

Biomedical Innovation  
And  
Health System Reform

Comments on papers by  
Prof. Samuel O. Thier  
And  
Ezekiel J. Emanuel

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Professor Thier has presented an analysis of innovation in health system reform that is notable for its scope and comprehensiveness. Indeed, in his manuscript, Professor Thier covers both the usual topics of cost, quality and access, and also ventures boldly into topics that others might timidly ignore. Thus, his paper considers innovation in the organization and delivery of health care, in research, and especially at the interface between academia and industry; in health professionals education, which can be seen either as inhibiting or facilitating innovation, and finally on financing considerations and their impact on innovation.

Professor Emanuel takes a different approach to the task of analyzing the impact of health system reform on innovations. He carefully and deeply analyzes the impact that technology innovation has on health care costs; considers the role of technology assessment and its potential for moderating those costs; and reviews the currently favored approaches to control technology related health care costs. In doing so, he focuses largely on several models: insurance benefit redesign, provider reimbursement redesign, including such newly popular strategies as pay for performance; health care system redesign, including expanding approaches to disease management. He then orients the remainder of his paper to a consideration of how these approaches to cost control would affect biomedical innovation, emphasizing its impact most notably on drug development.

It would not be possible for me to comment on all of the issues raised in the papers by Professors Emanuel and Thier, nor do I wish to restate their arguments. Rather, I plan to emphasize several of the critical considerations they highlighted, offer my

observations on them, and then refer to my own sometimes conflicting viewpoints. Being in the company of so many distinguished economists and health care administrators, I shall not be so foolish as to claim their expertise for my own. Instead, I hope to bring the perspective of a physician and clinical investigator to these discussions.

Professor Thier began his analysis with a detailed focus on the American health care system. He referred to an Institute of Medicine (IOM) report that offered a delineation of purpose for a health care system. Specifically, he noted that the IOM report suggested that its purpose is "... to reduce the impact and burden of illness, injury and disability, and to improve the health and functioning of the people of the nation." While it would be tempting to dismiss these goals as self-evident, or perhaps even extravagant, it is not so easy to argue that they are the exclusive property of our health care system.

Indeed, extensive research over the past 30 years has established the crucial role that social and behavioral features play on both rates of mortality and morbidity in Western nations. Perhaps the most celebrated research on this topic, which has even engaged the interest of the stray economist, comes from the Whitehall Study in the United Kingdom. In this long term follow-up of a civil service cohort, individuals were categorized into five groups determined by their civil service grade: at the top of the classification were administrators, next were professionals, then executives, then clerical and lastly other less skillful workers. It is well known and fully expected that those at the top of the employment grade scale would have better morbidity and mortality outcomes during follow up than those at the bottom. What was not expected was that with each step

down the scale there was a significant worsening in disease outcomes and overall mortality. Indeed, it was the gradient in health and health related outcomes by social class category that is perhaps the most notable feature of the extensive literature on the relationship between social class and health.

Numerous other studies have affirmed this relationship. It is observed in countries with universal health care coverage and those without, in countries with extreme levels of income inequality and those with less inequality, in countries with heavily stratified societies and those with more social equality. Despite this nearly uniform set of relationships, we know very little about how social class gets “under the skin” to cause the biological consequences that result in differences in disease rates, morbidity and overall mortality. Among the explanations being offered are considerations of self-efficacy and control, the role of allostasis, (in contrast to homeostasis) as a reflection of chronic stress and its biological effects, or the role of buffers, both physical and psychological, in modifying the impact of social equality.

I mention this line of investigation because it bears so heavily on the goal of improving the health and functioning of the people of our nation. It is simply not possible to imagine that this goal can be achieved by focusing on our health care system alone. There is much that we can and should do as physicians and allied health professionals to achieve the best outcome in the care of the sick. I take personal pleasure and pride in these accomplishments. Yet the impact of innovation in medical care will ultimately prove disappointing unless we succeed in broadening our focus beyond the customary

activities of clinical medicine, as important as that is. Indeed, as this audience knows well, health policy is not just about health care; it is also about housing policies and transportation policies and even tax policies. Medical innovation both its impact and its cost, must be better understood within this broader context.

