented to the patient's Ministry of Health, it might be willing to bear a substantial share of the true financial burden on the hospital.

In addition, if the institution in question accepts paying patients from this country, would not its ethical obligation to this man be similar to that of an indigent patient from the United States? The result may be that the treating hospital (or transplant center) will bear only a relatively small burden of actual cost associated with the care if the Ministry of Health picks up a portion and some of the providers forgo billing for their services or contribute in-kind products to help defray cost.

In this way all stakeholders (who also benefit from the reimbursable care) have an opportunity to contribute on a global scale. While not relevant to the specifics of this case, developing a treatment plan that includes a worst-case scenario (with attendant costs) will recognize the possibility of further, expensive care. Informed consent, both for the patient and the Ministry of Health of the home country, would make this explicit. If this plan were approved prospectively, expectations for the patient (autonomy) and the caregivers as to desired outcome (beneficence) will be realistic based on the approved therapy, avoiding the sense of an ethical dilemma posed by anticipation of further treatment. Ethically valid informed consent for all contributing agents should include realistic projections of costs of follow-up and continued care and not merely crisis care.

One might ask the question—why should it make a difference whether the patient is a foreign national or a U.S. citizen? Isn't it enough that the patient is a fellow human being with the same moral right to the pursuit of a healthy, productive life as we have? A discussion as to our ability to differentiate between "we" and "them," to the extent that humans seem able to live comfortably with the discomfort and misfortune of "them" as long as "we" are not affected, is beyond the scope of this response.

Humans (and other higher animals) have a recognized tendency to dichotomize intra-specific relationships (good vs. bad, friend vs. foe, we vs. them)<sup>1,2</sup> even to the point of inventing pseudo-speciations in order to deny basic human rights to individuals or groups,<sup>3</sup> or to demonize them to justify racially

based discrimination or extermination.<sup>4</sup> The key point here is that these "differences" are artificial, intellectual constructs that allow us to live with decisions we might otherwise find morally reprehensible (hence Erikson's use of the term "*pseudo-speciation*"). The classic article "The Tragedy of the Commons" is an introduction to the limitations of technology to solve problems that require moral solutions.<sup>5</sup> Just as none of us would turn away a critically injured trauma patient from the emergency room, regardless of his or her ability to pay, I maintain that this patient (who was already in our system) should receive life-saving care as appropriate.

Also relevant to this discussion are the issues of societal decisions for the allocation of limited resources, and the equitable distribution of those resources for the greatest social good (justice). We must recognize that we do not provide this level of high-technology care for all U.S. citizens, and so it should not surprise us that this patient's country (his "society") has made the decision that a stem cell transplant for him would not be a justifiable allocation of their resources. This fact leads us to the question of greatest good: Even if the true cost of this procedure were within his country's budget, might these dollars nonetheless be better spent immunizing 10,000 preschool children? We should no more withhold care from a patient in need from a country lacking in social equity than we should withhold food from a starving population in a repressive country.

At Dartmouth-Hitchcock Medical Center, we have had many such requests, which have in the past been dealt with on an ad hoc basis. In order to make our process more thoughtful and equitable, we have established an oversight committee, which includes the executive medical director and representatives from our Bioethics Committee, Care Management and Finance. The group is charged with evaluating and approving requests for this type of care. Working criteria for consideration and/or approval include: the develop-

*Ask the ethicist—continued on page 8*



## The legal column: Emergency research without informed consent

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**T**he first principle of the Nuremberg Code is that “[t]he voluntary consent of the human subject is absolutely essential.”<sup>1</sup> The requirement of consent remained an essential tenet of U.S. research ethics until 1996 when the Food and Drug Administration (FDA) developed an exception to facilitate research in the emergency patient population. That exception was granted to speed the development of new therapies and evaluate existing ones, for acute medical conditions, when the patient is unable to give consent to participate in a study, and where existing legal requirements for prospective informed consent would have prohibited such studies.