Professor Thier makes note of this consideration in his discussion of research as a principle source of innovation. Indeed, he acknowledges the importance of broadening medical and health care research beyond the customary biological and molecular sciences that have been the bedrock of academic medical centers. Modest advances in this direction are occurring, stimulated in part by the NIH Roadmap initiative and the recent efforts to re-engineer translational science through the Clinical Translational Sciences Awards. Institutions that have been funded in the earliest rounds of this competition are distinguished by their greater scientific inclusiveness and have reached out to nursing, psychology, anthropology, quantitative sciences and other disciplines.

It is not at all surprising that Professor Emanuel, with his particular focus on drug development, would make more than just passing reference to “personalized medicine,” which is being heralded by some as the latest research innovation that has the potential to reshape the practice of medicine. As commonly used, Burke and Psaty suggest that the term “...predicts a leap forward in disease prevention and drug treatment, based on knowledge of individual genetic susceptibilities”. Indeed, we are now on the cusp of a proliferation of so-called pharmacogenetic tests that promise to improve the safety and effectiveness of drug treatment. Among other implications, personalized medicine has the

potential to alter fundamentally the model for drug development, the methods and measures of treatment benefit, the differing value of new treatments for patients rather than populations, and the calculation of cost effectiveness ratios.

But the very compelling strengths of personalized medicine are also among its compelling weaknesses. Genetic risks associated with common chronic disorders are small; most of the genetic risks identified to date have odds ratios of 1.2 or 1.3. Risk estimates of this magnitude require large samples to obtain robust associations. Genome directed clinical interventions, either for diagnosis or treatment, will need to be justified by evidence that the gene variant or gene profile modified the effect of treatment, either by improving therapeutic benefits or the safety profile of pharmaceuticals. Will this evidence necessarily come from randomized controlled trials to receive approval by the FDA? Is personalized medicine a challenge to the traditional view that limits the use of “subgroup” analyses to guide clinical decision-making? Will studies that demonstrate clinical benefits by narrowing the population intended for treatment be embraced by pharmaceutical and biotechnology companies? And finally, will genome guided treatment for individuals be superior to traditional interventions directed at populations if overall societal health is the metric used to determine benefit?

Professor Emanuel relies on a deep analysis of a traditional model of drug development to argue that a cost conscious delivery system will shift the focus towards higher value research where a new drug is likely to have a bigger health impact, and to increasing the threshold for commercial development of a new compound or therapeutic

agent. Both predictions are speculative and lack an empirical basis. Such predictions may well be affected by advances arising out of genomic sciences, other research developments in the biological sciences and the profound effects of social and environmental factors on the clinical course and outcomes of disease. Indeed, I would propose that one of the most disappointing elements of our current policies for drug approval is the impoverished nature of the data and methods that are used to demonstrate the benefits of treatment.

Both professors Thier and Emanuel predicate much of their analysis on research innovation on the continued dominance of the randomized controlled trial as the basis for demonstrating clinical benefits. The RCT is a research technology that has emerged as a dominant methodology for reasons well known to this audience. In addition to randomization, RCT's employ eligibility and exclusion criteria to refine subject enrollment, often require placebo controls and double-blind procedures, and utilize rigorously measured outcomes. But it is also well known that the results achieved in RCT's are often not observed when treatments are introduced into clinical practice, and risks that occur uncommonly or after prolonged use may not be noted in the RCT's at all.

It is likely that a major challenge to the dominance of the RCT will emerge over the next decade as electronic health information becomes more widely employed throughout our health care system. When this occurs, information collected during routine clinical care may provide more accurate data on the benefits and risks of pharmaceuticals and devices. These data may identify new treatment benefits, may suggest populations in which effectiveness is attenuated when compared to the original

RCT's, may find subgroups at risk of adverse effects, and may provide the data with which to expand the potential role personalized medicine. Indeed, it is entirely possible that the analysis suggested by Professor Emanuel, relying so heavily as it does on RCTs, will be noted for its anachronistic link to a time when Medicine was rooted in a rigid framework of therapeutic evaluation that too often erred in estimating both benefits and risks. Fortunately, the new post -RCT era will usher in a more realistic and apposite appraisal process that will ultimately improve the care of our patients, while also making the health care system more efficient and effective.