Under this exception, found in the Code of Federal Regulations<sup>2</sup>, a series of requirements must be met before such a consent waiver is initiated. Among other requirements, (1) the subject is in a life-threatening situation; (2) available treatments are unproven or unsatisfactory; (3) obtaining informed consent is not feasible due to the subject's medical condition; (4) the intervention is necessary before consent from a legally authorized representative (LAR) can be obtained (though efforts must be made to contact such an individual or family members at the earliest time); (5) participation in the research has the prospect of direct benefit to the subjects; (6) the research could not be carried out practicably without the waiver; and (7) the institutional review board (IRB) has approved the protocol and informed consent procedures at the point at which obtaining consent would be feasible from the subject or where a family member (who is not an LAR if no LAR is available) is in the position to object to the continued participation. Additional protections include (8) consultation with representatives of communities in which the research will be conducted; (9) public disclosure of the study results to those communities before the research commences and after study completion; (10) creation of an independent data monitoring committee; and (11) FDA approval of the study.

Beginning in 1991 Northfield Laboratories sponsored Phase I clinical trials of PolyHeme and later in surgical studies used consenting patients. PolyHeme, a potentially lucrative blood substitute, is extracted from hemoglobin, the oxygen-carrying molecules in red blood cells. It is derived from chemically modified expired whole blood. Like “universal donor” O negative blood, it is compatible with all blood types. PolyHeme can be stored for more than a year whereas blood lasts only six weeks.

Between 2004 and 2006, Northfield tested the efficacy and safety of PolyHeme in treating patients with severe blood loss in ambulances where blood was not available. Trauma victims (other than those with severe brain injuries, needing CPR or pregnant) were randomized to receive either PolyHeme or saline. This study was approved under the emergency waiver exception. Once at the hospital, patients on PolyHeme continued to receive PolyHeme for up to 12 hours unless an LAR or family member or a patient who became competent objected, while those on saline received blood transfusions. The only opt-out procedure for a patient to avoid participation was to wear a Northfield-provided wristband that said, “I decline the Northfield PolyHeme Study.” In the Kansas City area, only 58 people requested the wristband.

Toward the end of the study, in 2006, the *Wall Street Journal* reported that in an earlier series of studies, Northfield may have hidden evidence of higher rates of adverse events generally and heart attacks in particular. These were statistically significant. There also had been twice as many deaths in the PolyHeme cohort.<sup>3</sup> Northfield responded that it had reported the information to the FDA and that it believed the adverse events were probably not due to PolyHeme.

In an article about the trauma study published in 2008, PolyHeme investigators concluded that “[t]he combination of PolyHeme's life-sustaining capability, the logistic benefits, and the acceptable benefit-to-risk calculus for the intended indication represent an opportunity to

provide an alternative to transfusion for patients at high risk of death when stored RBCs are not available.”<sup>4</sup>

The FDA's analysis differed markedly from that of the investigators. It disapproved Northfield's application to market PolyHeme, concluding that “the safety data of all controlled studies reveal that the administration of PolyHeme places the patients at a higher risk of significant adverse events (and) therefore, in the absence of clinical benefit, the risk/benefit assessment of the product in trauma is unfavorable,”<sup>5</sup> and that the trauma study failed to hit its primary endpoints of superiority and noninferiority 30 days post-trauma.<sup>6</sup>

The FDA's initial waiver regulation was controversial. Skeptics questioned the very concept of conducting research without patient consent and other provisions of the rule. There was consensus that waiver approval be contingent on careful analysis of the ethical dimensions of each study. In the PolyHeme study, for example, serious objections were voiced to the in-hospital phase because standard of care blood was available and could have been used.<sup>7</sup>

Ethicists have used the controversy to raise other concerns about the FDA waiver.<sup>8</sup> These include: (1) the perception of an overly loose requirement that existing treatments be unproven or unsatisfactory for research to be acceptable without consent; (2) how to balance the need to protect a sponsor's proprietary interests and the need to inform communities fully about an emergency research waiver; (3) the need to ensure that IRBs considering such a protocol are alerted not merely to formal disapproval of such research by other IRBs, but also to objections that have been raised leading to non-submissions or withdrawals of protocols prior to disapproval; (4) inadequate provisions for data safety monitoring on a site-by-site basis; (5) inadequate requirements for ensuring maximum opportunities to opt out of a study; and (6) the lack of procedural formality and

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# Ethics and the humanities: Whose sister's keeper?

A film review of *My Sister's Keeper*, directed by Nick Cassavetes, 2009

**T**his past summer, Nick Cassavetes's film adaptation of *My Sister's Keeper* (based on the novel by Jodi Picoult, 2004) made movie-theater audiences sob across the country. Like the novel, the film chronicles the struggle of a loving but strained family dealing with a daughter's protracted battle with cancer, raising a treasure trove of bioethical issues. Is it legitimate for parents to try to create a "savior sibling"? To what extent may those children justifiably be used to promote the health of a brother or sister? What does it mean for parents to act in the "best interests" of their children in nontherapeutic medical decision-making? These issues are not in the realm of science fiction; indeed, "savior siblings" have actually been created, even if the way in which the film portrays the use of a savior sibling is not completely realistic.

Whereas the focus of the novel rests primarily on Anna's conflicted feelings as her sister's keeper, the nexus of the film adaptation is the relationship between Kate (Sofia Vassileva), 16, and her mother, Sara (Cameron Diaz). Kate craves a normal teenage life, but her 13-year battle with acute promyelocytic leukemia (APL) has left her world-weary, and has brought her mother to the defiant point where she "will not let her die." We encounter Sara as a woman of Shakespearean determination, dropping her prominent law career soon after Kate becomes ill in order to focus single-mindedly on saving her daughter. In the process she neglects her eldest child (as does her husband) and demands like-minded sacrifice, in the form of bodily tissues, from their youngest daughter Anna (Abigail Breslin).

The ethical issue that received the most scrutiny when the novel appeared concerns Anna, the savior sibling.

Rather than awaiting a human leukocyte antigen (HLA) tissue match, Sara and her husband decide to utilize in vitro fertilization and preimplantation genetic diagnosis to create one for her, following a doctor's suggestion. Soon after Anna is born, her cord blood provides stem cells for Kate. But this innocuous procedure is just the beginning of an onerous and painful regimen of taking "spare parts" from Anna (blood, bone marrow, granulocytes) often while pinning her down in order to prolong Kate's life.

The action of the film picks up at the point where Kate is in renal failure and her mother demands that Anna give up one of her kidneys to save her yet again. But it appears that this time, Anna, now 13, has had enough; she meets with an ambulance-chasing lawyer she saw on TV, Campbell Alexander (Alec Baldwin) in order to sue for medical emancipation. She has been her sister's keeper for more than a decade, and wants to draw the line at an operation that would restrict her activities and render her own health more vulnerable.

But who exactly is her "sister's keeper"? While the ambiguity of the title suggests some reciprocity, in the film version, it is more clearly Kate who is her little sister's keeper. In fact, we ultimately learn that it is Kate who has put Anna up to waging this legal battle, one that infuriates their mother and threatens to rend the already frayed ties that keep this family together.

Kate does not want to take Anna's kidney from her, even if it will prolong her life, because she doesn't want to burden her sister any longer, nor does she want to continue to suffer. Kate is ready to die. She has already encapsulated her short but energetic life in a beautiful scrapbook that she presents to

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her mother at the close of the film. But how could she openly oppose the mother who has conceived a savior sibling for her, who has given up her career and devoted every waking hour for over a decade for the sake of her continued survival? Even if she could muster the strength to confront her mother, Kate doesn't have a legal leg to stand on: She is a mature minor but cannot legally refuse further life-sustaining treatment—a right that would be uncontroversial if she were a competent adult. In lieu of her own medical autonomy, Kate has Anna demand her own medical emancipation. Thus, in order to be her sister's keeper, to spare Anna further suffering, Kate has to prod Anna to seek an emancipation that would actually free both sisters: one for a more carefree life, the other for a better death.