In considering the possible future impact of Personalized Medicine and patient based technologies on the cost and effectiveness of health care we are faced with the need for intellectual breakthroughs that recognize that we are no longer suitably grounded by concepts of averaging, expected value and probabilistic reasoning. Similarly, in seeking to use evidence based approaches to improve the effectiveness and efficiency of our health care system, we are no longer able to rely on customary methods and measures of clinical benefits. Average benefits expressed as “relative risks” are being challenged by measures of “absolute risk”; intermediate or so-called surrogate end points are appearing frequently as evidence of clinical benefit; and information technologies are holding out the promise of fundamental change. We do not yet know whether these major modifications will increase or restrain the cost of health care. What we can be sure of, however, is that they will have as yet unmeasured impact.

Organization and Delivery

Professor Thier offered a number of important observations on the organization of our health care system. He referred at some length to the experience of other western countries where health care costs are lower and population indicators of health status are often higher. In each instance, as he noted, those health care systems have a more robust representation of primary care physicians. Many suggestions for health system performance would be strengthened by a larger number of primary care physicians.

I do not need to describe for this audience the abysmal state of primary care in the United States and its declining attractiveness to graduates of American medical schools. A recent suggestion that the US may be facing a physician shortage has encouraged the development of as many as twenty new medical schools in this country. It is unlikely that these incremental U.S. medical school graduates will result in an increased number of physicians practicing in the U.S. unless there is a corresponding increase in the number of Graduate Medical Education training positions in residencies across the U.S. If there are not, it is likely that U.S. Medical school graduates will simply occupy residency spots formerly taken by FMG's. And of course, there is no reason to expect that these newly added U.S. medical graduates will be any more likely to pursue careers as primary care physicians than those currently graduating from medical school. If we substantially increase the number of procedure-oriented physicians and surgeons, as seems likely, the pressure on costs for medical care will increase considerably.

I want to conclude my remarks by referring to two trends, that were noticeably absent in the papers by Thier and Emmanuel. The first is the relentless assault of the demographic reality that we are experiencing a remarkable growth in the number of Americans over the age of 65. And the second is the stunning and rapid influence of globalization.

With regard to the increase in elderly, there is little new to add except to remind ourselves how ill prepared we are to meet their medical needs. Most of the research on clinical effectiveness has excluded individuals over age 65 from their studies. Geriatrics, like primary care, has not flourished as a specialty in the U.S., our acute care hospitals handle transitions for elderly patients from community and long term care facilities poorly, and we have inadequate medical services for older adults. At a time when the health care and associated costs for elderly Americans is a critical issue, our health care system is noticeably deficient in capacity and expertise.

The effects of globalization are equally compelling. Many exciting scientific discoveries that may substantially affect medical care are occurring overseas. Increasingly clinical trials that are needed to demonstrate clinical effectiveness are highly reliant on recruitment of subjects in Asia and other places because U.S. citizens are not willing or not available in sufficient numbers to meet enrolment targets. Illnesses are spread more rapidly, putting greater pressure on emergency services and a public health infrastructure that is highly fragile. And yet at the same time, there has never been more

interest in International Health among students and trainees in our Academic Medical Centers.

In summary, Professors Emanuel and Their have offered quite different approaches to the analyzing the tension between innovation and cost in the health care system. Professor Emanuel considered health system structure and function, and then focused his further insights on the drug development process. Although he spent little time on device development, it will likely have a major role in future innovation and is unlikely to follow the patterns of evaluation and evidence generation that has characterized drug evaluations. Professor Their has proposed a more comprehensive model for analysis that has the advantage of identifying numerous places to reconcile innovation with cost and benefit. I remain confident that innovation will continue to pervade our health care system. But I also believe that innovation alone is unlikely to restrain the rising health care costs that are so embedded in our system of care.