In addition to the different foci of the novel and the film, the largest difference between them is the ending. The film *My Sister's Keeper* eschews the deus ex machina conclusion of the novel in which Anna conveniently dies in a car crash, rendering her an even more convenient source of spare parts. Rather, the film ends in a more believable and satisfying manner, with Kate dying peacefully, comforting her mother in the final hours, and with Anna learning that she has won her day in court. Anna has been emancipated both legally and psychologically: She is free to find her own path in life, knowing that she "had a terrific sister" whose life she prolonged but not beyond its utility to Kate. Thus, in offering a more verisimilar conclusion, the film version of *My Sister's Keeper* deftly treats the themes of freedom and obligation in the concrete context of one family's experience of terminal illness. □



## Dialogue: Synthetic biology: engineering life

**S**ynthetic biology, using engineering principles to create new life, is laden with human values. Indeed, it is values that drive the field in the first place. As Christina D. Smolke noted in her overview (*Lahey Clinic Journal of Medical Ethics*, Spring 2009) synthetic biology “holds great promise for developing solutions to many global challenges, including renewable energy production... and medical advancement.” J. Craig Venter, cofounder of Synthetic Genomics, Inc., went so far as to say that synthetic biology is necessary for “the future of life.” These are all claims about benefits, which are claims grounded in human values.

Because Smolke discusses the potential benefits, however, I’ll confine my comments to other moral issues. Suffice it to say that the potential benefit appears to be enormous. The most prominent of the other moral issues, and the flip side of the possible benefits, is that the field also poses potential harms, ranging from short-term catastrophe to long-term social problems. The worries about catastrophe fall into two sorts sometimes dubbed “bioterror” and “bioerror.” The first has to do with the possibility that synthetic biology could be deliberately put to bad uses. The 1918 flu virus has already been briefly re-created in the laboratory. In theory, entirely new pathogens could be brought into existence. Pathogens that target crops or livestock are also possible.

The concerns about “bioerror” are more prosaic. The worry is that synthesized organisms might escape from the laboratory or factory, turn out in their new environment to have properties different from those intended and predicted, or perhaps mutate to acquire them, and become established in the wild, posing a threat to public health, agriculture or the environment.

Perhaps most difficult to gauge are concerns about the broad societal and economic effects of synthetic biology. The activist organization ETC Group<sup>1</sup> (or Action Group on Erosion, Technology and Concentration) holds, for example, that success in creating a synthetic organism to produce biofuel would likely convert much arable land throughout the world from food pro-

duction to production of crops from which biofuel might be produced, with harmful consequences especially in poorer countries in the Southern hemisphere.

Other new technologies—traditional biological work on anthrax and other pathogens, “traditional” gene transfer technology and nanotechnology, among others—raise similar questions, of course, but synthetic biology raises them in a particularly sharp form. First, the consequences could be particularly significant, broad in impact and unpredictable. Moreover, if the field evolved such that important and even innovative work could be done by relatively inexperienced people, then it could prove particularly difficult to control. Small-scale and underground labs could flourish, and the threats about safety and “dual use” would be exacerbated.

To frame debate over benefits and harms, the key point is that they are *potential*, in the sense that a story with *some* degree of plausibility can be told about how they *might* occur. Concerns about bioerror are highly plausible—it is undeniable that pathogens can be created and let loose—but the likelihood it would happen is harder to assess. Proponents of the technology argue that terrorists have much better ways of attacking their enemies than by reintroducing smallpox, which would wreak general havoc and harm everybody.

What motivates concerns about bioerror is mostly just the long history of industrial accidents. Proponents of synthetic biology argue that organisms created to produce (for example) vast quantities of fuel in specially designed environments will simply be too weak to survive in the wild—and that for added assurance, they can be deliberately engineered so as to be flatly *incapable* of surviving in the wild. Perhaps this is assurance enough. Smolke describes synthetic biology as targeting the simplification of organisms—the creation of stripped-down bacteria that can be augmented in controlled ways to carry out precisely specified functions. If the field achieved that goal, it would provide some reason for accepting biologists’ predictions about how synthesized organisms will perform if they escaped into the wild. Still, one of the general

themes of traditional “analytic” biology is that living things in general and genomes in particular are usually more complex than they first appear, leaving room to wonder whether the simplification of life will be as easy as synthetic biologists hope.

Most difficult to assess are the worries about long-term economic and social consequences. However, there should be ways of avoiding these consequences other than by avoiding the technology itself. Further, if current industrial methods are environmentally unsustainable, which could itself lead to disastrous long-term social consequences, then the potentially better methods offered by synthetic biology are attractive.

In general, we do not yet know enough about synthetic biology to make any final policy decisions about it. The potential benefits are too great to let fear of the risks stop us in our tracks, but the potential harms are too significant and too plausible to let our hopes carry us away.

In addition to questions about how synthetic biology will make people better or worse off, there are also questions about how the synthesization of organisms squares or conflicts with other kinds of moral values—values that have to do with what is good or bad *in itself*, rather than likely to generate good or bad outcomes. These values, too, might tell both in favor of moving ahead with the field and in favor of some constraints on it. Generally, Westerners favor a fairly broad range of personal freedom and experimentation, not merely because it might lead to an improvement in the human condition but also because it just is part of the human condition we want, and this value provides some reason for letting the field go forward.

It is also interesting to listen to synthetic biologists discuss their work. In addition to the potential benefits, they will often stress that the work is its own reward. Learning about the world and building things can be valuable in themselves. The advancement of science and industry is the advancement of human mastery, and synthetic biology advances human mastery especially dramatically. It is also the pursuit of understanding, the refinement of human intelligence.

The flip side of the value of understanding and triumphing over nature is the value of preserving nature. At least to some people, the prospect synthetic biology seems to offer of still-greater human control over life is itself troubling. The touchstone for this sort of concern is environmentalism, which is not just about making sure the environment is good for humans, but also about saving endangered species, untrammeled wildernesses, "untamed rivers" and old-growth forests. We should approach the natural world with reverence or gratitude. Some worry that synthetic biology and other kinds of biotechnology do not square with this value.

Smolke holds that objections to "tinkering with nature ... can be met by noting the various other ways in which man has altered nature and emphasizing that the goals of synthetic biology are constructive." In fact, the many other human alterations of nature do not necessarily quell misgivings about tinkering by means of synthetic biology any more than the many instances of humans cutting down trees establishes that there is no value in preserving old-growth forests. If one has a preservationist stance toward nature, one obviously must accept that there is a balance to be struck. Even if we save some

tracts of old-growth forest, we will still sometimes cut down trees. There might also be a balance when it comes to the alteration of organisms. Mostly, creating species variants through breeding seems unobjectionable. But breeding seems to amount to something less than "engineering life," as Smolke put it in her title. The misgiving is that engineering life goes too far. Some argue that synthetic biology takes human control over nature to the ultimate level, at which humans are not merely altering existing life forms but are in effect creating new forms.

The better point Smolke makes is that the goals of synthetic biology are constructive. Objections to genetically modified crops and livestock notwithstanding, what has most troubled people is not the creation of new biological systems but the destruction of existing ones. (Even the objections to genetically modified organisms in agriculture are linked to and partly grounded in concerns about their possible destructive effects.) If synthetic organisms were confined to the laboratory or the factory, they might not be destructive, and they might well be constructive. In fact, they may well be constructive even from a nature-preservationist standpoint: They could have great environmental benefits.

Synthetic Genomics, Inc. recently announced an agreement with Exxon-Mobil to engineer algae that produce gasoline in ways that not only eliminate some of the usual environmental costs of producing gasoline but simultaneously absorb large amounts of carbon dioxide, thereby offsetting some of the environmental costs of *burning* fuel (no matter how it is produced).<sup>2</sup> If that could be achieved, many who care deeply about the human relationship to the natural world, and who feel that humans should tread more lightly on the world, would find the project attractive.

Thus, even with the intrinsic objections to synthetic biology, much can hinge on the outcomes. We need to monitor the field, assess its possible outcomes realistically and weigh them appropriately in light of our values. □

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<sup>1</sup><http://www.etcgroup.org>

<sup>2</sup><http://www.syntheticgenomics.com/media/press/71409.html>

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transparency in the FDA's own review process of consent waivers.

In 2006, the FDA issued a "Draft Guidance,"<sup>9</sup> but the regulation itself has not been revised and the guidance has remained unchanged, and in draft form. As of 2006 the agency had approved only 21 protocols under the consent waiver exception although several large, federally funded, multicenter research studies are ongoing or planned.

The fact that the PolyHeme study may have been successful in the eyes of the PolyHeme Study Group is no reason to encourage such consent waiver studies if they are not ethically sound. Neither should the alleged ethical violations in the PolyHeme studies or the negative outcomes of other consent waiver studies necessarily be seen as a reason for abandoning these investiga-

tions. The FDA must better address the ethical issues relevant to research without informed consent. Public trust in the entire research enterprise requires confidence not only in the actions of sponsors, institutions and investigators but in the government agencies charged with oversight. □

<sup>1</sup><http://ohsr.od.nih.gov/guidelines/nuremberg.html>

<sup>2</sup>21 C.F.R. § 50.24. For a thorough analysis of the regulation, see Gillenwater G. FDA's emergency research rule: An inch given, a yard taken. *Food and Drug L J* 2008; 63: 217–250.

<sup>3</sup>Burton T. Amid alarm bells, a blood substitute keeps pumping, *Wall Street Journal*, February 22, 2006, A1.

<sup>4</sup>Moore E, et al. Human polymerized hemoglobin for the treatment of hemorrhagic shock when blood is unavailable: The USA multicenter trial. *J Am Coll Surg* 2008; 208:1-13.

<sup>5</sup>Hansel J. FDA rejects faux blood tested at Mayo Clinic. *Post-Bulletin*, Rochester, Minnesota, May 17, 2009.

<sup>6</sup>Arno Therapeutics. Other news to note. *BioWorld Today*, May 12, 2009.

<sup>7</sup>See Kipnis K, et al. An open letter to institutional review boards considering Northfield Laboratories' PolyHeme® trial. *Am J Bioethics* 2006; 6:18–21.

<sup>8</sup>Kipnis K, et al. Trials and errors: Barriers to oversight of emergency research. *IRB: Ethics & Human Research* 2006; 28(2):16–19; Dicket N and Sugarman J. Getting the ethics right regarding research in the emergency setting: Lessons from the PolyHeme Study. *Kennedy Inst. Ethics J.* 2007; 17(2) 153–172; Apte S. Blood substitutes—the polyheme trials. 2008; *Mcgill J Med.* 1(1): 59–65. Gillenwater, supra note 2 at 240–250.

<sup>9</sup>Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors Exception from Informed Consent Requirements for Emergency Research, <http://www.fda.gov/OHRMS/DOCKETS/98fr/06d-0331-gdl0001.pdf>.



*Ask the ethicist—continued from page 3*

ment of an institutional budget for “in kind” care; partnership with a foundation, individual or community group to ensure appropriate transportation, governmental paperwork, housing and personal/emotional support for the patient and family; an identified, accountable medical staff sponsor; partnership where appropriate with vendors who might supply needed devices or pharmaceuticals; a fully developed care plan; and a goal to promote highly effective interventions that will maximize benefit to the most number of individuals. Formal relationships directly with national Ministries of Health might include agreed-upon lines of communication between physicians and the ability to appeal decisions through an objective process. In this way, we believe that our medical center can help fulfill its role as a global citizen.

**John R. Butterly, MD**  
Executive Medical Director  
*Dartmouth-Hitchcock Medical Center*  
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**O**utcome: The patient was sent home by the Ministry of Health before he could be evaluated at the transplant center. When he returned home, his remission was consolidated with chemotherapy. He became neutropenic and died of sepsis soon after leaving the United States. □

<sup>1</sup>Lorenz K. *On Aggression*. London: Methuen; 1966.

<sup>2</sup>Wilson EO. *On Human Nature*. Cambridge: Harvard University Press; 1978.

<sup>3</sup>Erikson EH. *Identity, Youth, and Crisis*. New York: WW Norton; 1968.

<sup>4</sup>Fredrickson GM. *Racism: A Short History*. Princeton, NJ: Princeton University Press; 2002.

<sup>5</sup>Hardin G. The tragedy of the commons: The population problem has no technical solution; it requires a fundamental extension in morality. *Science* 1968;162:1243–1248.

# Medical Ethics

*Lahey Clinic Journal of Medical Ethics* encourages reader participation. We welcome comments for our “Dialogue” column and invite submission of ethical dilemmas for “Ask the ethicist.” Send correspondence and requests for complimentary subscriptions to David Steinberg, MD.

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